PEDIATRIC ENDOCRINOLOGY AND DIABETES

2020 UPDATE

Editors:

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EDITURA MIRTON

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Preface

In Romania, "endocrinology and pediatric diabetes" is not a recognized specialty, which is why the diseases of children and adolescents are divided between endocrinologists and adult diabetologists, and some pediatricians interested in this pathology.

In the current pandemic conditions, when our whole life has been turned upside down by the SARS-Cov2 virus, the efforts to manage these pathologies even through "telemedicine" consultations require an improvement in the level of knowledge of all those involved in the diagnosis and the treatment of these children.

Following the recommendations of the European Academy of Pediatrics (EAP) and the European Society for Pediatric Endocrinology (ESPE) to standardize pediatric training in this field throughout Europe, we offer participants in the 7th National Congress of Diabetes Nutrition and Pediatric Endocrinology organized in the virtual environment, a new volume “Pediatric Endocrinology and Diabetes - 2020 Update”.

Professor Iulian P. Velea MD, PhD
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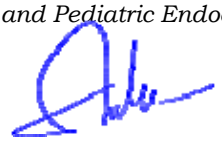

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PARTIAL REMISSION IN TYPE 1 DIABETES.

Iulian Velea, Corina Paul, Oana Alexandra Velea-Barta

Introduction

The remission, in any disease, defines a temporary, spontaneous or secondary improvement of a treatment.

The "appearance" of diabetes in childhood and at younger ages increases the duration of exposure to the disease in periods of maximum vulnerability (periods of growth, puberty, adolescence, etc.) increasing the risk of chronic complications at a young age.

After the clinical onset of type 1 DM and the initiation of insulin therapy, spectacular improvements in diabetes have sometimes been reported in children, even to transient hypoglycemic coma, with a quasi-total reduction of insulin intake (1).

Lately, more and more researchers are paying special attention to this stage in the natural evolution of type 1 diabetes in children. The growing interest is determined by the fact that this stage would be particularly important in maintaining the functional pancreatic beta-cell reserve, the reserve with a positive impact in obtaining and maintaining the metabolic balance of children with type 1 diabetes in periods of growth, puberty, periods of disease, etc.

There are authors who claim that partial remission is associated with a lower prevalence of chronic degenerative complications both micro- and macrovascular. (2)

Definition of remission

In order to define remission in type 1 DM also known as "honeymoon", metabolic factors are taken into account (absence of glycosuria, normal value of pre- and post-prandial blood glucose, HbA1c normal), the presence of endogenous insulin secretion (proven after the introduction of insulin therapy by dosing C peptide which must have normal value both basally and after stimulation), required for low or no exogenous insulin.

Most often, as insulin therapy is not discontinued, with very low doses in all circumstances, partial remission is discussed.[1] When fasting blood glucose remains below 7.8mmol/l and postprandial blood glucose is less than 11mmol/l, the term complete remission is used in the absence of insulin treatment. Thus, discontinuation of insulin therapy is the decisive argument for complete remission.[1,3]

A complete remission, allowing complete cessation of insulin therapy and maintaining optimal glycemic control was achieved by Drash et all. only in 3% of diabetic children.[4] Similar results (low percentage of complete remissions), regardless of the applied therapy, are reported by most authors. Thus Knip and all.[5] in a complex study on 178 cases, obtain complete remission in 3 cases (2%), and Tanae et all.[6] obtain complete remissions in a percentage of only 3,1%.

There is currently no consensus on the definition of partial clinical remission (CPR).

Proposed by Agner et all after 1980, starting with the 2006 ISPAD guide, partial remission was defined by 4 mandatory criteria:

- absence of clinical signs;
- insulin requirement less than 0.5 i.u. / kg / day;
- duration longer than 4 weeks,
- HbA1c < 7% (< 53 mol / mol).

Recently, a new formula for defining partial clinical remission has been proposed based on the value of "insulin dose-adjusted HbAc1" (IDDAA1C) which is calculated according to the formula:

HbA1c (%) + 4 x (insulin dose in u.i./kg body / 24 hours)

According to this formula, proposed by the Hvidovre Study Group, an insulin dose-adjusted HbA1c value would indicate partial remission.[7] This definition best correlates with a stimulated C-peptide value greater than 300pmol/L.[8]

Partial clinical remission in type 1 DM is therefore not a remission in the true sense of the word, because daily fluctuations in insulin therapy are inevitable and the essential element remains the indispensability of insulin therapy, less important being the dose, since its discontinuation is impossible.[1]

Under these conditions, the use of IDDAA1C is recommended after 2009 as a "*gold standard*" for defining partial remission due to:

- both insulin doses and metabolic balance,
- a better correlation with peptide C level,
- it's validation in large cohorts of children with type 1 diabetes.

Remission frequency

If the frequency of total remission remains below 5% of cases of type 1 DM in children, the same cannot be said about partial remission.

The frequency of partial remission reported over the years increases from 30% (as White reported in a 1953-1958 study) to 40.5% in those treated with conventional insulin therapy, to 65% as reported by Knip in 1982 [5] and even at 84.2% as reported by Tanae in 1986 for those treated from the beginning with the insulin pump therapy.[6]

Regardless of the applied therapy, remission may begin a few days or weeks after the initiation of insulin therapy, may last several weeks or months [9] occurs only once, rarely referred several remissions[10], thus confirming once again the evolution of the autoimmune destruction of the β pancreatic cells.

Another noteworthy factor is the different frequency reported from one country to another. Stefano Passanisi [11] in a study conducted in Messina obtained a partial remission in 63.5% of patients, while the observational study conducted in 255 centers in Germany and Austria partial remission was obtained in 71% of patients followed for 6 years. Poland reports close results (61.8%,) superior results (80%) are reported in Sweden while Chiavaroli et all (cited by 11) on a group of 678 patients in New Zealand reported a percentage of only 42.4% after 3 months from onset.

From these data, a significant number of children and adolescents will not develop partial clinical remission.[12]

Pathophysiology

The natural course of remission in type 1 DM is difficult to establish.

As early as 1944, Brush suggests that the phenomenon of remission defined by reduced insulin doses after 6-10 days of treatment (diet and insulin injections) is due to a temporary functional recovery of the Langerhans Islands. This theory was partially confirmed by C-peptide levels in the months following diagnosis while reducing the need for exogenous insulin. Over time, however, insulin secretion decreases until extinction in most patients.

The decrease in the need for exogenous insulin can be determined by several factors, among which insulin secretion and peripheral insulin sensitivity stand out.

At the onset of type 1 diabetes, there is an insulin resistance that will gradually subside with the initiation of therapy. The role of insulinopenia and hyperglycemia in the development of insulin resistance, respectively, is still partially elucidated. In this regard Selam[13] suggests that hyperglycemia may initiate a vicious circle: hyperglycemia → cell destruction survivors (and / or insulin resistance and / or worsening of immune abnormalities) → decreased cell function → worsening of hyperglycemia → metabolic more cyclical disorders severe.

The true measurement of insulin resistance induced by hyperglycemia is that of ketoacidosis. The mechanism is still incompletely known and depends on multiple factors:[14] insulinopenia, acidosis, hyperosmolarity, electrolyte disturbances, high levels of hyperglycemic hormones (especially hyperglucagonemia).

The elimination of hyperglycemia as soon as possible by introducing insulin therapy can stop this cycle by restoring metabolic and hormonal functions more or less completely.

Stopping this process while maintaining good metabolic control explains the patient's decreased need for exogenous insulin.[2]

The decrease in exogenous insulin requirements and the increase C-peptide secretion, observed after the beggining of the treatment, seems to be determined by the recovery of the functionality of βcells that are no longer required by hyperglycemia.

The last element worth analyzing in the genesis of the remission phase is the possibility of a βcell regeneration, demonstrated in the experimental animals.

In humans, the possibility of regeneration probably plays an important role in the intensity and duration of the remission period and is suggested by the presence (in the months following onset) of hyperplastic islands containing degranulated and bulky β cell nucleus (a sign of hyperactivity).[15]

Predictive parameters of remission

The installation and especially the duration of remission is limited in time by a number of factors, which brought into discussion various therapeutic regimens that through their intervention can slow down, but without stopping the autoimmune destruction of pancreatic β cells.

After Schiffrin et all.[16] three parameters allow the anticipation of the remission onset: male gender, age at diagnosis and absence of anti-insulin antibodies.

Age at onset.

The younger the child's age, the shorter the remission period compared to older children and adolescents. Drash found remissions installed only after the age of 5, and the younger the child is, the more he needs insulin at onset.[4] Basically, it can be said that the older age at the onset is a predictive factor of the installation of the remission period.[11]

The answer to the question: "*Why small children under 5 are more difficult or not at all in the remission period*", was given by the study of HLA haplotypes, studies that showed that DR4 haplotypes are more common in young children - which would be the genetic support of the low number of remissions in this age group. Other studies show that the destruction of beta cells takes place faster compared to older children, thus leading to a more severe metabolic decompensation and implicitly a lower residual beta cellular function, as evidenced by the higher (basal and stimulated) elements of peptide C plasma in older children.[17,18]

According to Atkinson et all, low age at the onset of type 1 DM would be associated with higher levels of pro-inflammatory cytokines such as CD20+, CD45+cells, TCD8 + cells that would lead to the destruction of pancreatic beta cells.[19]

sex

It seems that sex influences the installation but especially the duration of remission. Tanae[6] reported a statistic in which boys were remitted in a proportion of 61.3% compared to girls (50%). Knip[5] in a study of 178 cases reported 113 cases of remission, of which boys accounted for 71 cases (62.8%) while girls only 42 cases (37.1%), remissions with longer duration for 6 months, being obtained in 55 boys and only in 20 girls. In both studies complete remission was found only in boys.[5,6]

Autoimmunity

Another observation considered to be a predictor of remission installation would be related to the presence of

markers of insular cellular autoimmunity that influence the decline of pancreatic beta cell function. A study conducted on children and adolescents in Brazil shows that the presence of DRB1 *03-DQB1 *0201 allele would favor remission. Interestingly, all patients with this HLA genotype were GAD positive and most with a single autoantibody.[20]

In addition to genetic markers, special attention has recently been paid to immunological markers.

A recent experimental study in NOD mice suggests that an allele of the prostaglandin receptor EP4 (PTGER4 - one of the 4 prostaglandin E2 receptors) activates regulatory T lymphocytes and inhibits the autoimmune response [21,22] while being a risk factor for other autoimmune diseases such as: rheumatoid arthritis, multiple sclerosis.

On the other hand, it was found that a low serum concentration of IFN-γ at the clinical onset of type 1 DM correlates positively with partial remission.[23]

A higher frequency of CD4+, CD25+, CD127hi cells, correlated with a slower rate of progression of type 1 diabetes,[24,25] seems to support the hypothesis of a protective role of immune mediators for PCR. A similar study reported that the highest levels of CD4+, CD25+ hiTcell apoptosis were observed in subjects with type 1 DM at onset or in those with an increased number of autoantibodies associated with diabetes.[26]

The interval between the installation of the first clinical signs and the institution of therapy

In slow-onset type 1 diabetes, there was a low insulin requirement / kg body weight, with a relatively high postprandial value of peptide C. In evolution there is a progressive increase in insulin requirement, with concomitant decrease of peptide C and implicitly with a low incidence of remission in cases of type 1 diabetes with slow onset or even without partial remission.

Severity of ketoacidosis at onset

Inaugural DKA is present in approximately 67% of cases with type 1 DM at onset.[27]

Children with severe ketoacidosis at onset appear to have a shorter remission period than those with minimal or no ketoacidosis. A milder initial metabolic imbalance would therefore favor the installation of partial remission compared to a severe initial metabolic imbalance. In other words, an early diagnosis offers the chance to preserve a larger number of pancreatic β cells, implicitly high levels of C-peptide.[11]

There was a directly proportional relationship between the duration and severity of the initial metabolic imbalance and the value of HbA1C at onset, so that the value of HbA1C at onset could predict the onset and duration of clinical remission.[10]

DKA at diagnosis was associated with poor long-term metabolic regulation in relation to probable and functional cellular beta reserve, assessed by both HbA1c and IDDAA1c;

IDDAA1c, an indirect marker of beta cell function, was found to be significantly higher at 6-18 months after the onset of type 1 diabetes in children with moderate / severe DKA (involving reduced beta cell function). At the same time, IDDAA1c was significantly higher during monitoring of these patients, reflecting increased HbA1c and/or lower insulin sensitivity and, consequently, a higher need for exogenous insulin to achieve normoglycemia. This is consistent with a higher HbA1c value observed during follow-up in patients with moderate / severe CAD.[28] Insulin pump treatment (CSII) has been associated with improved glycemic regulation and residual beta cell function, altering the DKA effect at the beginning of the study group.[28]

Pancreatic functional reserve

Remission involves the functionality of β cells. The presence of detectable C-peptide values in children finding themselves in remission confirms the relationship between endogenous insulin secretion and immediate remission. Children with long-term remission had elevated serum C-peptide concentrations compared to children without remission. These children also showed better metabolic control confirmed by lower HbAlc values.[5]

The secretory capacity of residual cells was studied by dosing peptide C from fasting blood or after stimulation (with glucose, glucagon, arginine, tolbutamide) or from urine.[23,24]

The response of βcells after stimulation with tolbutamine or glucose is more important than that produced by glucagon. Glucagon stimulation test (with determination of blood glucose and C-peptide at 15 minutes and 6, 15, 30 and 45 minutes after iv administration of 1 mg of glucagon is most commonly used as a reliable and reproducible method for assessing residual capacity. The disadvantage of this test is that it is often accompanied by nausea and vomiting.

A significant secretion of C peptide was observed in both phases of the investigation. If βcell function was minimal in the period immediately following the diagnosis of type 1 DM, there was a significant increase in their sensitivity during the remission period. It is NOT yet known whether an immunological mechanism by anti-cell specific-specific antibodies and / or the abnormal destruction of β cell balance would be responsible for the cells's discordant response.[12] The data suggest that partial remission attributed to C-peptide secretion begins early after treatment and that other factors, possibly decreased peripheral insulin resistance, may be involved in better metabolic control.

The study by Couper [31] who followed a group of children for one year after the diagnosis of type 1 diabetes, determining the basal and stimulated values of peptide C at 7-14 days after diagnosis, at 3, 6 and 12 months, shows that among the predictive factors for the function of residual β cells in type 1 diabetes, a special importance is atributed to the age of the child at the time of diagnosis of the disease.

The relationship between C-peptide secretion and more or less prolonged remission and the presence of autoantibodies (particularly ICA and IAA) have been the subject of conflicting reports.

Insular cytoplasmic antibodies (ICA) are the best markers of autoimmune processes that determine type 1 DM and consequently the possible influence of ICA on β cell evolution after diagnosis attracted the interest of researchers.

Thus, Montana[32] on a group of 40 subjects studied the influence of age, sex and ICA titer in relation to cell secretion and metabolic control during the first year of evolution of type1 DM. C-peptide secretion (stimulated with glucagon) was measured 5-10 days, 3, 6, and 12 months after diagnosis. ICA and CF-ICA (ICA complement fixatives) were determined at diagnosis and 12 months later. ICA and CF-ICA were positive in 75% and 35% of patients at the time of diagnosis and in 48.7% and 20.5%, respectively, 12 months later. The persistence of ICA was more common in females but was not associated with a particular evolution of C peptide secretion (males had a lower secretion of C peptide compared to females).[32]

The observation according to which the initial value of C-peptide and remission are not associated with the presence or absence of ICA, suggests that ICA cannot be directly involved in β cell destruction.[33]

Intensity and precocity of insulin treatment

In order to be as effective as possible, the initial treatment in type 1 DM in children must correct metabolic disorders as soon as possible, because hyperglycemia with ketoacidosis maintains a low sensitivity to insulin.[12] Thus, intensive insulin therapy, for the normalization of blood glucose, could be a factor favoring the onset of the remission period, by maintaining the function of β cells during the first year after onset.[33]

Using insulin infusions in the first 2-3 days after onset, Mirouze[1] obtains remissions much more frequently than with conventional treatment. The same results are obtained by Tanae[6] by continuous subcutaneous insulin infusion (CSII) used for 4-5 days after onset, and finds (15 days after the start of treatment a significant increase in urinary C peptide levels as in 30 days from onset to increase to more than 20 μg/24h.

De Beaufort,[34] in a prospective randomized study, treats 30 children with type 1 diabetes immediately after diagnosis, half with CSII and half with conventional insulin therapy. In

both groups semi-synthetic human insulin is used, causing monthly HbAlc and endogenous insulin secretion. After one year of follow-up, better glycemic control and increased urinary secretion of C peptide were observed in the CSII-treated group. Interestingly, after one year the insulin dose and IAA titer did not show significant differences between the 2 groups.

Immunological therapy

Today it is unanimously recognized that type 1 diabetes is an autoimmune disease that occurs in a genetically predisposed field. As a result, the prevention of the disease has become a permanent concern of specialists, especially since it mainly concerns the child and the young subject.

Prevention of type 1 diabetes, the ideal of all diabetologists and researchers, remains a hope.

Depending on the etiopathogenic stage at which the intervention is expected, prevention is classified into primary and secondary:

- *primary prevention* involves preventing the onset of the autoimmune process by measures aimed at genetic susceptibility (currently impossible to eliminate) and the elimination of environmental factors,[35]

- *secondary prevention* aims to stop or slow down the destructive autoimmune process, which now seems to be more realistic and possible.[36]

Most secondary prevention studies include patients recently diagnosed with type 1 DM in whom the effect of immunotherapy is assessed by the drug.[35]

Numerous therapeutic attempts have been made in the idea of secondary prevention, but they have not given satisfactory results.

Although the results obtained during the studies carried out in the last decades have been more or less promising, we will mention some of them.

Tabel 1 - A number of drugs were used for this purpose (after Harrison - cited by 35)

Method		The drug used
1.	nonspecific immunosuppression	Glucocorticoids, cytostatics (azathioprine), anti-lymfocytic globulin, monoclonal antibodies
2.	Nonspecific immunomodulation	Plasmapheresis, gamma-globulin, α interferon, Levamisole, ciamexone, theophylline, polyunsaturated omega-3 fatty acids,
3.	Semispecific immunotherapy	Cyclosporine A, antibodies against IL-2 and IL-1 receptors, TNFα, γ interferon.
4.	Specific immunotherapy	- anti-idiotype monoclonal antibodies against T cell receptors, - vaccination with clones or receptors of T cells specifically inactivated with autoantigen, - induction of oral immune tolerance.
5.	Anti-inflammatory agents	- against oxygen free radicals (nicotinamide, superoxidismutase, vitamin E), - antimalarials (hydroxychloroquine), - gold salts, cyclooxygenase inhibitors, indomethacin, ketotifen, glutathione.
6.	Beta cell regeneration activators	insulin

Nonspecific immunosuppressions

Glucocorticoids

Elliott (cited by 38) in a group of 17 children with recently diagnosed type 1 DM, administered prednisone (2 mg/kg/day) for 10 weeks. The loss of pancreatic functional reserve is slowed down, the secretion of urinary C peptide being significantly higher than that held in the group without corticosteroid therapy, obtaining an increase in the duration of complete remission and normalization of HbAlc value.

Balancing the advantages and disadvantages the use of glucocorticoids is contraindicated today due to side effects.

Azathioprine

Maclaren et all. more than 30 years ago, performed a comparative study on 3 groups: group I (24 patients) who received azathioprine + prednisone, group II who received only treatment with azathioprine (2 mg / kg / day) and group III (control group) consisting of 24 patients who did not benefit from any treatment associated with insulin therapy. Although after one year of treatment, the percentage of complete remissions in group II was higher than in the next group, the percentage did not change significantly with the combination of azathioprine and prednisone (group I).

A similar study was performed by Jennifer Cook on a group of 49 patients aged 2-20 years who received azathioprine at the same doses of 2 mg/kg/day. Although, compared to the control group, the value of peptide C was significantly higher (at 3 months and 6 months, respectively), no complete remission is obtained in any case, the partial remission abruptly ceasing upon discontinuation of treatment.

The conclusion that emerges from these observations is that the treatment (to maintain the remission period) should be kept indefinitely over time. Given that the benefits of such treatment do not outweigh the disadvantages (side effects), such therapies were abandoned.

Non-specific immunomodulators

Gamma globulin administered at a dose of 400mg/kg/day for 5 consecutive days and repeated in the same dose at one week, in a group of 10 children with a mean age of 7.9 ± 3.9 years, treated with human insulin, caused partial remission in 5 cases and total remission in 1 case, given that C-peptide and the immunological profile did not show significant differences compared to the control group.

Intravenous immunoglobulin (IVIG) is a combined preparation of normal IgG obtained from several thousand healthy donors and is widely used in the immunotherapy of a

large number of autoimmune and inflammatory diseases. The mechanisms of action of IVIG are complex and experimental and clinical studies support the therapeutic benefit of IVIG therapy. The effect appears to be the result of intervention on soluble mediators, as well as on the cellular components of the immune system. These mechanisms depend on 2 fragments: Fc and/or F (ab ′).[39]

Although IVIG has been widely used as an immunomodulatory agent for more than 30 years, little is known about the factors that predict the success of this therapy. Therefore, exploring biomarkers that predict which patients will be respondents and non-respondents to IVIG therapy, respectively, remains a major area of research.

A number of inflammatory mediators, downstream signaling molecules of inflammatory cascades and dynamic changes in the frequency and / or activation status of immune cells have shown the potential to predict the response to IVIG therapy.[40]

A better understanding of the action mechanisms of IVIG should reduce the empirical use of IVIG and help determine the appropriate dose, "window" (time of administration) and duration of IVIG treatment for various autoimmune and inflammatory diseases in which this immunotherapy is still be a promise.[41]

Semispecific immunotherapy

Cyclosporine, a fungal metabolite with immunosuppressive effects, acts by blocking lymphocyte function, inhibiting IL-2 activity, and proliferating tumor cells. It has no impact on macrophages or hematopoietic organs, having no significant myelotoxicity.

Several studies have shown the effectiveness of cyclosporine A in altering the initial course of type 1 DM in older children and adults, but none have reported effects in very young children. M. Jenner et all (*London Diabetes Study Group*) initiated treatment with cyclosporine A in 14 patients with type 1 DM, recently diagnosed, aged between 22 months and 95 months. The mean insulin dose at study entry was 0.7

+/- 0.07 i.u/kg/day. The initial dose of cyclosporine A was 10mg/kg/day. The insulin dose reached a lower level of 0.13 i.u. kg/day by 180 days. Mean glucagon-stimulated peptide C levels were maximal at 6 months (0.75 nmol/l) and were maintained throughout treatment with cyclosporine A. Insulin was discontinued in four patients for 4, 12, 15 and, respectively, 30 months. In five other patients, the insulin dose was less than 0.15 u.i.kg/day for at least 3 months. HbA1c for all patients were within normal limits. Side effects included anorexia, stomach pain, weight loss, hypertrichosis, gum hyperplasia, mild anemia and high creatinine. All patients discontinued cyclosporine A and all but one were followed for 5 years after discontinuation of treatment. With discontinuation of treatment, side effects disappeared, insulin requirements and HbA1c levels increased, while glucagon-stimulated C- peptide levels decreased dramatically.[42]

The effects of this therapeutic approach were not evaluated on the long term, as no reported studies exceeded 1 year. De Filippo et all [43] analyzed 130 children with type 1 DM in the first years of the disease. In 83 children, cyclosporine was given at an initial dose of 7.2 +/- 0.1 mg/kg/day, a dose that was gradually reduced and discontinued after 6 to 62 months, depending on response to therapy. After 4 years, the cyclosporine-treated group maintained C-peptide at values approximately twice as high as the control group ($P < 0.02$). After 5.8+/-0.6 years the secretion of C-peptide (stimulated by glucagon) became undetectable in the cyclosporine group compared to 3.2+/-0.6 years in the control group ($P < 0.02$). The mean insulin dose remained 0.2-0.4 u.i./kg/day, and HbA1c was ≈1% lower than the control group ($P < 0.02$). The percentage of hypoglycemia was lower than reported in the control group ($P < 0.05$).

After 4 years, the differences between the groups became insignificant and no significant side effects of cyclosporine were reported.

Following this study, the authors conclude that the positive effects of cyclosporine in low doses in patients

recently diagnosed with type 1 DM extend beyond treatment discontinuation.

However, the extent and duration of the benefit do not appear to be sufficient to justify this immunosuppressive treatment in clinical practice, which is why the International Diabetes Immunotherapy Group has indicated the replacement of cyclosporine with less toxic compounds such as nicotinamide, which is one of the most promising substances used in secondary prevention in type 1 DM.

Anti-inflammatory agents.

Nicotinamide, a B-group vitamin (water-soluble, derived from nicotinic acid), is a possible inhibitor of poly-ADP-ribos-polymerase, an enzyme involved in the repair mechanisms of DNA after an aggression.[44]

As a mechanism, nicotinamide reduces oxygen free radicals produced by lymphocytes and macrophages in the island infiltrate, improves insulin secretion through an intracellular increase in NAD and helps regenerate β cells.

Ignoring the existing differences in the adopted methodology, the used dose (the doses used for animated models are 20 times higher than the doses currently used in human clinical trials), the age of the studied groups, the favorable effects on the duration and frequency of remission complete evidence that the drug slows down the evolution of the destructive β cellular process.[45]

The results reported by the European Nicotinamide Diabetes Intervention Trial Group (ENDIT) show that the number of serious adverse events did not differ between treatment groups (nicotinamide versus placebo). Nicotinamide treatment did not affect growth in children or first-line insulin secretion.

The conclusion from this study conducted in 18 countries in Europe, Canada and the USA, shows that large-scale interventions to prevent the onset of type 1 DM are feasible, but nicotinamide was ineffective at the used dose (1.2g/m2).[46]

Specific immunotherapy

Monoclonal antibodies

The toxic effects of the drugs used (cyclosporine, azathioprine, prednisone, anti-thymocyte globulin etc), but also the question marks that arise regarding the suppression of immunity and the need for continuous treatment in a young, otherwise healthy population are the most important factors that limit the use in clinical practice of these agents.[47]

Given these disadvantages, Kevan et all [47] initiated a study in which 12 patients with early onset diabetes aged $7^1/_2$ and 30 years received a 14-day anti-CD3 hOKT3 monoclonal antibody, intravenous injection, in increasing doses (1.42 μg/kg body weight on day 1; 5.67 μg/kg body weight on day 2; 11.3 μg/kg body weight on day 3; 22.6 μg/kg body weight on day 4; and 45,4 μg/kg body weight on days 5-14).

The levels of IL-6 and TNFα were determined on days 5 and 6 of administration. IL-6 was detected in 8 of the 12 patients with values between 14-225 pg/ml) and TNFα in all 12 patients with values between 7-158 pg/ml. IL-2 was not detected and IFNα was detected in a single patient. Ab Anti-CD3 treatment led in the first year of treatment to a significant decrease in HbA1c (p=0.008) and insulin requirement compared to the control group (p = 0.03).

C-peptide level was higher in patients who had a response to treatment, but was not an absolute predictor of a clinical response to the monoclonal antibody, as was the case with cyclosporine treatment at the newly diagnosed type 1 DM although it seemed to stop the deterioration of insulin production.

The importance of vitamin D in the progression of type 1 diabetes

Vitamin D exerts its action on the innate and adaptive immune system through vitamin D receptor (VDR).[48]

In general, the immunomodulatory effects of vitamin D depend largely on the ability of the biologically active form (calcitriol) to regulate the expression of several genes involved in cell proliferation, differentiation and function.[48] Calcitriol

promotes the induction of immune tolerance and exerts anti-inflammatory effects through various mechanisms. It regulates the production of cytokines by immune cells, increasing the production of anti-inflammatory cytokines (e.g., IL-4, IL-10) and decreasing pro-inflammatory cytokines (e.g., IL-1, IL-2, IL-6, IL- 17, IL-22, TNF-, IFN-).[49]

In the type 1 DM pathogenesis, inflammation plays an important role, contributing to beta cell dysfunction and apoptosis through cytokines and chemokines produced by both beta cells and immune cells.[50]

In this regard, calcitriol has been shown to increase the level of antiapoptotic protein A20 and reduce the production of IL-6, nitric oxide synthesis and MHC class I expression in isolated human pancreatic islets exposed to pro-inflammatory cytokines such as IL-1, TNF-α and IFN-γ. [51]

The efficacy of vitamin D in stopping or reversing island autoimmunity seen in experimental animal models, as well as epidemiological evidence supporting the involvement of vitamin D deficiency in the pathogenesis of type 1 DM have led researchers to investigate the role of vitamin D supplementation as adjuvant immunomodulatory therapy in type 1 DM treatment. Different doses, formulations and analogues of vitamin D were investigated during the studies.

Vitamin D deficiency may play a role in determining the risk of developing type 1 DM in the first years of life, especially in children at high genetic risk. Moreover, vitamin D deficiency is widespread in patients with type 1 DM. However, data on vitamin D supplementation and preservation of beta cell function in type 1 DM remain inconclusive.

The importance of inducing the remission period

The most important benefit of remission is, by definition, to temporarily suppress dependence on insulin injections which is for most pediatric patients and not only, a major disability.

The partial clinical remission period seems to be an optimal stage for the child and family to accept the need for insulin therapy and the chronic nature of type 1 DM, to make

changes/adjustments in the diet, to institute immunotherapies and even to initiate therapeutic strategies intended to maintain the pancreatic functional reserve.

From the above, it appears that the remission period is of great immunological and metabolic interest, its knowledge can offer patients better metabolic control and thus removing more over time the risk of developing chronic degenerative complications.

The remission period, even if only partial, is the stage in which the family and the child understand the ambivalence of diabetes which is both an acute disease (every day in the life of the child with type 1 diabetes is fragmented by blood sugar, insulin injections, carbohydrate calculation) and a chronic disease because it hovers over each patient the risk of developing chronic degenerative complications.

It is recommended that during the partial remission period, no changes be made to the insulin therapy regimen for the sake of reducing the number of insulin injections per day. Even maintaining a very low dose of insulin (eg 0.5 u.i. at one administration) may be beneficial for the period of action of the insulin. The proof of this statement was brought by the results obtained by using CGMS, the interval of "Time in range" the small percentage of hyper- and hypoglycemia respectively and last but not least of good value of the coefficient of variability (see *Figure 1*)

There is, however, a consensus on improving the quality of life obtained through remission, but no studies have been performed on subjects to determine the personality of the child and family to see if the remission period allows for acceptance of insulin therapy.

The study by Ziegler et al. on the psychological effects induced by the remission period shows that the vast majority of patients consider it useful. A psychological support effort must be made to alleviate the disappointment caused by the end of the remission period.[52]

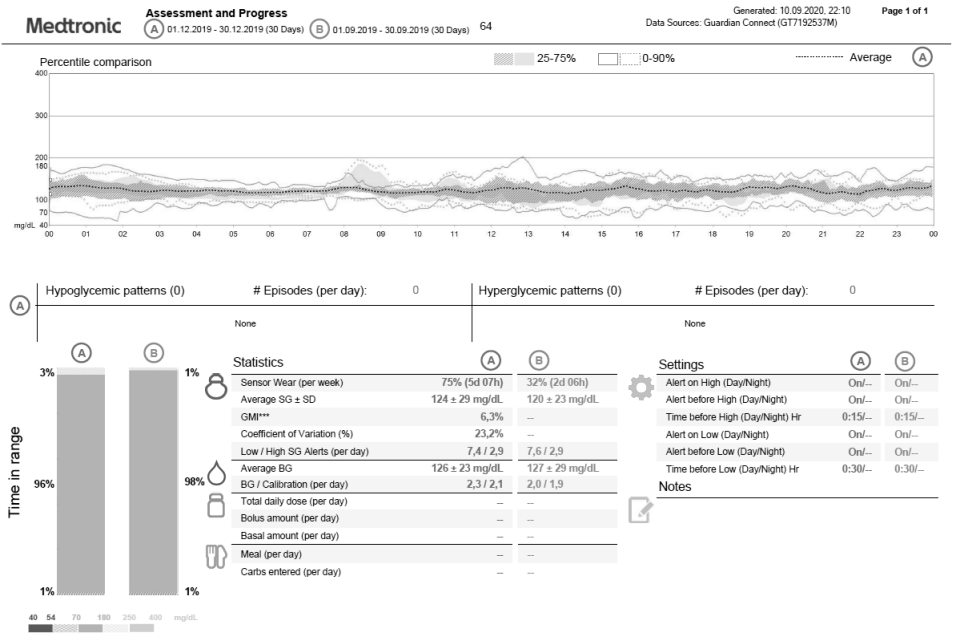

Figure 1 - C. Luca, boy, 12.5 years - Partial clinical remission. (Insulin requirement = 0.24 u.i./kg/day, HbA1c = 5.8%) Time in range = 96%, CV = 23.2%, hypoglycemia: 70-54 mg/dl =1%)

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PEDIATRIC AND ADOLESCENT DIABETES MELLITUS EMPOWERMENT AND MOTIVATIONAL EDUCATIONAL APPROACHES FOR MULTIDISCIPLINARY CHRONIC CARE

Stuart J. Brink

Establishing philosophy of treatment based on DCCT

The Diabetes Control and Complications Trial (DCCT) established the basis for optimized treatment of type 1 diabetes around the world. While there were many previous proponents of "strict" or "tight" control, there was no scientifically validated research studies to support these concepts and many scientific battles occurred between the two groups for many decades. Studies by Pirart[1,2] documented the benefits of improved glycemic control in an unselected population using available methods of glycemic stratification available at that time. The results of the DCCT were announced and published in 1993[3] and 1994[4] setting new standards for near-normalization of blood glucose as well as hemoglobin A1c and utilizing a multidisciplinary team

approach[5], frequent blood glucose monitoring and patient-centered adjustments of food and insulin based upon blood glucose data generated by the patient[6] at home and not just in the office, clinic or hospital setting.

While there were no pre-teenagers recruited in the DCCT, the standard for youngsters with type 1 diabetes was also established with some modifications[7,8,9] to take into account the risks of hypoglycemia as well as the difficulties of dealing with growing children; more efforts since that time have tried to include younger children in diabetes treatment studies and recommendations as well as guidelines. DCCT followup studies[10] as well as Belgian[11,12] and Swedish studies[13] involving pediatric and adolescent cohorts followed for many years confirm the benefits of this approach as well as the safety of this treatment philosophy. Initial studies from Pittsburgh[14] suggested that the prepubertal years "did not count" when assessing long term complications risk. These were refuted from later studies in Berlin,[15] Leicester[16] and Sydney.[17] Pediatric diabetologists no longer believe that it is prudent to allow higher blood glucose levels in prepubertal children than is necessary to minimize serious and recurrent episodes of hypoglycemia. Many studies[18,19,20,21] suggest that it is possible to achieve "tight control" akin to the levels obtained in the DCCT in adolescents and young adults - as well as in the very young - as long as there is adequate education about and attention to prevention of serious hypoglycemic episodes. While there are individual children as well as teenagers and adults who are at high risk for severe hypoglycemic episodes, an overall policy applied to all children to keep glycemic levels "safe and high" is no longer warranted with current guidelines allowing individualization. The Hvidore[22] multicentered pediatric diabetes study showed wide ranges in glycemic control in different diabetes centers around the world and suggests that philosophy of care may well be the hallmark of health care professionals' as well as patients and family's ability to achieve near-normal hemoglobin A1c values. Many studies reported from Israel, Slovenia, Germany, Sweden, Switzerland and the USA and, more recently,

country-wide attention and adoption of these successful interventions/changes in treatment team philosophy in Sweden and the UK have documented significant improvement not only with insulin pumps and continuous glucose monitoring/feedback but in helping multidisciplinary team members to adapt similar teaching styles and goal setting adapted for the individual patient and family with less costly multidose insulin regimens as well as with pumps and sensors.[23]

The DCCT was not a study of multiple insulin doses or insulin pump treatment since both could be used to help achieve optimized glucose control in the study. The DCCT was a prospective, randomized multi-centered clinical trial whose focus was targeted blood glucose levels to help lower A1c levels safely. It succeeded not because of any single treatment strategy but with individualized treatment determined by an extraordinarily close working relationship between highly trained diabetes nurses, educators and dieticians working with physicians and, importantly, with the patient as the focus of self-care decisions between office followup visits. The physician role in the DCCT was critical in establishing *a philosophy of care* and keeping the treatment focused on improved and lowered blood glucose targets. The nurses and dieticians translated this treatment philosophy as part of the study using frequent telephone contact between visits (pre-e-mail, mobile phone proliferation and the internet), more frequent outpatient visits and a general atmosphere of positive problem-solving behaviors to sustain these efforts; psychosocial support either with social workers, psychologists or psychiatrists were also important members of the DCCT multidisciplinary team. Supporting self-management of a chronic problem such as diabetes remains an important concept to understand and discuss with all health care professionals involved with diabetes care [24] including behavioral endeavors.[25] Empowerment and motivational interviewing ideas and techniques can often be the key toward achieving such improved goals when learned by the health

care team and passed along and utilized with diabetes patients and his/her family.

Empowerment

The empowerment concepts allow patients and their families to become the focus of self-treatment and the directors of their own care. The health care team instead of being the "bosses" or "policemen" become the "guides" who set the stage, provided advice and oversight and help re-focus efforts when goals are not being met - all centered around the patient and family[29] (*Figure 1*). Rather than the diabetes health care team being the only ones to initiate treatment, patient and parents are empowered to analyze their own data, identify patterns, problem solve with food and activity and do so between visits to the clinic, office or hospital based upon their own actual blood glucose results and circumstances. Home record keeping and memory meters facilitate such analysis just as the algorithms currently in use attempt to mimic the basal-bolus pattern of endogenous insulin secretion previously provided by a working pancreas whether by older intermediate insulins like NPH or with prandial fast-acting analogue insulin coupled with basal analogue insulins. Improvements with insulin pumps and continuous glucose monitoring are ongoing; these communicate not only with the patient but also with other family members, health care providers and, ultimately, communicate bidirectionally with insulin pumps to become more automated.

In the past, often disaster control was the modus operandi for the person with diabetes. Parents and health care providers were involved with criticism and accusations about "cheating" rather than learning how better to supervise and provide oversight. Empowerment concepts have helped to change this and are being adapted with diabetes care teams around the world.[26]

Work by Andersen et al[27] as well as Andersen and Funnel et al [28] highlight this changing paradigm in diabetes care not only for children and adolescents but also for adults

with diabetes. Instead of "blaming" the victim (ie. the person with diabetes, PWD), the empowerment paradigm shifts the responsibility for self-care to the patient with support by the family and significant others at home. When this is successfully taught and established, frustrations about care decisions often are decreased and actual glucose control improves. The paradigm shift removes the onus of decisions from the health care team and so they often no longer are so frustrated when alternative choices are made or other problems arise.

Health care professionals (HCPs), in order to use the empowerment model of chronic illness, also are encouraged to elicit and explore the emotional content of a diabetes problem that the patient or parent has identified. Health care professionals must resist the tendency to always "give orders" and make specific recommendations or solve problems unilaterally. Their knowing some of the common myths and misconceptions about empowerment is likely to be a helpful step in adopting such concepts as reviewed by Anderson and Funnel in some of their followup writing.[29] Instead, HCPs must assist patients and parents of patients to problem solve, make small steps towards resolution of a bigger problem and tease apart a particular problem into its component parts in an effort to then resolve the dilemma. The job of the health care professional is to create an environment in which the patient and parent's emotional experience of diabetes is validated and can be expressed freely. This will usually involve some strong and often negative feelings so this should be expected and may even be reviewed when describing this new system to the PWD and their family. When actual technical information is missing or faulty, then the healthcare professionals should, of course, supply such information or provide resources to bring to bear on the particular problem at hand.

Many particular barriers that occur with chronic illnesses like diabetes will involve psychological solutions. For instance,

- how to engage a father to help a mother care for a child with diabetes ?

- How to facilitate school nurses in helping to care for a child's needs while at school ?
- How to stop overeating and follow a meal plan at school or when a parent is not at home after school directly supervising snack choices ?
- How to not feel guilty about frequent blood glucose monitoring hassles and discomforts especially for a very young child or soon after diagnosis ?
- How to prevent a child from manipulating a parent ?
- How to set up a positive behavior modification program rather than a negative one to change a teenager's behavior? Stop smoking? Not juuling? Monitor more frequently? Keep a written logbook? Actually use carbohydrate counting to help plan an insulin dose? Call to set up a retinal evaluation? The list is very long and almost always presents as a behavior block to initiate a specified activity rather than a piece of information that is missing.

Helping patients or family member to solve such problems on their own reinforces their self-efficacy and personal responsibility for treatment decisions. As a consequence, similar decisions in the future are likely to be promoted and empowered so that self-care is enhanced.
Patients have barriers to implement such empowerment just as health care professionals need assistance in retraining themselves as to how they might respond. These are based upon societal roles and previous health-care experiences in acute care models. The paradigm shift can be defined as a mutually acceptable approach to problem solve and change those behaviors which the patient and family identify as needing change. Ultimately, if the patient or family does not acknowledge the need for change, any change is unlikely to occur or be sustained.[30]

With a newly diagnosed patient and family, the focus will be on acquisition of new information and the skills necessary to make informed choices about diabetes care. With an already diagnosed patient, the focus will be on what is

being done and what might be done in an improved fashion to improve overall health functioning at present and into the future.

Motivational Interviewing

In addition to an empowerment philosophy, motivational interviewing is a counseling or discussion style that no longer uses direct persuasion and confrontation comments to try to change behavior.[31]

FRAMES stands for the intervention concepts that are involved with motivational interviewing (MI):

- **Feedback** provided, emphasizing the person's own ideas,
- **Responsibility** for change, letting them know they are in-charge,
- **Advice**, providing their own suggestions,
- **Menu** of alternative possible considerations, demonstrating
- **Empathy** from the authority figure (parent, boss, health care professional, coach etc.) and
- **Self-efficacy** reinforcing the persons' hope and optimism for being successful. It has been suggested that correct application of these FRAMES concepts into discussions about what be problematic or need (difficult) change helps to reduce ambivalence and "noncompliance" in many areas of life including dealing with a chronic illness like diabetes. Health care professionals who adopt MI into their style of discussions with the person with diabetes and/or family members, can help intrinsic motivational capacities[32] directly or indirectly to help move towards possibilities to consider and actual change and persistence with such change.

During application of FRAMES and MI strategies it is key to avoid argumentation and authoritative phrases, to expect resistance especially when just beginning the process, and to provide discussions that show one's empathy for the difficulties expected. Supporting self-efficacy and the

"ownership" of making such difficult choices is also key as is positive suggestions that steps can be taken under such circumstances. Often this requires breaking down into smaller steps to accomplish ultimate goals that are more complex and/or more difficult. Since arguing tends to evoke resistance, opposition and defensiveness as well as outright anger or walking-away behaviors, figuratively or stylistically, harsh confrontations and labelling and accusations need to be avoided.

Acknowledging the difficulties and frequent reluctance to actually change a behavior that might be very entrenched can be spoken about as natural and understandable. Having the person with diabetes (PWD) hear that one understands, is empathic, without being pejorative or looking down on that person is also a key component of successful MI adaptation and takes a great deal of practice since the authoritarian problem solving HCP remains so common in health professional behavior often without even being acknowledged or recognized. Such empathy often directly and rather quickly breaks down resistance so tears should not be unexpected during such sessions. Hearing what has been called "change talk" - sometimes for the first time - allows the PWD (or family member) to affirm their own decision to consider change or actually change.

It is often critically important to no longer speak of the "diabetic" but rather the person-with-diabetes (PWD) since it helps to reframe such discussions and problem-solving. [33] In similar fashion, no longer talking about "noncompliance" but changing to "adherence", a less pejorative word and avoiding "lazy," "unmotivated," "resistant", "bad" are all important for HCPs and maybe other family members as well as the PWD themselves.[34,35,36,37] Counselor style and consistency may be a powerful determinant and when successful may help make such interactions more productive for both patient and HCP. Resistance may also decrease as interpersonal interactions improve between patient and provider. If the entire team learns and utilizes such techniques successfully, the intra-team consistency may also assist with achieving desired goals.

HCPs should also learn to "roll with resistance" since is not always so easy to come to terms that are satisfying for everyone; some situations are more or less difficult than others.

Clarifying goals and values for the PWD and their own values and exploring consequences of present behaviors that may conflict with those goals and values are also part of the FRAMES technique for MI. Utilizing MI successfully allows for one's own self-efficacy to be perceived to manage expected obstacles of change. Frequently the PWD will believe and state that they cannot make such changes since they have never been able to do so previously. The response that helps remains the same type: "self-stating" expressions and then re-stating in a manner which allows for such difficulties empathetically to be clarified and perhaps broken down into smaller steps that many be more doable. Bolstering this confidence and hope becomes then a part of the process of MI even if there may likely be ongoing barriers and difficulties to overcome during further discussion sessions.

Some common opening "safe" questions to consider with MI on the part of the HCP utilizing empowerment principles in combination with **FRAMES** techniques vis-à-vis diabetes include:

- what part of living with diabetes is the most difficult or unsatisfying?
- how does this make you feel?
- how would this have to change for you to feel better about it?
- would you be willing to take action to improve the situation?
- what are some steps that you could take to bring you closer to where you want to be?
- is there one thing that you might do when you leave here to improve things for yourself?

Other open-ended questions to be considered might include: What resources are needed? Is there an obvious first barrier or key "thing" to overcome? Are there other people who can help? How important is this change for you? Can you

imagine what it may be like if things actually changed? Imagine the feelings you might have if there was no change? Where would you like to be in a week (month, 3 months)? Be prepared to discuss the feelings associated with a particular issue and be prepared for some strong feelings to surface. These feelings are important not only as potential barriers to acknowledge and help to overcome or discuss further but also may help energize some specific action or behavior. Anger, sadness, frustration, dissatisfaction are just some of these emotions that may surface, sometimes for the first time in such sessions These emotions shouldn't be considered only as negative feelings since they may hold a key to opening up the need for more detailed therapy and even consideration of the diabetes issues at hand.

In similar fashion, empowerment strategies and motivational interviewing FRAMES questioning both strive to open up the possibility for change and to literally "frame" such possibility of change directly in the concepts of the PWD and family. The PWD is not persuaded to adopt a suggestion of the authority figure (HCP or parent) but is encouraged to consider alternatives of their own that may emerge through ongoing discussions. Discussions can open up the possibility to consider alternatives compared to the ones that are "stuck" in operation at present or even to consider multiple perspectives. These discussions allow the possibility and even promote the possibility of successful change. With an assumption that most people ultimately would like to change such difficulties, this is sometimes also difficult to consider with so many HCPs so entrenched with negative experiences - and so the HCP has to re-educate themselves and their colleagues just as much as the PWD and family members have to have some initial acceptance of a reason for and a possibility of change to occur. More severe and restricting resistance to change, feeling overcome and that change "has already been tried and has been impossible either to start or sustain" also may need discussions of alternative ideas.[29]

Transtheoretical Model and Stages of Change

All of these questions are designed to help utilize the transtheoretical model[38] (TTM) of stages of change that ought to facilitate managing a chronic illness like diabetes in the child, adolescent and young adult as well as help with members of the family interacting with the PWD, school and sports personnel, co-workers or significant others in older patients etc. Self-management often is promoted and more positive health-related behaviors and outcomes have been demonstrated when incorporating principles not only of empowerment and motivational interviewing but understanding learning needs and the transtheoretical model for making change. There are five stages of change ibid as part of the TTM:

1. **Stage One** – **Precontemplation** occurs when the individual is not considering a change in the next 6 months. He or she may not believe the behavior is important ("I won't") or that he or she is incapable of change ("I can't").
2. **Stage Two** – **Contemplation** occurs when an individual is thinking about changing behavior some time in the next 6 months ("I might") but there is no compelling motivation to overcome inherent barriers to change that is evident at that moment.
3. **Stage Three** – **Preparation** occurs when the individual is planning to start a new behavior in the next 30 days ("I will"). He or she may experiment with small steps that will lead to the desired behavior change.
4. **Stage Four** – **Action** occurs when the behavior has been changed to meet external standards to produce a certain benefit or to meet individually set goals ("I am"). and
5. **Stage Five** – **Maintenance** is when the behavior change has not only occurred but has been maintained for at least 6 months. At what developmental and intellectual age a child can be expected to "participate" in such decisions makes these somewhat difficult to apply to the

very youngest patients or when there are intellectual or other emotional compromises with such assessment - but these constructs have been found useful for helping to understand the process and assisting in movement from one to another stage by counselors and HCPs. Individual assessment of such stages of change are, of course, invaluable in assisting discussions as are understanding and acknowledging the existence of intellectual barriers for the PWD or family members. Strategies for applying the TTM with empowerment models and motivational interviewing overlap and involve open empathic discussions, commitment, cues and rewards, role modeling, social norms, self-efficacy and sometimes simplistic lists of pros and cons that might move the process in more positive directions. Collaborative discussions are the centerpiece as are non-judgmental words utilized.

When the environment for such discussion is truly nonjudgmental and avoids argumentation, the self-healing capabilities may also become easier to consider.[39] Avoiding the "I know best, you're impaired, listen to me" mentality may be difficult to consider but, when changed successfully using the empowerment and motivational interviewing model, removes the HCP need to prescribe/order action - usually only one action - and minimizes the anger, aggressive confrontations that usually get no place except for unhelpful moralistic blaming when change does not take place. Using a gentler cooperative style to open up such discussions can be learned and utilized successfully to promote personal responsibility that is age-appropriate, family-appropriate, culturally-appropriate and situation-appropriate. The PWD and their family become an ally in the process instead of "the enemy" and the process may become more positive rather than negative, paced according to the individual circumstances and always discussed with empathy allowing more of the participants to feel supported and open for future possibilities and directions. "*You have the ability…*", "*you can change…*, "*you've already taken a key first step…*" are phrases that also

can be adopted for such discussions to move toward more progress and bolster self-efficacy and strategies. Such sessions need not be very long, but can be broken into small steps so that they can occur in busy office or clinic consultations as well as hospital discussions.

Individual members of the multidisciplinary team can all utilize such approaches with improvement documented compared to structured diabetes education[40] and with their own discussions without overburdening the situation if there are good communications between HCP team members. Moving towards talk about problems to discussion about solutions also can be a helpful general strategy for helping kids developmentally moving from childhood through adolescence and young adulthood since such strategies have been documented to help in such situations[41] involving other chronic situations.

Diabetes Education

Initial education is really survival education. What must the patient and his or her family learn in order to leave the hospital, clinic or office ready to take on the tasks of diabetes management. Too much information too soon is likely to be just as frustrating as too little information in the years to come after diagnosis. Behavioral goals should be acknowledged and incorporated into educational goals for, without appropriate behaviors, applying knowledge is likely not possible. The patient and his or her family should be at the center of educational goals so that assessment is a key component of education. Being ready to learn may occur at diagnosis or later and involves a multitude of factors including chronologic and developmental age, ability to read, process information, accept abstract concepts and apply them in practical day to day living situations, having supportive friends and relatives and understanding why obtaining such information is likely to be helpful. When feelings such as denial, anger, nihilism, depression, frustration and low self-esteem get in the way of learning, barriers can be enormous.

The actual treatment of diabetes is predominantly an educational process that is ongoing, changes with new scientific and medical information, new medications and new mechanisms for achieving the goals of treatment. Most of the actual treatment occurs away from the hospital, office or clinic by the PWD and their family members. Initial education must include ways for coping with the diagnosis and its management for the child, the teenager and the family. If these goals are not met, then it will be unlikely that more in-depth training and application of knowledge can occur.

After survival education, reassessment for gaps in knowledge or attitudes must take place in an effort to maximize information transfer, make such rules and regulations specific for the individual circumstances of one patient and promote adaptation rather than frustration and noncompliance. Grief resolution must be addressed, and issues of anger and denial acknowledged and placed into proper perspective; sometimes this has never been addressed and often such emotional barriers become the main barriers to advancing self-treatment. Diabetes, far from any other chronic illness, requires ongoing behavioral changes, abstract thought and processing information many times each day to try to achieve metabolic balance. The tools at hand, although far improved over the decades since insulin was introduced in 1921, are still imprecise and basically insufficient without application of how food and activity interact with insulin, what needs to be done based upon blood glucose monitoring results and how to be reactive in a given situation (correcting a high or low blood sugar right now instead of waiting, for example) as well as proactive (anticipating blood glucose changes with illness or a change in food or activity and compensating in advance of the event, for example).

There are many studies validating the importance of a multi-disciplinary team approach, including how the DCCT was run, to believe that utilizing nurses, nurse educators, dieticians, mental health professionals trained in diabetes care and chronic illness and working in a unified manner with the diabetologist helps couple such members of a diabetes

team with the patient and his or her family. One of the earliest reports of a multidisciplinary team approach for childhood diabetes was published by Laron et al.[42] When such individual disciplines do not work together as a team, however, their mere existence in the life of the child or adolescent with diabetes is not likely to add much and might be counter-productive. Only when such members interact with each other, function in a cohesive fashion and provide a consistent educational and management philosophy does the multidisciplinary team add value to the patient with diabetes. Sharing information means meeting on a regular basis, documenting educational and treatment sessions so that other members of the team are aware of what has been discussed and ultimately increasing the patient and his or her family's fund of knowledge with empathic support. Efforts of providers to utilize empowerment techniques also confirm the benefits of such a fundamental change to interview techniques, words and gestures utilized by health care providers.[43,44,45,46,47]

Followup sessions with educators and dieticians should promote honest interchange to promote flexibility with meal planning as well as insulin administration. Fewer insulin injections (ie. twice a day insulin schedules) often work quite well when there is high consistency of meal portions, time of meals and snacks are held relatively constant and there is little change in activity duration or intensity from day to day. These are commonly employed in medium and low resource situations in an effort to reduce daily costs. Multidose insulin (MDI) regimens offer greater flexibility especially when combined with frequent blood glucose monitoring, pattern control and carbohydrate counting. This allows even the older less-expensive insulin preparations like regular and NPH insulin to be adapted against food and activity changes rather than forcing food to counterbalance specific insulin kinetic effects.[9] Especially when using MDI with the newer very rapid insulin analogs, lispro and aspart insulins, greater flexibility exists while improved post-prandial coverage and decreased hypoglycemia can be demonstrated.[48] Introducing or moving

towards fancier insulin pumps and meters/continuous glucose sensors and their interactions also can be facilitated with cohesive, unified multidisciplinary diabetes teams.

Followup educational assessment has similar goals in identifying gaps of knowledge or gaps of applying such knowledge, determining barriers to behavioral change and promoting improved glycemic control as the end result. A checklist approach often facilitates such assessment as it standardizes minimum information to be evaluated as well as actual use of such information in an age-appropriate and family-appropriate setting. Energy diverting issues such as concomitant co-morbidities, family functioning, financial resources, health system resources are important to learn about and overcome when they introduce further barriers to improved care.

Learning Styles

Learning style[49] of the patient as well as significant others is also key to determining how one should approach a particular barrier. Dogmatic determination on the part of the health care professional usually backfires and either the patient no longer returns for followup care or a system of dishonesty or denial is established which further complicates patient-family-health care team relationships. Having finite and small goals may help prevent being overwhelmed just as working to improve targeted goals keep them in focus or reminds patient and health care provider together that the end result is about glycemic control within the construct of the patient and the family in society. A behavioral approach to education and the use of different health care disciplines working together as a team should foster application of new knowledge. Ideally, decisions should be more proactive - and less reactive - but both will always be needed. All such decisions will always be imprecise because how insulin works and how food is absorbed coupled with activity and stress effects are always estimates within the confines of current treatment options. Repetition without being boring also keeps

positive problem solving at the forefront of useful behaviors for the patients at home, school or at work. Incorporating video games, computers, written information, oral presentations and handouts/ books/ manuals for home review and reference all play a role in modern diabetes education assuming that such resources not only are available but also age-appropriate, language-appropriate etc.

Styles of learning as adapted from *Diabetes Youth Curriculum: A Toolbox for Educators*[50] suggest that there are four major types: concrete sequential learners, abstract sequential learners, abstract random learners and concrete random learners. Determining style of learning can help decrease frustration and increase retention of complex information.

Concrete sequential learners learn by doing. They tend to be very orderly and move from one basic step and build on this knowledge base. Diabetes can be frustrating for people who learn in this fashion because of the vagaries of carbohydrate absorption, differences in glycemic index of foods and food-food interactions, inconsistencies of insulin absorption and changing needs with growth and development. They tend to be perfectionists so that frustration of diabetes management on a day-to-day basis must be placed into the context of the impossibility of the task outcome always being perfect. Important to discuss this vis-à-vis blood glucose monitoring results too. Helping make lists is useful since it helps create some order out of chaos and then the glucose monitoring serves to facilitate information gathering and not inducing guilt. Understanding and living with the limits of current diabetes management is very important for preventing burnout and frustrations from mounting.

Abstract sequential learners like to think and debate about new concepts before they can be accepted and applied. They are also logical and systematic, eager to learn but like to debate with their teachers. They may overintellectualize problems and not move towards applying these principles until they are comfortable with new situations. In our modern world, such learners may be argumentative, may seek out

several alternative sources (manuals, internet, other physicians, nurses and dieticians, other patients) and need some help coming to terms with alternative approaches to similar problems.

Abstract random learners are emotion-based learners. Without acknowledging this emotionality, new concepts may not be so easily incorporated into their repertoire. They may not do well when presented information in a logical, step-by-step fashion but need to understand the final goals in order to get each step. Using alternative teaching styles and tools such as art, drawings, cartoons and video games may be extremely valuable compared to written manuals and handouts just as focusing on themes and ideas allows them to bring their own individual ways of understanding to be utilized.

Concrete random learners often are experimenters. They like to learn on their own without so many rules and regulations. They like to problem solve and thrive on their own intellectual abilities to incorporate new information into their treatment plans. In diabetes terms, teaching them to utilize blood glucose measurements and letting them learn for themselves the difference between fast and slow acting carbohydrates, fast and slow acting insulin or what happens with exercise may be very powerful. Using their own color-coded logbooks to assess patterns of glycemic control may be more helpful than having the computer generate the same data (or the HCP pronounce what is present) since it utilizes their own creative problem solving approaches.

Three models used frequently from the educator's perspective include the Health Belief Model[51], Locus of Control[52] and the Self-Efficacy model.[53]

The **Health Belief Model** explains the failure of people to prevent or detect diseases and suggests that readiness to take action and perception that the benefits of such action outweigh the costs is the core of this model. Value expectancy theories of social psychology are incorporated into the Health Belief Model. With very little children, such concepts may be too abstract since they may developmentally think the whole

world controls them and their bodies. As children get older and become more abstract in their own thought processes, they learn that they have some control over what they do and the outcomes that are generated. A teenager must believe that they can control their food intake in an effort to control their weight and their glucose levels in order to have a chance of following a meal plan – or learn how to take extra insulin to compensate for extra food.

Locus of control is another theoretical framework for controlling one's behavior. If one has an internal locus of control, one's diabetes health is determined by one's own behaviors. If one is doing more blood glucose checks, then this information will be helpful (learning about patterns, adjusting insulin, changing food choices, changing activity for example). If one has an external locus of control, one's diabetes health is determined by outside forces.

Young children, by definition, start with an external locus of control (their parents, doctors, nurses' choices) and then learn, over time, to have more say in what they do and what their choices might be. Too much external locus of control often translates into therapeutic nihilism, anger, depression, noncompliance, insulin omission, lack of blood glucose testing and/or lack of keeping followup appointments since there is not much use, in the patient's view, of doing all such work when no benefits are possible. Those with low self-esteem or severe depression may fall into this category for other reasons as well. Those with internally oriented locus of control may need greater emphasis on individual responsibility while those with external locus of control may need greater importance placed upon social support systems.

Self-efficacy theory suggests that how one perceives one's own capabilities affects not only behavior but also thoughts, motivation and emotional reactions to stress. If one has confidence and feels capable of doing something, it is more likely that such behaviors actually will be done. Because so much self-care behavior is part of diabetes self-care, having self-efficacy should help incorporate these behaviors in a useful fashion.[54] Being able to communicate about new

behaviors, why they should be done and how they should actually be used is complicated by communication skills of health care providers, having sufficient time to teach such skills and also to practice them and, finally, also being able to support sustained use of diabetes-related behaviors that influence overall glycemic control in a positive fashion. Individualizing such teaching approaches and knowing something about the personal styles – emotional, learning, concrete vs abstract thinking processes, etc – will be able to facilitate such changes as children and their parents grow and mature, adapt to changing life-style requirements and new treatment strategies that work for them..

Multidisciplinary team membership roles

Patient, parent, spouse or significant other take on different roles in diabetes self-care depending upon age, learning style, personality traits, fears and interests.
An important issue in diabetes care for children and adolescents is never to force too much self-care and independence " too early" since this may backfire and result in total lack of adult supervision, omitted insulin and major eating difficulties as well as lack of monitoring.

Parent and many health care providers mistake independent diabetes care behavior as a primary goal when it really should be independent self-care responsibility expressed through self monitoring, meal planning, use of blood glucose data, insulin adjustments and problem solving but chronologically and developmentally age-appropriate. Most youngsters are really not able to take on such total responsibility without frequent adult responsibility without making major errors or getting overwhelmed and giving up. Restitution of glycemic control then does not occur until a responsible adult resumes such care. Exactly when a child or adolescent is capable of full self-care does not take place at an exact age but at an age of maturity that does not occur until late adolescence. Many adults, in fact, never reach such a pinnacle and are forever bogged down in being dishonest not

only to health care providers and family members - but also to themselves - because of the vicissitudes of insulin administration, food choices and imperfections in diabetes treatment even with today's modern technologies. When honest problem solving and realistic goals are established or re-established, then such patients and families not only function better but function in a healthier emotional as well as medical model.

Grandparents need to be involved with diabetes child care as do school teachers and school nurses since children must be cared for by others besides their parents at times. Both mother and fathers should not only be educated but also directly involved with children's diabetes needs. In societies where divorce is common and the two parent home does not always continue, such difficulties with communication of very subtle care needs is further compromised. Fathers who view their roles as workers while mothers, even when they also work out of the home, assume the role of nurse and dietician as well as mother provide a message to the child with diabetes that may be at odds vis-a-vis the importance of diabetes treatment.

For children and teenagers, there are further issues that occur because age and developmental changes that make the child or teenager not only need repetition of previously available information but also changes occur in how such information is provided and processed intellectually as well as emotionally. Addressing the issue of honesty, imperfect treatment and frustrations of estimations that are such a major part of diabetes treatment removes the concepts of "good" and "bad" BG readings, "test" and other similarly emotionally charged word descriptions that slip into our vocabulary so often.

The health care team must communicate with each other as well as with the patient and family, coordinate treatment with school officials and keep the door open to provide optimum and individualized care.

Frequent ambulatory visits, telephone consultation, fax and e-mail via the internet can all be utilized to promote such

communication and to emphasize problem solving. While the dietician may focus initially on food exchanges and label reading, progress to carbohydrate counting and address sick day and activity management issues, the dietician must be well versed in insulin kinetics as well as medical issues and psychosocial concepts involving diabetes care at home to highlight the interchangeability of such treatment.

Specific co-morbidities like gluten-restriction and celiac disease, bulimia and other dietary concepts and difficulties are outlined in *Table 1*.

Table 1:
Some Open Ended Diabetes Questions using the Empowerment Model [22] of Anderson and Funnell:

1. What part of living with diabetes is the most difficult or the most unsatisfying for you?
2. How does this make you feel?
3. How would this have to change for you to feel better about it?
4. Are you willing to take action to improve the situation or yourself?
5. What are some steps that *you* could take to bring you closer to where you want to be? Is there anyone else who can help you? Is there one key barrier to start the process?
6. Is there ***one*** thing that *you* will do when you leave here?

Exercise specialist

Some teams have the luxury of a separate professional whose main responsibilities are to focus on idealizing activity, promoting future cardiovascular health and preventing obesity. Other teams have such topics incorporated into the activity of the physician, nurse educator and/or dietician. However this works for an individual diabetes health care team, it is important to not only recognize the issues of daily activity needs, how insulin and food must be adjusted and how such changes develop but also the ways in which exercise

and activity specifically can be utilized to gain more enjoyment out of life while also helping – not interfering – with diabetes management.

Inadequate insulin availability whether from inappropriate low insulin prescriptions, omitted insulin or unavailable insulin interferes with proper cardiac and other muscle activity since insulin is required for cellular energy metabolism.

During exercise or other types of activity, hyperglycemia may reflect overeating because of fears of hypoglycemia ("hypophobia") during or after activity but also may reflect under-insulinization as well.

Blood glucose monitoring and problem solving allows one to identify such problems and try out different solutions so that they may be overcome.

Psychosocial issues: Social Workers/Psychologists as Key Participants of the Diabetes Multidisciplinary Team

Some teams have psychologists, counselors, therapist and psychiatrists available for ongoing consultation while other team members must take on such roles and responsibilities if separate HCPs in these disciplines are unavailable or unaffordable.[55]

Periodic assessment of such problems as major barriers to glucose control particularly come to one's attention when there is recurrent ketoacidosis, recurrent hypoglycemia or goals chronically are not being met.

Many of the barriers to improved glycemia are psychosocial barriers that are very difficult to change. Nevertheless, identifying such problems in and of itself may allow some resolution and respite if for no other reason than they are less powerful when less secretive.

Re-involvement of parents and other adults in a child or adolescent's life can be lifesaving.

Some energy-diverting family issues as well as patient issues are listed in *Table 2* and *Table 3*.

Table 2:
Childhood & adolescent Diabetes Mellitus: NEDEC Educational Checklist [56]

	At diagnosis	soon after diagnosis	within 1-2 months after diagnosis	yearly
Documented "survival" education: -how to administer insulin, how and what to monitor, who and when to call, beginning meal planning	X			
Documented daily telephone support and consultation for about a week after actual diagnosis: -review any questions or problems with monitoring, insulin, food choices, logging -on review, focus on specific difficulties and decide if earlier face-to-face followup needed than what is set up -ask if any questions with family, friends, school or work situation -ask if reading is progressing for both parents and PWD		x		
Documented in-depth assessment and review: -insulin kinetics and administration, monitoring and use of SMBG data, meal planning, activity changes, sick day guidelines and DKA prevention/treatment, hypoglycemia identification, recognition, prevention and treatment -short term and long-term treatment goals -identification of barriers to improvement including school, learning and psychosocial and family issues -establishment of followup guidelines and goals and responsibilities			x	
Documented in-depth assessment and re-education: -all of the above plus additional needs including age-appropriate peer pressure, alcohol, sexual education, smoking prevention, eating disorders including bulimia, anorexia and obesity, diabetes associated complications assessment and ongoing barriers to control				x

adapted from Brink, New England Diabetes and Endocrinology Center (NEDEC)

Table 3

Type 1 Diabetes Dietary Concepts (from Brink [33])

1. Dietary consistency of meals and snacks
2. Timing and portion control
3. Satiety and individual idiosyncratic likes/dislikes
4. Culturally appropriate foods
5. Financially acceptable foods
6. Label reading
7. Carbohydrate counting and consideration for more restrictive carbohydrate restrictions to facilitate weight loss, ease of diabetes management, lipid or blood pressure co-morbidities[57]
8. Insulin to carbohydrate ratios
9. Sick day adjustments
10. Activity adjustments
11. Growth and development tracking.
12. Obesity prevention
13. Lowering saturated animal fats to decrease cardiovascular problems
14. Lowering animal-source protein to decrease renal problems
15. Healthy nutrition for entire family
16. School lunch issues
17. Hypoglycemia treatment, prevention of overtreatment and prevention of nocturnal hypoglycemia with appropriate bedtime snacks

Diabetes, as a chronic disease, involves major psychological issues at diagnosis and throughout the course of diabetes treatment with more specific issues that are developmentally and age-dependent vis-à-vis toddlers, preschoolers, school age, pre-teenage and teenage [58] as well as young adult issues. Adaptation experiences at diagnosis are based upon previous experience with the health care system and with health as well as illness issues.

- Are/were both parents available and involved at diagnosis?
- What's the message if only the mother and not the father remain involved?
- Are there or were there other family issues at the time of diagnosis?

- How sick was the person with diabetes?
- Was death a possibility and did the family understand the seriousness of the diabetes at the point of diabetes diagnosis?
- Are/were there siblings and how did they experience the diagnosis of diabetes?
- What about other family members?
- Grandparents? Anybody else with diabetes as a diagnosis?

Table 4:
Type 1 Diabetes Mellitus: "Energy" diverting family issues (from Brink [33])

- Alcoholism
- Drug abuse
- Parents or siblings who are smokers
- Parent or sibling obesity
- Poverty
- Low education status/illiteracy
- Parent with chronic illness: diabetes or other time/emotion consuming illness
- Sibling with chronic illness: diabetes or other time/emotion consuming illness
- Single parent home, parents who are separating or divorced; multiple parent homes with remarriages
- Inadequate parenting responsibility, unequal parenting
- Parental or grandparental sabotage
- Mental illness of parent or sibling

Cognitive stage of parents as well as the child or adolescent with diabetes matters a great deal and helps to explain how information may be presented and how such information may be processed.

Individual concrete thinking precedes abstract thought so that information must be provided in a manner appropriate for the stage of logic and thinking. Understanding the need for painful procedures (venipuncture, fingersticks, insulin injections) may be difficult to explain so that the health care

team should strategize with parents to help them complete such tasks with minimal angst on their part. Letting a child do a finger stick learning exercise with a HCP directly shows that the pain is not as bad as may be feared; same with other family members learning about not only blood glucose checks but also using pens or syringes. Allowing young children to act out their own fears and anxieties with play – coloring, puppets, stuffed animals, dolls – can be very powerful and very rewarding. Special attention at recognizing and preventing as well as treating severe episodes of hypoglycemia is important. Hypoglycemia fears can become a major barrier to achieving overall glycemic control particularly once a convulsive or unconscious reaction has occurred and such hypophobia can be unverbalized but still powerful.

Family functioning also plays a role in how diabetes is handled in a young person just as personality styles of all family members matter and interact with day-to-day as well as long-term handling of the many needs of a person with diabetes.[59] Excess guilt, excess anxiety or fear as well as excess anger all are common feelings that can, at times, become excessive enough or sustained for long enough time so that they interfere with needs of the PWD.

For infants and toddlers, parents who should be protecting them are now hurting them with blood testing and insulin injections. Food must be limited instead of being freely available. Parental guilt about how long they waited to get medical assistance, how sick is their child, why did they wait so long, "why me?" and "why us?" are common. Both mother and father, if possible, should share care of the very young child with diabetes so that respite can be offered by the other parent and so that decision making can be shared frequently. Older siblings may participate just as close relatives (aunts, uncles, grandparents) and close adult family friends can learn diabetes care skills. Having parents meet other parents and other families either via group activities, camp programs or through the internet (www.childrenwithdiabetes.org, www.jdf.org or www.diabetes.org) can help provide

information and support in addition to that provided by the diabetes health care team.

As children grow and develop, they have different needs educationally just as they have different needs medically. As they move towards being independent, there is a concern of providing too much independence from adult supervision too soon. This can occur when parents desperately want their own breathing space and give up insulin injections and blood glucose monitoring just as it can occur when parents abrogate their responsibility to supervise meal choices and snack choices.

Going to school offers a new set of dilemmas for parents of children with diabetes: who will supervise the child when away from the home, is there a nurse or teacher willing to learn and accept such added responsibilities, make decisions about insulin and testing results, actually give an insulin injection correctly, decide how much food should be changed to counterbalance unexpected school or sport activities etc. All these became big concerns and a source of fear and frustration particularly if the school system is not perceived as a helpful and safe environment by the family for their child with diabetes.

Parents should meet with school educational as well as administrative and health personnel in advance of each school year and remain available to problem solve throughout the year. Parents assume primary responsibility for education of school personnel and to ensure that their child has diabetes incorporated into an educational plan in a safe and forthright fashion.

The diabetes health care team should review such plans and also be available for school personnel to deal with school and after-school activities and maximize each child's individual strengths while ensuring safety. All too frequently diabetes HCPs will also need to become direct political advocates for the PWD and family to help focus school situations and ensure safety as well as medically appropriate decisions.

For children, the fears of injections, blood testing and how parents respond to such fears, who provides comfort and the approach of the diabetes team to such questions set the stage for immediate future potential problems or solutions. Peer problems for school age and teen age children must be handled because of many myths about diabetes.

- Is it contagious ?
- Is there any teasing or bullying ongoing focused on diabetes ?
- Did it happen because of too much candy?
- How to tell friends ?
- How do the school authorities respond ?
- What about after-school programs?

Group learning not only are great fun and safe education sites but allow a PWD to meet another their same age with the same illness.

These can occur as weekend retreats, day camps and residential winter and summer camp programs[60] or simple group encounters coordinated around ambulatory followup appointments and can be of tremendous assistance for school age children in dealing with the daily pressures of school, peers and general activities since they provide a safe haven to learn and explore the child's independent self-care.

For adolescents, fear and concerns of being different are magnified and coupled with loss of health, injections themselves and blood testing worries. Peer pressures mount during adolescence and issues concerning independence from parents increase in relation to health matters. Sleeping late, partying, food issues, sports, driving, alcohol and drug use, nicotine smoking and juuling are big issues. All have an impact on diabetes care either directly or indirectly. Future career and education planning may also be impacted by having to weave diabetes into such plans. The trials and tribulations of adolescence are well known and frequently compounded by the demands of living with a chronic disease like diabetes which involves so many decisions without any vacations each day.

The transition from child to teenager to adult need not be an impossible task even when diabetes needs must be addressed. When parents have mistakenly given too much responsibility to a child too early, the chaos of adolescence can be the final straw that produces recurrent ketoacidosis from omitting insulin, refusing to check blood glucose levels or recording "false" blood glucose results as well as refusing to follow a meal plan or counterbalance food choices with appropriate insulin choices.

Eating disorders such as overt anorexia nervosa or omitting insulin ("diabulimia") require major psychosocial interventions just as severely out of control glycemia requires recognition of such problems and thorough planning on the part of the parents as well as the diabetes health care team. Recurrent ketoacidosis is psychological in origin until proven otherwise.[61] An initial solution to all these major psychosocial events is identifying a responsible adult to actually prepare and inject insulin and actually do all blood glucose testing ensuring initial safety. If this cannot be arranged for any reason, then immediate hospitalization and supervision by staff will be needed.

With supervision, this allows the adolescent some "breathing room" to begin therapy, know that they will be safe and address real underlying concerns.

Dysfunctional families or families with a single parent pose separate problems since they may not have the individual emotional resources or energy to also address acting out expressed vis-à-vis diabetes. Teen support groups as well as parent support groups whether provided on the internet or via weekend retreats or winter/summer camp programs not only for teenagers but also for entire families hold much promise to address these issues with role modeling, discussion formats and positive peer pressure. Adolescence is also a time for normal experimentation with sexuality as well as with nicotine, alcohol and drug use. Issues of contraception and discussions of preventing fetal malformations must take place in a sensitive yet didactic fashion in order to have any chance of being adopted by

teenagers. The normal adolescent sense of invincibility must be overcome in a manner that does not frighten or coerce yet empowers the adolescent to become aware of the risks and make decisions, hopefully, to decrease those risks that are possible to be decreased. Exactly who is available on the diabetes HCP team must be determined and someone assigned to such tasks whether a subspecialist or generalist working with the PWD – it must not be assumed to be taken care of without direct discussions of team members according to individual circumstances.

The Diabetes Nurse Specialist

Not every situation allows a dedicated, well-trained nurse specialist who is familiar with diabetes but this is preferable, if available. If not currently available, it may be a possibility to consider - depending upon staffing, costs, training and interest. Having a clinical diabetes nurse educator (or nurse practitioner) who is well trained and can facilitate caring for more patients in different clinical situations similar to the role of the physician supervising the diabetes care can then be shared with another health care professional working on the same team with the same philosophy and treatment goals. This must be done if the health systems allows nursing to function in such a semi-independent fashion since a nurse whose only job is to obtain height and weight, blood pressure and place the patient in an examination room, doesn't add much to the multidisciplinary team function or outcomes. This is a paradigm shift of major proportions that has taken place in many high resource facilities around the world (including the DCCT) but needs also to take place in medium and limited resource facilities since it helps the team, helps reduce the costs of such a team and, most importantly, helps with the patient and family outcomes in many studies. Adjusting insulin, working on nutrition choices, exercise options and home monitoring with options for insulin pump and continuous glucose monitoring technologies all can be done quite well by trained nurse

specialists working in the diabetes arena. Such nurses help with the burden of care on physicians but also with learning and education programs at diagnosis and during followup and review sessions, clinical followup protocols, technology options and utilization and also psychosocial issues. Well trained nurse educators function in all these areas not only with patients, family members and other members of the multidisciplinary team and they helped achieve these goals in the DCCT and in many diabetes specialty programs for the past several decades around the world with a high degree of success.[62]

The Diabetes Nutritionist

As with having a diabetes specialist who is also a pediatric endocrinologist trained to work with families, children, pre-adolescents and adolescents as well as young adults, and a certified diabetes nurse educator trained in the same fields, dieticians who are certified diabetes educators and who participate as educated and interested members of the multidisciplinary chronic diabetes team are an invaluable part of the team.

They, of course, focus on the dietary needs and balancing all aspects of diabetes care to help adjust insulin doses, maximize daily options, work with changes in daily activity/exercise programs at school and after school and maximize therapeutic education and the decisions of the PWD and his or her family. In similar fashion to the diabetes nurse specialist, such diabetes nutritionists have been shown to help produce the desired effects of minimized complications, maximizing education and its application and working together in a patient-centric system utilizing the empowerment and motivational interviewing techniques outlined for the past two decades since the DCCT but, in actuality, suggested by some of the world's original diabetologists like Dr Elliott Joslin in Boston even before insulin was discovered and used by Banting and Best in Toronto.[63,64]

The Diabetologist

Common sense would suggest that children and teenager should receive diabetes supervisory care from a pediatrician trained as an endocrinologist/diabetologist. In many parts of the world, including the richest countries of the world, this is not always available so only an adult diabetologist or general physician may be available. Nevertheless, under such circumstances all the same information needs to be addressed. While this may be an ideal to have someone trained to work with families and children in developmentally appropriate fashion, the most important factor would likely be an interest in and knowledge about diabetes issues for children and adolescents as they grow and evolve from infants to children, adolescents to young adults and what are the differences with adult needs and the growing child/family needs. Paying particular attention to the physiologic changes of young and how they may interact with insulin and food needs is important just as paying attention to the emotional needs of family members and of the child him or herself in a developmentally appropriate fashion. In places where entire diabetes treatment teams do not exist, the physician must then assume responsibility for **all** aspects of diabetes treatment.

In places where physicians trained in internal medicine and diabetes/endocrinology assume care of the children with diabetes and endocrine problems as well, cooperative consultation with family physicians, general practitioners and/or general pediatricians will be most helpful.

The physicians should set the tone of the diabetes care philosophy and aim for the best possible glucose control while always minimizing and avoiding severe or recurrent episodes of hypoglycemia. Long distant consultation may be available by internet or through large university/academic programs at some distance from primary care settings, and these should be utilized based on individual patient needs, hemoglobin A1c results, complications assessment etc. The needs of the adolescent in transition between pediatric and internal

medicine systems of care is an especially difficult time when patients can be lost to followup when the transition is not facilitated. Efforts to coordinate such transitional care should acknowledge the systemic problems inherent in many health care systems and creatively promote ways to facilitate improvement.[65]

Table 5.

Energy diverting patient issues (from Brink [33])

- Mental retardation such as Down Syndrome
- Emotional or mental illness: depression, schizophrenia, Asperger's syndrome, obsessive-compulsive disorders, hypophobia (especially if past history of a severe hypoglycemic episode or witnessed such an episode), diabulimia or any other eating disorder, any past history of physical or sexual abuse with post-traumatic distress syndrome
- Learning disabilities and attention deficit disorders
- Alcohol, nicotine, drug abuse
- Concomitant severe chronic medical illness: celiac disease, hypothyroidism or hyperthyroidism, Addison's, severe asthma, severe allergies, pancreatitis, enuresis or diabetes insipidus, cancer, cystic fibrosis, eating disorders, obesity, epilepsy
- Associated severe clinical diabetes complications: retinopathy, cataracts, hypertension, gastroparesis, painful neuritis, nephropathy

Retina evaluations[7,66]

Because most physicians are not skilled in idealized retinal examination nor do they always have the tools or experience for indirect ophthalmoscopy, retinal photography or fluorescein angiography, consultation should take place with a bona fide retinal specialist periodically.

The American Diabetes Association as well as ISPAD recommend that this be done at diagnosis, annually after five years of diagnosis and/or entry into puberty since retinopathy research suggests that these are critical times for assessment of early and still reversible retinopathy. This also allows for interventions that might reverse severe cases of retinopathy

likely to lead to blindness and promote optimum eye assessment strategies. There is some discussion recently about decreasing the frequency of dilated ophthalmologic examinations in the group of well controlled young diabetes patients who have regular eye examinations by their diabetes team, excellent A1c levels for a prolonged period of time near consensus target range and/or excellent time in range and without any other clinical complications present.

Kidney and blood pressure monitoring[7,33]

Blood pressure abnormalities often start in adolescence and reflect degree of glycemic control as well as family history/predisposition. Because the combination of hypertension and hyperglycemia adds so much additional risk, and because of the ability to modify the risk of hypertension with well tolerated and efficacious anti-hypertensive agents (diuretics, ACE inhibitors or calcium channel blockers, for example), early identification of hypertension is extremely helpful and possible even in limited resource setting if blood pressure is measured correctly and regularly – and a response mandated if abnormalities are present and sustained. Just having BP measured but having no protocol in place for a response also still occurs too frequently. Similarly, monitoring the presence or absence of microalbuminuria with relatively inexpensive screening methodologies that are not labor intensive nor heavily technique dependent, allows identification of early kidney abnormalities that would eventually lead to more devastating kidney failure or be associated with other microvascular or macrovascular angiopathies. Life for a Child and Changing Diabetes in Children support programs co-sponsored by ISPAD, insulin and equipment companies often provide microalbuminuria kits for annual evaluations so that early identification of abnormalities is possible. Evidence suggests that such early identification of either mild hypertension or microalbuminuria or both will decrease morbidity and mortality very significantly.

Record keeping and technology

Ideally, computers which download memory meters can be utilized at home and also by all members of the diabetes health care team to share information. Written daily logbooks promote problem solving when used in an open-ended and positive system which focuses on looking for patterns of glucose levels, identify sick day issues early to avoid emergency room/hospitalization and also identifying potential problems with excessive or severe hypoglycemia so that these may be avoided. Keeping records, however, is a difficult task, often extremely abstract and frustrating for many patients as well as parents. The benefit of keeping records and responding at home for the well-educated PWD or family members can be overshadowed by the hassles of keeping records.[67] This may be very evident when patients do not feel empowered - or educated - to make changes in insulin, food or activity on their own so that the records merely reflect their day to day difficulties without giving them any ability to respond. Educational efforts to teach the rationale for record keeping and self-assessment not only should focus on communication between family members responsible for diabetes care supervision but become crucial when children move between divorced or separated parents homes, from school to home, camp to home or from home to office and upwards in age and interest. Home computers can be used to download information from memory meters and used in the same fashion as they are with the health care team. Summary of such information can be shared with primary physicians as well. Newest technology improvements include automatic downloading of meters and pens, semi-automatic carbohydrate counting, insulin pump downloading and continuous glucose monitoring downloading as well as bidirectional communication with pumps and CGM devices to become more hybrid close loops systems or ultimately more like an artificial pancreas. How to help select which patients are best for consideration of such high technology, how may be the optimal way to education and support such technology

systems and how to continue ongoing discussions to learn about such issues. Skype[68] and other methods of telecommunication also allow for interactions with the health care team at some distance from where the PWD is residing.[69]

Health care professionals should develop, document and track a series of medical parameters in a prospective and longitudinal fashion: date and age at diagnosis, gender, ethnicity, detailed family history, weight and height obtained and plotted on standardized growth charts, pubertal Tanner staging, initial and followup A1c and time-in-range (TIR), baseline and followup lipids, baseline and followup renal status and BP, baseline and followup documentation of dilated eye examination and any abnormalities detected, baseline and followup thyroid functions etc. This is not merely a research endeavor but rather allows the identification of trends that may lend themselves to inexpensive interventions rather than wait for blindness, kidney or other angiopathic abnormalities. Simple plotting of weight and height should be obvious but is not always accomplished.

Growth deceleration or frank growth failure should be a "red flag" to identify possible contribution of hyperglycemia to such pubertal or growth problems. Sequential thyroid functioning, lipid analysis, blood pressure and microalbuminuria assessment all need to be done at regular intervals and repeated at regular intervals to detect trends and changes with a specific member of the diabetes professional team responsible for followup analysis and double-checking interventions are done and appropriate. Guidelines by ISPAD[7] as well as many other organizations (ADA, IDF, Australian Diabetes Association, British Diabetes Association, Canadian Diabetes Association, for example) all stress such longitudinal assessment with the hopes that more aggressive identification well decrease further morbidity and mortality.

Table 6 and 7 list the type of routine evaluations and testing that should be considered for patients with type 1 diabetes mellitus.[4,70]

Table 6:
LONG TERM TREATMENT GOALS FOR CHILDREN AND ADOLESCENT WITH IDDM (from Brink [4])

1. Normal growth without obesity
2. Normal sexual maturation and age-appropriate function
3. Normal psychosocial development
4. No cigarette smoking or juuling
5. No hyperglycemia symptoms
6. Ideally no hypoglycemic symptoms but at least no severe or recurring hypoglycemia requiring assistance of others for treatment and no unconscious episodes or convulsions
7. No ketoacidosis requiring emergency room treatment or hospitalization
8. No interference with schooling
9. No interference with age-appropriate activities; normal quality of life
10. Age-appropriate knowledge about diabetes treatment
11. Age-appropriate acceptance of living with diabetes as a chronic illness
12. Ability to ask for assistance as age-appropriate and to wear/carry emergency identification
13. Age-appropriate responsibility for self-care
14. Family-appropriate sharing of care
15. Appropriate followup and monitoring of diabetes regimen: a). height and weight plotted; b). sexual maturation; c). A1c
16. Appropriate followup and monitoring of diabetes-associated complications: a). lipids; b). microalbuminuria/proteinuria; c). BP; d). ophthalmologic status; e). neurologic status; f). LJM; g). thyroid functioning; h). awareness of and early identification and treatment of diabetes associated illnesses such as Addison's disease, celiac disease
17. Appropriate transfer of care after adolescence/young adulthood
18. Near-normalization of blood glucose as produced in DCCT or other pediatric studies or documented improvement with sequential followups
19. Near-normalization of A1c or documented improvement with sequential followups
20. Ideally prevention of significant retinopathy; if not, then no blindness or diabetes-related cataracts
21. No or minimal hypertension or hypertension treated and normalized with appropriate medication
22. No diabetic nephropathy
23. No diabetic neuropathy
24. No limited joint mobility
25.No premature cardiovascular events: heart attacks, strokes, amputations

Table 7:

NEDEC FOLLOWUP CHECKLIST for CHILDHOOD & TEENAGERS with IDDM (from Brink [4])

	At diagnosis	Within 1-2 months	6 months after diagnosis	1 year after diagnosis	18-24 months after diagnosis	Annually if normal; every 6 months if abnormal
History and Physical exam						
Family History	X		X	X	X	X
Cardiovascular risks	X			X	X	X
Smokers, juulers, substance abusers	X		X	X	X	X
Diabetes	X			X	X	X
Other endocrinopathies	X		X	X	X	X
Seizures	X		X	X	X	X
Systems review	X	X	X	X	X	X
Psychosocial and school evaluation	X	X	X	X	X	X
Physical exam	X		X	X	X	X
Plotted Ht & Wt	X	X	every 3 months			
BP	X	X	X	X	X	X
Thyroid evaluation	X		X	X	X	X
LJM evaluation	X	X	X	X	X	X
Injection Sites	X	X	every visit at least every 3 months			
Lens & dilated fundoscopy	X		X	X	X	X
Ophthalmologist				X		X
Laboratory						
A1c	X	X	and at least every 3 months thereafter indefinitely and ***with the same laboratory***			
Fasting lipids	X	X	X	X	X	Can be nonfasting if normal triglycerides
Urine protein	X	X	X	X	X	X
If > Tanner II or if abnormal proteinuria or BP, urine microalbumin	X	X	X	X	X	X
Creatinine	X		X	X	X	
T4, TSH	X		X	X	X	X
Thyroid antibodies	X		X	X	X	X
Celiac screen: transglutaminase antibody	X		X	X	X	X
Adrenal and gastroparietal cell antibodies	With specific clinical symptoms and/or signs of adrenal insufficiency or pernicious anemia or if thyroid antibodies positive, abnormal thyroid function tests or positive family history of thyroid or other autoimmunopathies					
ICA , GAD65, IA2, ZnT8 or HLA testing	Only if part of scientific research protocol					

(adapted from Brink, New England Diabetes and Endocrinology Center (NEDEC)

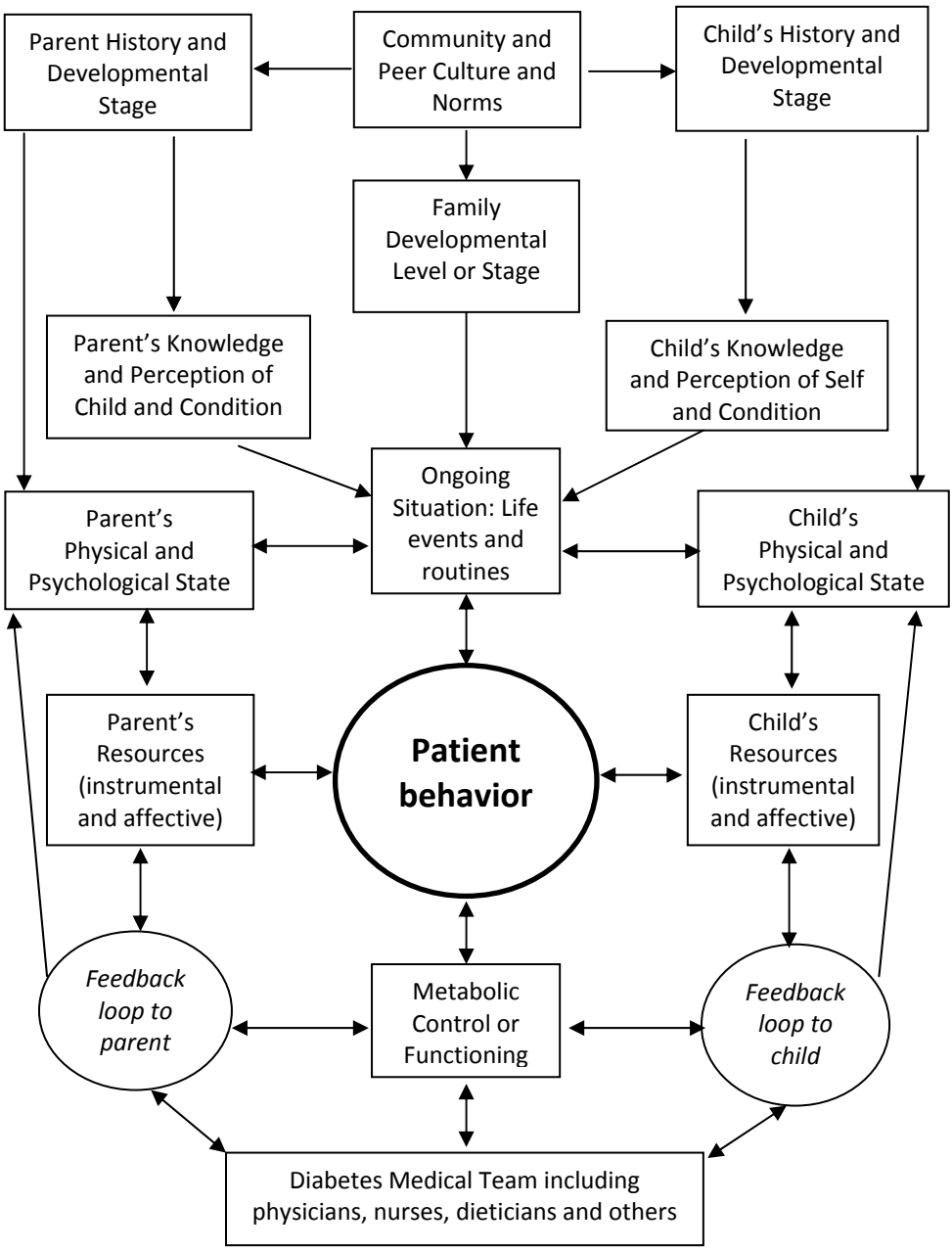

Figure 1: Patient Centered Care Model of Newbrough et al [29]

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YOUNG PEOPLE WITH TYPE 1 DIABETES AND ALCOHOL

John W Gregory

Introduction

It has been long established that drinking alcohol for someone with Type 1 diabetes (T1D) is potentially problematic, leading to short-term adverse metabolic effects and longer term adverse outcomes. As a consequence, education is provided to teenagers with T1D on how to drink alcohol safely. There are few data on the extent to which young people with T1D consume alcohol and little is known about the social context or personal impact of this.

Prevalences of alcohol intake vary from study to study due to differences in methodology and limitations of self-reporting (particularly in young people in whom alcohol may be legally prohibited) and sample size [Hogendorf 2017]. Several studies both in Europe and America, suggest that adolescents with T1D have generally only slightly reduced alcohol intakes compared with their non-diabetic peers [Martinez-Aguayo 2007; Hermann 2017; Hogendorf 2017; Pastor 2017; Tetzschner 2018; Potter 2018] with ranges of alcohol intake being reported to vary widely from 10-90% in teenagers and young adults [Hermann 2017; Cameron 2018].

A significant proportion of those with T1D report occasional 'binge-drinking' which represents a particular acute risk [Weitzman 2015; Roberts 2020].

Teenagers and young adults are at a stage in their lives when many patterns of behaviour are starting to change, especially as they leave school and their parents start to have less influence on their life-styles which become more influenced by peer pressure. Those young adults who succeed in limiting their alcohol intake, report doing so by avoiding drinking games and pacing their alcohol intake when with their peers [Ravert 2009]. A US study from the Mid-West has suggested that after leaving school, 14% of young people with T1D report a persistent high intake of alcohol, whereas a further 30% report increasing amounts of alcohol intake. Those with high intakes are more likely to have experienced major life-events and those with increasing intakes are more likely to be living independently from their parents. Both groups were more likely to have tried marijuana or cigarettes. By contrast, those with minimal to non-existent alcohol intake had the best self-reported diabetes management [Hanna 2014].

Acute physiological effects of alcohol in T1D

Alcohol is known to affect glucose metabolism in different ways. Alcohol is metabolised by oxidation to acetaldehyde and then through dehydrogenase activity to acetate. The redox shift during alcohol metabolism, increases the NADH/NAD ratio (nicotinamide adenine dinucleotide = NAD) and less NAD is available as a cofactor for glucose synthesis, thus reducing hepatic gluconeogenesis [van de Wiel 2004]. Normally, when glucose levels fall, glycogenolysis is increased but this is also impaired by alcohol. After alcohol has been metabolised, hepatic insulin sensitivity is increased leading to restoration of glycogen stores and reduced blood glucose values. Thereafter, insulin sensitivity and glycogen stores are normalised. Experimental studies have also shown that when glucose and alcohol are given together, the latter is

preferentially metabolised, leading to decreased glucose consumption and higher blood glucose levels; these findings along with an attenuated fall in triglyceride in response to insulin suggests that alcohol in moderate does induces insulin resistance [Yki-Jarvinen 1985].

Studies on the acute metabolic effects of alcohol in people with T1D have reported mixed findings. In experimental circumstances, several studies have shown little effect on blood glucose values of alcohol consumed with a meal [Koivisto 1993]. However, when alcohol is consumed in the evening without food, although there were no differences in blood glucose profiles that evening or overnight, an increased tendency to hypoglycaemia the following morning has been reported [Lange 1991; Turner 2001]. No effect was shown on circulating cortisol and glucagon levels but a blunted overnight growth hormone response was observed [Turner 2001]. A recent review [Charlton 2020] suggests that low carbohydrate beer with a high alcohol content and vodka both represent particular risks for hypoglycaemia.

So, to what extent do these largely experimental observations translate into adverse clinical consequences? Relatively small studies have suggested in an uncontrolled social context that moderately heavy alcohol consumption in teenagers is associated with greater glycaemic variation shown by continuous glucose monitoring but no evidence of increased hypoglycaemia [Ismail 2016]. Others have reported an increased risk of hypoglycaemia [Kerr 1990] and also ketosis, a likely risk factor for developing ketoacidosis [Kerr 2009]. However, in keeping with the experimental studies reported above, the large Austro-German DPV Registry has reported, using questionnaire data in about 30,000 young people with T1D, that episodes of ketoacidosis and severe hypoglycaemia rates are lower in patients who abstain from alcohol, compared to those that drink alcohol [Hermann 2017]. Consistent with these findings, our own unpublished whole population-based analyses in Wales have shown that young people with T1D diagnosed under the age of 15 years have a significantly increased risk of alcohol-related hospital

admissions of relatively short duration (presumably to manage the acute metabolic consequences of excess alcohol intake), compared to age-, gender- and social class-matched non-diabetic individuals.

In addition to the direct effects of alcohol on metabolism, it has been suggested that, the increased risks of developing hypoglycaemia are caused by alcohol-reduced awareness of the physiological symptoms of hypoglycaemia (including slowed reaction times and increased sweating and finger tremors [Kerr 1990]), at a time when the individual may be able to take corrective action by consuming carbohydrate. Also, there is evidence that alcohol may impair cognitive performance [Cheyne 2004]. Furthermore, symptoms and signs of hypoglycaemia may be mistaken for features of alcohol intoxication by onlookers [Richardson 2005], who may then fail to provide appropriate help.

Longer term effects of alcohol on T1D

Drinking alcohol regularly is known to have adverse long term health consequences in the general population. A US study in older adults has shown that drinking alcohol is inversely associated with adherence to key diabetes self-care behaviours such as blood glucose testing [Ahmed 2006]. It is therefore unsurprising, that a study in a cohort of Italian teenagers with T1D, has shown that those who confess to drinking alcohol have evidence of increased glycosylated haemoglobin (HbA1c) [Valerio 2019]. However, it should be noted that not all studies have shown that poorer glycaemic control is associated with increased alcohol intake [Kynchala 2015].

The link between alcohol intake and developing microvascular complications is complex, demonstrating a U-shaped relationship with moderate drinkers (30-70g alcohol per week) showing a lower risk than non-drinkers and heavy drinkers for proliferative retinopathy, neuropathy and macroalbuminuria [Beulens 2008].

Alcohol contains plenty of calories and teenagers who drink alcohol have relatively increased body mass indices [Valerio 2019]. Furthermore, the same study also showed an association of drinking alcohol with markers of cardiovascular disease, including abdominal obesity, dyslipidaemia and a poor adherence to a Mediterranean diet [Valerio 2019].

Data are conflicting on whether alcohol intake is associated with an increased mortality in the long term in people with T1D. A UK-based study investigating premature mortality in adults with T1D, showed an increased standardised mortality ratio (SMR) in those abusing drugs but not in those abusing alcohol [Laing 2005]. By contrast, studies from Scandanavia have shown an increased SMR in alcohol-related deaths in adults with T1D. A study from Finland suggested a slightly increased SMR of 1.5 for alcohol-related deaths [Harjutsalo 2011], whereas a study from Norway showed that alcohol had contributed to death in about 15% of cases, leading to a much increased SMR of 6.8 where alcohol had either contributed to or caused death in those with T1D [Gagnum 2017]. A recent review [Pastor 2017] has concluded that overall, it seems likely that alcohol has made some contribution to the premature mortality that is observed in adults with T1D onset in childhood or young adult life.

Prevention of alcohol-related harm

It has been suggested that from teenage years onwards, screening for alcohol use should occur when young people attend clinic to identify problem drinkers [Pastor 2017]. Questioning should ask about how often and how much the young person drinks alcohol and how often, more than four standard drinks suggestive of binge-drinking, are consumed on a single occasion.

The latest ISPAD Clinical Practice Consensus Guidelines [Cameron 2018] advise that prohibitionist approaches to alcohol intake in the young are unlikely to succeed. It is clear that young people with T1D seek

information about how to manage drinking alcohol, with online resources of variable quality commonly accessed in this regard [Jones 2013]. The ISPAD Guidelines [Cameron 2018] therefore advise, that clinical services must provide education about the interaction between alcohol and carbohydrate intake. This should have a specific focus, on the avoidance of nocturnal hypoglycaemia by ingestion of carbohydrates with alcohol, checking blood glucose levels before sleep and consuming carbohydrate then to reduce the subsequent risks of nocturnal hypoglycaemia. These guidelines also advise that friends of the young person with T1D, should be aware of the effects of alcohol in a young person with diabetes and the warning signs that all is not well. Providing this education before young people leave home to work, attend college or university is highlighted.

A useful review of the challenges drinking alcohol for people with T1D has been published [Charlton 2020]. This review highlights a number of key messages that young people need to be aware of when consuming alcohol. These are adapted from this article and summarised in the Table below.

However, knowledge alone does not always ensure that appropriate behaviour is put into practice [Potter 2018]. Motivating young people to apply that knowledge is not simple.

Formal testing of Motivational Interviewing as a technique to help young people with T1D change their behaviour has shown promising results [Channon 2007], though this methodology seems rather less successful in studies that have focussed on reducing alcohol intake in young adults with problem drinking in a non-diabetes context [Foxcroft 2016].

The addition of cognitive behavioural therapy to techniques based on motivational interviewing may however, provide additional effectiveness in a diabetes context [Ismail 2008].

Key messages for clinical practice about drinking alcohol in people with T1D
• Carbohydrate intake with alcohol may affect insulin requirements
• Many young people with T1D adopt behaviours to cope with alcohol through trial & error
• A strategy used to prevent alcohol-induced hypoglycaemia is to deliberately induce hyperglycaemia by eating
• Alcohol can effect an individual's ability to monitor their diabetes & awareness of symptoms
• During and after drinking alcohol, blood glucose should be monitored regularly
• People with lower HbA1c may be at bigger risk of hypoglycaemia when drinking alcohol
• Risk of hypoglycaemia is most likely 8-12 hours after drinking alcohol
• Risk of ketoacidosis is increased in heavy drinkers
• White wine and spirits usually lower blood glucose
• Beer may cause either hypoglycaemia or hyperglycaemia
• Red wine can cause hyperglycaemia
• Education about alcohol is important for young people with T1D
• Prohibitionist approaches to alcohol do not work
• Motivational approaches to behaviour change may be helpful

Although alcohol intake seems common in young people with T1D, research has shown that their understanding of alcohol and carbohydrate content is poor. Only 7.3% of young adults could correctly identify the alcohol content of six or more out of 10 drinks and none could correctly identify their carbohydrate content [Barnard 2014]. Young people with T1D drink alcohol to integrate better into their social group and to 'resist' the influence of diabetes on their lifestyles and identities [Barnard 2012]. Unfortunately, there is a lack of evidence of effective interventions to support young people with T1D, to reduce their risks of experiencing alcohol-related harm [Barnard 2012]. Much better awareness seems required to reduce risks for young people with diabetes and it is

imperative that diabetes services produce educational resources for young people with T1D to ensure that they can access accurate advice and guidance about lower risk drinking [Barnard 2014]. To do this, we need a better understanding of the social context of drinking alcohol in young people with T1D, to inform the development of appropriate interventions [Pastor 2018]. Although health care professionals might be trusted to give such advice, young people with T1D report that such topics are rarely discussed in their contacts with clinical services [Pastor 2018]. When they are, clinicians are often accused of being judgemental and stigmatising which is counter-productive.

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APPROACHING THE CHILD WITH PRECOCIOUS PUBERTY

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Background

Puberty is a transition period between childhood and adulthood when gonadal maturation occurs, leading to the development of the secondary sexual characteristics and attainment of the reproductive capacity. This process is the final stage of sexual differentiation.

The key element in the initiation and completion of this process is the activation of the hypothalamic-pituitary-gonadal axis. This is a central process influenced by peripheral (intrauterine and postnatal growth, fat mass) and environmental signals (light, stress, pollution- endocrine disruptors) which may influence the timing of pubertal onset and development.[1,2]

The onset of puberty is caused by the pulsatile secretion of GnRH by the hypothalamus. The suppression of the GnRH high pulses is achieved through the hypothalamic-pituitary-gonadal axis, which is highly sensitive to small amounts of sex steroids, and central neural pathways.

The essential role of the GnRH (gonadotropin-releasing hormone) pulse generator in puberty onset was confirmed by the identification of some key genes whose natural or experimental loss of function abolished GnRH production (fig

nr.1).[3] These genes are contributing to the correct timing of puberty.[4]

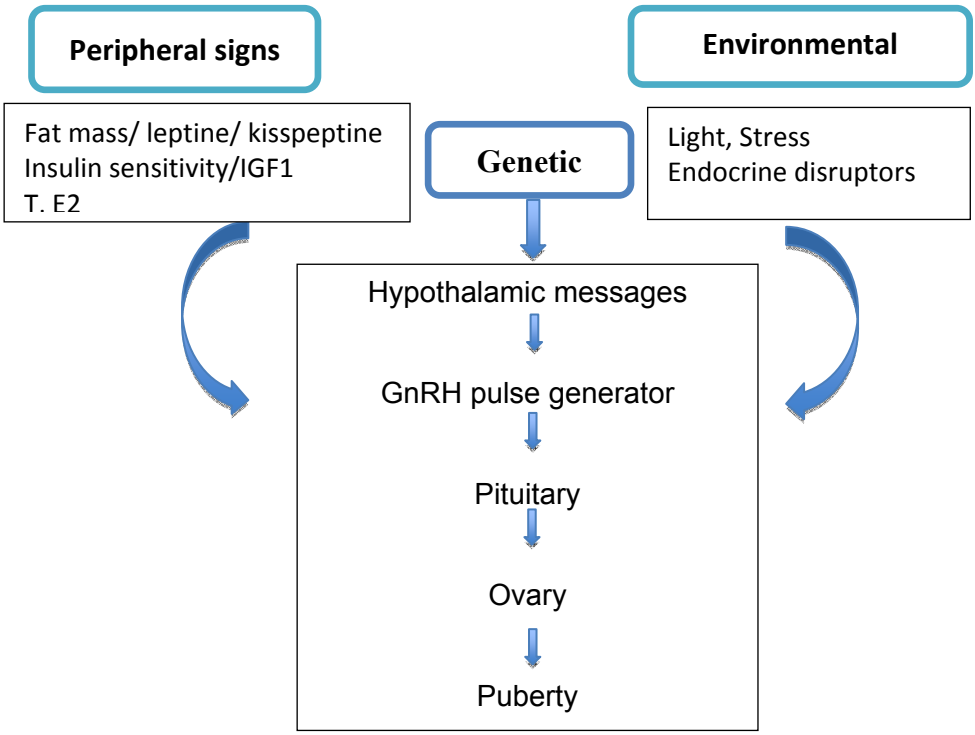


Fig nr.1 The onset of puberty[3]

Leptin is not only involved in the control of energy balance and body weight, but has an important role in the metabolic control of puberty and fertility, with a permissive role for stimulatory signals.[5]

Kisspeptin acts as a gatekeeper for puberty being responsible for initiation of transition from the juvenile stage of development, associated with a hypogonadotropic state, to GnRH release at the time of puberty.[6]

The interaction leptin–kisspeptin is very important for the metabolic regulation of puberty, which, also, involves additional peripheral signals (insulin, ghrelin) and central

neuropeptides (neuropeptide Y, melanocortin). Neurokinin B signaling seems to be also important for the pubertal initiation

Despite the progresses in neuroendocrinology, the mechanisms that influence the onset of puberty are not completely clarified yet.

One of the most frequent concerns for the family to consult a pediatric endocrinologist, is the premature occurrence of secondary sexual characteristics, either pubic hair or breast development in girls, and genital development in boys, respectively.

Definition. Epidemiology

For many years, it was considered that the occurrence of the secondary sexual characteristics before the age of 8 years in girls and 9 years in boys, is suggestive of precocious puberty.[7,8,9]

According to more recent data from US, the age limits tend to decrease to 7 years in white American girls and 6 years in Afro-american girls. Same reports reveal that in Mexican American girls, thelarche occurs at the same age as in white girls, and, pubic hair appears slightly later.[10,11,12]

Reviews and reports over long time periods are showing a decline in the age of puberty, in many parts of the world.

A recently published large literature review, revealed that, the age of thelarche decreased worldwide, by a mean of 3 months per decade, between 1997 and 2013. The authors concluded that, the medical community should redefine precocious puberty, because the traditional definition may be outdated, at least in some parts of the world.[13]

However, most clinicians, continue to use 8 years as limit for the definition of PP in girls.

Concerning the age limit that defines PP in boys, there are fewer reports. In the 1990s, the American population - based study NHANES III renewed the focus on possible secular trends in male puberty. More recent, one large Danish study, showed that the age at onset of puberty - defined as age at attainment of testicular volume above 3 ml - has

declined significantly, during the recent 15 years. This decline was associated with the coincident increase in BMI.[14] The results suggest that more boys may be starting puberty before age 9 years.

No current evidence shows that black boys mature earlier than white boys; thus, the incidence of precocious puberty among boys is similar in both races.[15]

There are very few studies concerning the incidence of PP in the general population. In what concerns the frequency of PP in boys, a clear estimation has not been published yet, and is unclear if it becomes more common overtime, as in girls.

Even if there are only few results concerning the incidence of PP in boys compared to girls, PP is more frequent in girls than in boys, with a reported sex ratio between 5/1-10/1.[7,8,9]

Etiology. Classification

Depending on the involvement of the activated hypothalamic – pituitary – gonadal (HPG) axis, precocious puberty has two forms:

- central or gonadotropin-dependent precocious puberty (GDPP, the "true" PP), involving a premature activation of the hypothalamic – pituitary - gonadal(HPG) axis, and
- gonadotropin-independent precocious puberty (GIPP or pseudo PP or the "false" PP) without the involvement of the hypothalamic-pituitary–gonadal axis. This later form is caused by the activation of the ovaries or testes independently of the gonadotropin secretion

The partial (incomplete or dissociated) forms of PP include the abnormal patterns of gonadotropin secretion: premature thelarche or thelarche variant (isolated early development of breast tissue), slowly progressing variants of CPP and premature adrenarche (isolated appearance of pubic/axillary hair).

Patients with GDPP have isosexual PP (the sexual characteristics are consonant with the sex of the child) while

in patients with GIPP, the sexual maturation is incomplete, and can be isosexual, or contrasexual (the characteristics of the opposite sex are manifested).[16]

The various causes of the premature sexual development are listed in *Table 1.* [12]

Table 1

Causes of premature sexual development [12]

I. Gonadotrophin-dependent precocious puberty (central/ true PP)
a. Idiopathic central precocious puberty – commonest cause in females
b. Secondary central precocious puberty
- congenital anomalies (e.g. septo-optic dysplasia SOD)
- brain neoplasms (e.g. optic nerve gliomas, hamartomas, etc.)
- cysts
- hydrocephalus
- post infection or trauma or cranial radiotherapy
- neurofibromatosis
- adoption

c. HCG-producing neoplasms (e.g. choriocarcinoma, hepatoblastoma,
germ cell tumors of CNS or mediastinum)
II. Gonadotrophin-independent precocious puberty (false /pseudo PP)
Ovarian cysts
Defects of LH receptor function: - McCune–Albright syndrome
- testotoxicosis
Environmental pollution (pesticides)
III. Abnormal patterns of gonadotrophin secretion
Premature thelarche (isolated breast development)
Thelarche variant and slowly progressing variants of CPP
Hypothyroidism
IV. Sexual precocity due to adrenal androgens
Steroid secretion by the normal adrenal gland (adrenarche)
Adrenal enzyme defects – (Congenital Adrenal Hyperplasia CAH)
Adrenal tumors – Cushing syndrome and virilizing tumor
V. Gonadal tumors secreting sex steroids
VI. Exogenous sex steroids

Gonadotropin - dependent precocious puberty (GDPP, central PP, true PP, complete PP)

The most frequently encountered form of GDPP in girls, (more than 90 % in girls but only 10% in boys) is the idiopathic CPP and is a diagnosis of exclusion. This form of GDPP seems to be due to premature triggering of the normal pubertal mechanisms.

Secondary forms of GDPP are the consequence of the premature activation of the hypothalamic pulse generator by various intracranial disturbances (hydrocephalus, cerebral palsy) or acquired disorders (trauma, infections, irradiation, tumours of the hypothalamic region). These disturbances may increase the excitatory inputs or may interfere with the neurogenic inhibition of hypothalamic secretion.[15]

Literature data are showing that some pathologies are more frequently associated with GDPP: type 1 neurofibromatosis (NF1) (3-33%), neonatal hypoxic - ischemic encephalopathy (4,3%), hydrocephalus with or without mielomeningocel (5-18 % and 10-11% respectively).[7,17,18]

An interesting form of GDPP is encountered in girls adopted from developing countries. The risk of developing PP depends on the country of origin and is increased the older the age of the child at adoption.

Insufficient intrauterine environment, resulting in low birth weight for gestational age, postnatal catch-up growth following adoption, relief from stressful conditions or from exposure to endocrine disruptors in the country of origin, may all seem to contribute to early development and sexual maturation of these girls. For example, the exposure to high concentration of DDT (dichloro diphenil trichloro ethane) which acts as a mild estrogen, stimulate the hypothalamic maturation while the pituitary gonadotropins are inhibited via negative feedback, preventing the manifestation of central maturation. Withdrawal from the exposure, will interrupt the negative feedback, allowing the onset of puberty. [19,20,21]

Gonadotropin-independent precocious puberty (GIPP, pseudoPP, peripheral PP, false PP)

In the GIPP forms, the secretion of sex steroids is autonomous and independent of the hypothalamic GnRH pulses. Actually, there is a loss of the normal feedback regulation, thus the sex steroids levels can be very high, but with low gonadotropin levels.[12] An abnormally high level of estrogen, and, more rarely, androgens, because of a tumour in the gonads or adrenal glands, might be the cause. Mc Cune - Albright syndrome, testotoxicosis and ovarian cysts are, also, GIPP forms.

Attention should be given to GIPP secondary to environmental contamination by chemical products, such as pesticides, herbicides or fungicides. Endocrine disruptors with the capacity to mimic oestrogens, may cause thelarche, or, even isolated menarche. [22]

Abnormal patterns of gonadotropin secretion

1. Premature thelarche

Thelarche represents the isolated breast development which may be unilateral or bilateral and is not accompanied by other signs of puberty. Volume varies: 60 % at B2, 30 % at B3, 10 % at B4.[22] Breast is often tender at palpation and, sometimes painful. It, usually, occurs in girls younger than 2 but, also in girls aged 2 - 7 years.

It should be differentiated from the genital crisis of the newborn, whose breast development (associated with strong estrogenization and even milk production) may last for the first 12- 18 months of life.[22,23,24]

The exact mechanisms that are causing premature thelarche are not clarified yet, but there are some considered hypotheses:[23,24]

- partial and temporary activation of the hypothalamic-pituitary -gonadal -axis, explaining the increased level of FSH;
- increased sensitivity of breast tissue to normal concentrations of estrogen ;

- transient secretion of estrogen from a follicular cyst;
- endocrine disruptors (estrogen-containing food).

A detailed history and physical examination corroborated with the growth curve review, can help distinguish these normal variants from true PP.

In the girls presenting premature thelarche, the growth velocity and bone age are usually normal, although some might progress into precocious puberty. More often, evolution is towards spontaneous remission or persistence, or even progression. It is typically associated with increased FSH levels, basal and GnRH stimulated, while LH levels are prepubertal.[12,22,25]

Contamination by products with estrogen-like activity (soy- rich food, pesticides) should be taken into consideration if increased uterine volume is noticed on pelvic ultrasound examination.[22]

2. Thelarche variant

This condition also called „a slowly progressive variant of precocious puberty in girls" or "incomplete puberty" refers to children who present with premature thelarche later than 2 years of age [26] which advances slowly and is accompanied by increased growth velocity and advanced bone age.

The investigations are not specific: the gonadotropin pulsatile secretion - FSH predominant is variable, between premature thelarche and GDPP; LH secretion are more like in normal puberty. [9,27]

This form is considered a variant of normal puberty but it may be caused by an undelaying pathology that should be sought or, it may be a sign of GDPP that will develop in the future.[22]

3. Isolated menarche

The occurrence of a vaginal bleeding in the absence of other signs of precocious pubertal development is called premature menarche.

This might be due to an unusual sensitivity of the endometrium to very low levels of estrogens.[28]

The environmental factors might be incriminated in the abnormal bleeding patterns, as shown in some literature data.[29] It is a diagnosis of exclusion and, is, usually, associated with normal growth. Work-out should exclude non-endocrine causes of vaginal bleeding (foreign body, sexual abuse, infections) but also endocrine (ovarian cysts, McCune Albright syndrome).

Sexual precocity due to adrenal androgens

1. Premature pubarche / adrenarche

Premature pubarche refers to the early appearance of the pubic hair before 8 years in girls and 9 years in boys. Usually it is isolated, but, sometimes may be associated with the presence of the axillary hair, adult-type axillary body odor, acne, oily skin and hair (premature adrenarche).

Growth velocity and bone age are usually normal or only slightly accelerated.

The clinical examination should be focused on other signs of hyperandrogenism, like acne or clitoral hypertrophy, which, if associated with advanced bone age and growth velocity will suggest a possible form of CAH or a virilizing tumor.

Work-up will include the androgens (testosterone, 17 OH progesterone, DHEAs, Δ4Androstendione) and completed by a Synacten test (if the basal level of 17 OH Progesteron exceeds 2 ng/dl).

The etiology of premature pubarche is an earlier-than-usual increase in the secretion of weak androgens by the adrenal glands. The reason for the early adrenal maturation is poorly understood, but is, generally, not a cause for concern.

The evolution is normal although, some girls, might present functional ovarian hyperandrogenism as teenagers and metabolic syndrome as adults.[22]

Approaching the child with premature sexual development

The management of the child with precocious puberty (PP) is quite challenging, especially because of the unusually wide range of clinical expression. Moreover, not all presentations of precocious puberty are true precocious puberty (1/sultan). Many of them are incomplete forms.

According to the literature data, *in girls:* [22]

- 10-20 % of all cases are central PP (CPP);
- 50- 60% of all cases present with incomplete forms of PP (premature thelarche,[30] or pubarche,[31] or even premature menarche;
- 10 % of all cases, are of adrenal or ovarian origin, leading to overproduction of estrogens, causing peripheral precocious puberty. The exposure to environmental chemical pollutants may also cause GIPP

Evaluation of the pubertal stage

The evaluation of the child will begin with a thorough history. The timing of puberty has a genetic component, this is why, if a parent or sibling of the child experienced premature pubertal development, the patient is more likely to present early puberty, too. Anamnesis will search for the neonatal parameters (gestational age, birth weight, length), if the child is adopted, any signs of chronic illness or cranial radiotherapy, neurological signs (headaches, visual disturbances) suggesting a CNS disorder.

The clinical evaluation will start with a detailed general exam completed with the evaluation of the pubertal stage. The Tanner stages are still used as reference to estimate the pubertal stage, as they are well codified. (*Table nr 2, 3*)

The children with precocious puberty, show the normal signs of puberty, earlier than normal, but in the same order as in normal puberty, except for incomplete forms, or those caused by adrenal androgens.

Tabel 2

Mean ages for normal pubertal development stages in grils based on Tanner stages for breast development (B) and pubic hair (P) [22]

Pubertal stage	Age (years)
Breast buds (B2)	10,1
Sparse pubic hair growth (P2)	11,2
Darker, coarser pubic hair growth (P3)	12,2
Growth spurt	12,2
Menarche	12,7
Adult pubic hair in type and quantity	14
Mature breast	14

Tabel 3

Mean ages for normal pubertal development stages in boys based on Tanner stages for genitalt development (G) and pubic hair (P)

Pubertal stage (G/P))	Age (years)
Testes and Scrotum begin to enlarge(G2)	10 – 13,5
Scanty, long pubic hair growth (P2)	13,4 ±1,04
Darker, coarser,start to curly pubic hair (P3)	13,9 ±1,04
Growth spurt	13-17,5
Further growth of testes, scrotum, penis (width/length) (G4)	14,3±1,08
Adult pubic hair in type and quantity (P4)	

The first clinical sign, usually occurring **in girls** with early puberty is thelarche (the breast enlargement).

The diameter of the breast increases gradually, the mammary areola darkens and the nipple becomes more prominent. Sometimes, especially in overweight patients, is difficult to distinguish the glandular breast tissue from fat. When an ultrasound exam is not possible, it is recommended that examination should be done in the supine position. The growth spurt occurs quite early in girls with PP compared to boys with PP, in whom, accelerated growth occurs later, during the pubertal development.

Pubic and axillary hair may appear before, at about the same time, or well after the appearance of breast tissue. Axillary odor usually starts about the same time as the appearance of pubic hair (pubarche).

The color of the vaginal mucosa is deep red in prepubertal girls it becomes light pink once the estrogen secretion increases with puberty.

An enlarged clitoris (clitoromegaly) is significant for androgen excess and if associated with acne, advanced growth velocity and bone age will be suggestive of a possible form of CAH or a virilizing tumor.

Menarche is a late event and usually occurs 2-3 years after the onset of thelarche.

In boys the earliest clinical sign of puberty is the testicular enlargement (volume above 4 mL - with Prader orchidometer, or length > 2,5 cm).

Usually this sign is overlooked by the parents and postpones the consultation with a pediatric endocrinologist.

If a boy presents with progressive signs of androgen excess, without increased testicular volume, the pediatrician should consider a possible GIPP, CAH, testotoxicosis, Leydig cell tumors or other causes of androgen excess.

Growth of the penis and scrotum and other signs (reddening and thinning of the scrotum, increased pubic hair) are the consequence of increased testosterone production and, usually, occurs at least one year after the testicular enlargement. The pubertal growth spurt occurs later than in girls, by the time other physical changes are noted.

Later signs of puberty include also voice changes, acne, the appearance of the facial hair.

The clinical exam should reveal signs that might be suggestive for other forms of PP: large café-au-lait spots with irregular borders suggestive of McCune-Albright syndrome (MAS); multiple café-au-lait spots, with smooth borders are characteristic of type 1 neurofibromatosis, hirsutism suggestive of androgen excess.

Emotional disorders are common in these children as their psychic-emotional maturation is not concordant with the somatic and sexual development.

Laboratory investigations

In boys with PP, measurement of serum *testosterone* is useful (preferable a sensitive method-radioimmunoassay RIA). Because LH and testosterone levels rise with sleep onset in early puberty, early morning testosterone levels are higher than afternoon levels.

The testosterone levels are correlated with the stages of puberty [32]:

- <30 ng/dL – generally prepubertal (testosterone levels of 11-30 ng/dL may represent early puberty depending on the laboratory)
- 30-100 ng/dL – early pubertal
- 100-300 ng/dL – mid-to-late pubertal
- > 300 ng/dL – adult

In girls, the measurements of estradiol are less reliable as indicators of pubertal stage, (levels may fluctuate), but, levels above 20 pg/ml are suggestive of puberty. High levels of estradiol (> 100 pg/ml) may suggest ovarian tumours or cysts (GIPP).

Adrenal androgens (DHEA, DHEAS) are slightly increased in girls and boys with early adrenarche (pubic hair present) but might increase significantly when an adrenal tumour is present.

17 OH progesterone should be measured if CAH is suspected.

The Synacten test should complete the investigations of the androgen excess, with the measurement of basal and stimulated cortisol and 17 OH Progesteron.

Basal, random measurement of LH and FSH were considered to have limited value in diagnosing PP, but with the new developed assays -the immunochemiluminometric (ICMA) method- the random LH became an useful screening test. Before puberty, an LH level of less than 0.1 IU/L is usually found, so, the new assays should have a detection

limit close to this level. An LH level above 0,3 IU/L is suggestive for central precocious puberty.[33-36]

Increased levels of random LH (above 5- 6 UI/l) and an increased LH/FSH ratio (>0,3) are suggestive for GDPP in girls. *In boys* there are limited data. LH levels above 10 UI /L are considered significant for the diagnosis. [32]

Random follicle-stimulating hormone (FSH) levels do not discriminate between prepubertal and pubertal children.

Suppressed levels of FSH and LH with increased serum testosterone or estradiol are suggestive for GIPP.

The GnRH stimulation test (with 2,5 μg/kg to a maximum of 100 μg GnRH) which is positive if a rise in LH, which is higher than the rise in FSH, occurs 40-60 min after the administration.[12]

Usually, in GDPP, the response of LH is above 5 IU /ml, and is higher than the FSH response, while the LH / FSH ratio is >0,3.

The cut-off limits for the increase of LH after stimulation are different between studies, but it depends also, on the specific LH assay used.[37,38]

Normal prepubertal children have an increment of 3- 4 UI/L for LH and 2-3 UI/L for FSH. In GIPP there is no increase in LH and/or FSH after stimulation.

Imaging studies

The evaluation of bone age with a hand and wrist radiography, is mandatory in children with premature sexual development and, usually, is the first investigation recommended after the clinical examination.

Standardized methods (e.g Greulich-Pyle) are used to evaluate bone age. Advanced bone age is a usual finding in PP. If the bone age is advanced by more than 2 years compared to the chronological age, it means that puberty has been present for about 1 year or more, or is progressing rapidly.

An *MRI examination of the* hypothalamic-pituitary area is essential in the etiological evaluation of GDPP, mostly in boys, in whom idiopathic GDPP is very uncommon and in

children younger than 6 years, as the chance of finding a CNS pathology (malformations, tumours etc) is increased in this groups.

Pelvic ultrasonography will provide important data in what concerns the uterine and ovarian sizes.

A uterine length exceeding 3,5 cm is the first sign of estrogen exposure. Morphology of the uterus is also important as the tubular form encountered in the prepubertal girls, becomes more pear-like in shape during puberty. A uterine volume greater than 2 ml in a girl with premature breast development makes the diagnosis of precocious puberty very likely. The presence of an uterine vacuity line (thickening of the endometrium) is suggestive for significant estrogenization.

Ovary size and number of follicles are not criteria for the assessment of pubertal development. The US exam is also useful in girls with GIPP because it might detect an ovarian tumour or cyst.[30,35,39,40]

An US exam of the testicles is recommended if their volume differ or if GIPP is suspected, to exclude Leydig cell tumors which are not palpable.

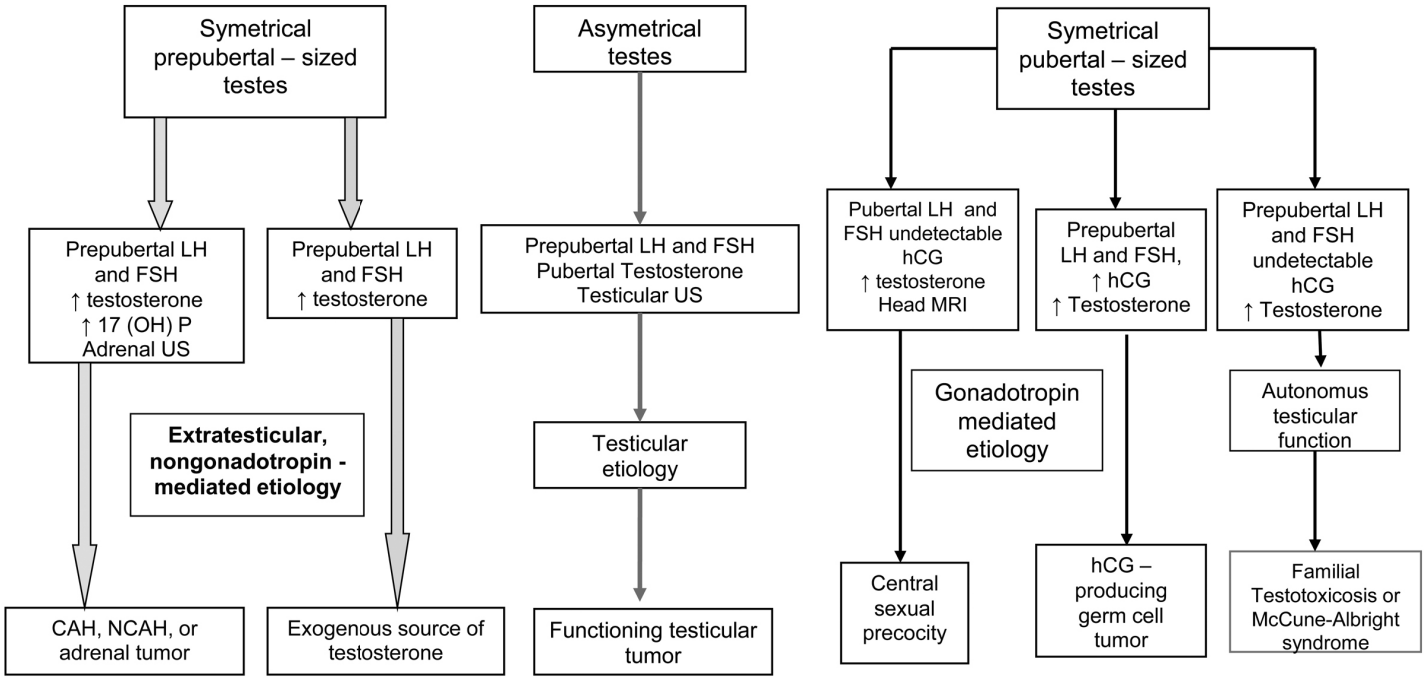
Breast ultrasound may be useful to confirm the presence of the mammary gland, especially when adipose tissue is abundant.

Conclusions

The wide range of clinical expressions of precocious puberty highlights the importance of an etiological approach to these increasingly frequent situations, through clinical, biological and imagistic examinations. A better understanding of the clinical presentation should improve the therapeutic recommendations.

Anexa 1

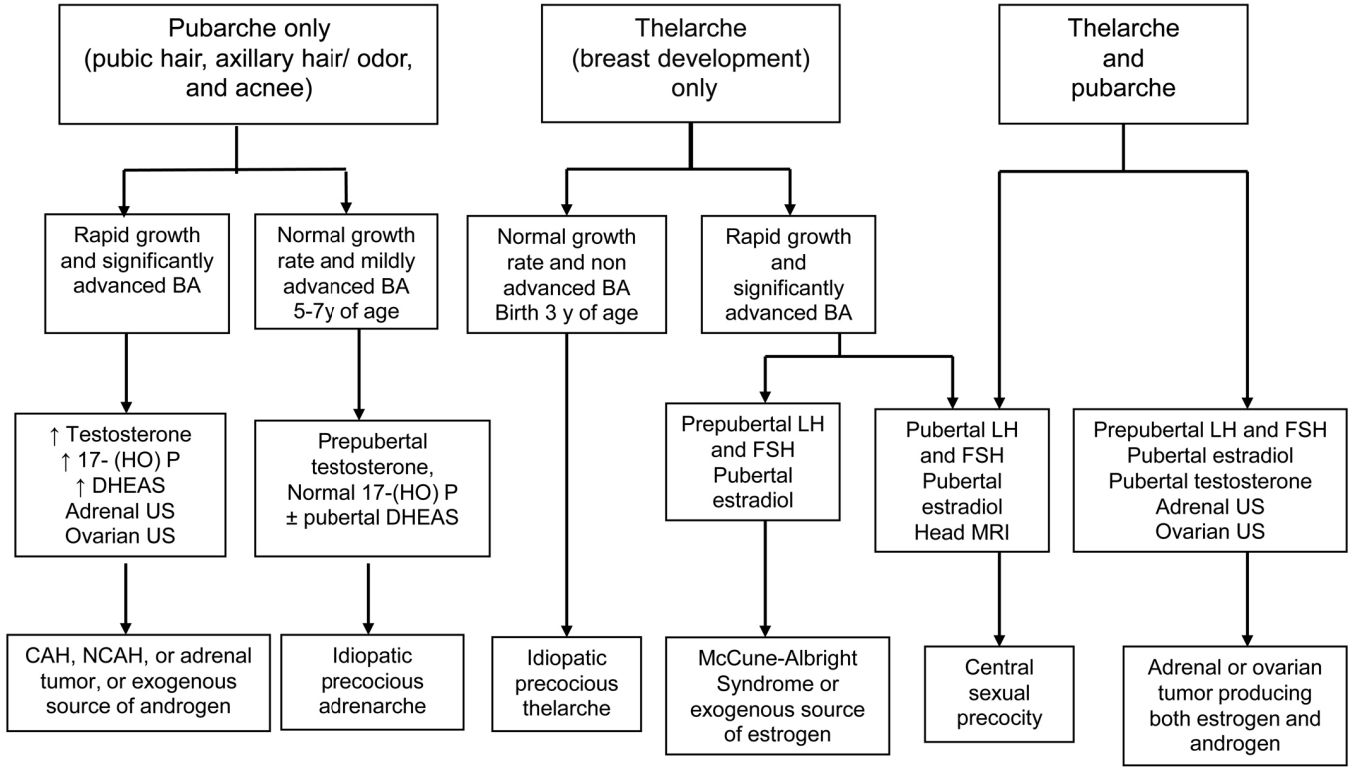
Diagnostic algorithm for precocious puberty in boys (*)



Nakamoto JM, Franklin SL, Geffner ME, "Puberty" in: Kappy MS, Allen DB, Mitchell EG, Pediatric Practice Endocrinology, McGraw Hill Medical 2010, 257-298.

Anexa 2

Diagnostic algorithm for precocious puberty in girls (*)



Nakamoto JM, Franklin SL, Geffner ME, "Puberty" in: Kappy MS, Allen DB, Mitchell EG, Pediatric Practice Endocrinology, McGraw Hill Medical 2010, 257-298.

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SHORT STATURE
AND
GROWTH HORMONE TREATMENT

Stuart J. Brink

Growth charting:
height and weight standards and height velocity charts.

Careful monitoring of childhood and adolescent growth is an excellent indicator of a person's general as well as disease-specific health status. Growth[1] can also be a key to evaluating how the child or adolescent is doing when that person has no chronic illness and more importantly when they have some chronic illness that potentially may interfere with optimal growth and development.

Growth related to weight and height changes should be measured and plotted longitudinally provided the health care provider takes reasonable measures to obtain accurate weight and height data obtained in a standard fashion, ie. using a weight scale that is periodically checked for accuracy and reproducibility and using a stadiometer, home-made or manufactured, but also used in a consistent fashion to obtain accurate and reproducible data from one measurement to another and even from one health care provider to another.

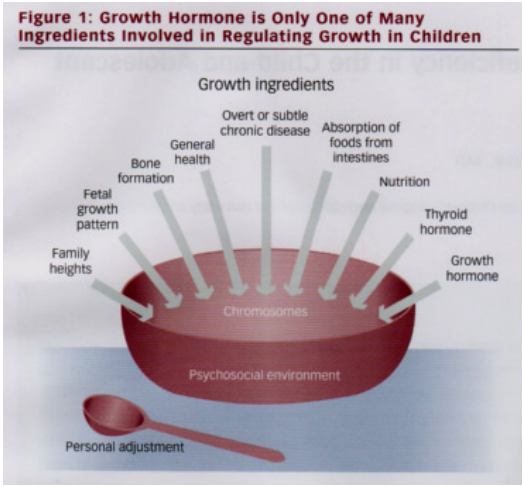


Figure 1 – Growth hormone is only one of many ingredients involved in regulating growth in children (compliments of Dr Susan Rose, US Endocrinology, 2011)

This is too often not done appropriately in high resource countries and the equipment and rationale for its importance increases in middle or lower resourced facilities around the world all too often. Wall mounted stadiometers should be the standard even if they need to be constructed from home-made materials and this should be brought to attention of all health care providers seeing growing children and adolescents.

Attention should be given to family height histories since this may provide clues to discordancies, pathology or normal variation.[3,4,5]

When there are unexplained discrepancies and especially when there is discordance comparing weight and height percentiles with other family members, attempts should be made to explain whether these are physiologic variations of normal patterns or deviations suggesting possible pathology – or measurement errors.

General practitioners, nurse practitioners and health care workers, general pediatricians and any pediatric or adult subspecialists caring for infants, children and adolescents all should be aware of growth parameters and methodologies for correctly tracking weight and height.

Prior to 2 years of age, supine length without shoes should be obtained with a right-angle device, head looking straight upwards and with 3 repeat measurements at each

visit to allow average length to be ascertained. This procedure is referred to as the “Frankfurt plane”.[1]

After age 2 years of age, standard height should be obtained using a vertically mounted stadiometer and measurements should be made 3 times and then averaged to minimize "wiggle noise". Measurements should be made with the eyes straight forward, the head not tilted or bent and with the back of the head, shoulders, buttocks and heels touching the vertical plane of the stadiometer (ibid).

Health care providers should have access to standardized growth charts not only for boys and girls (*Figure 2*) but also for such special conditions as Down Syndrome, Noonan’s Syndrome (*Figure 3*) and Turner’s Syndrome (*Figure 4*) (www.magicfoundation.org) to be able to assess healthful progress or deviation by sequential plotting of height and weight on these charts.

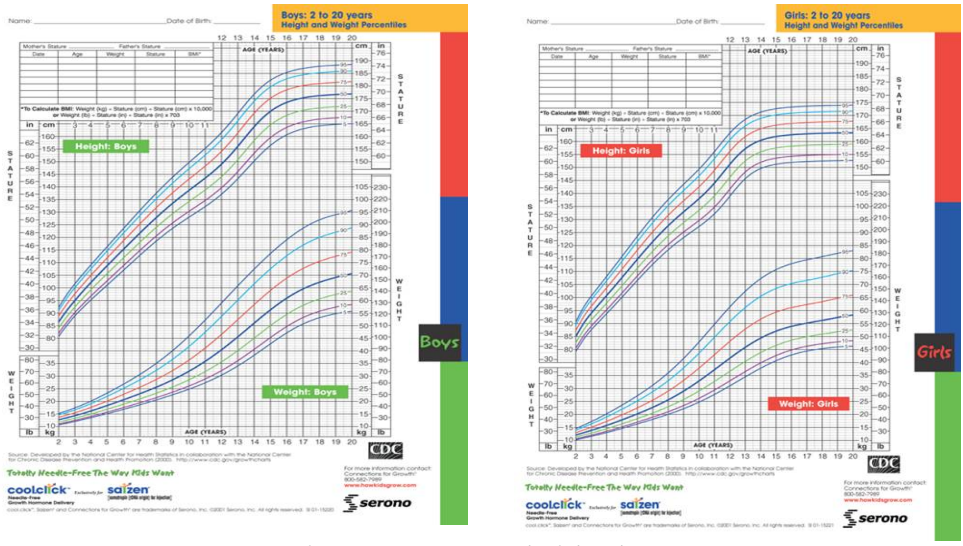


Figure 2. Boys and girls charts

Many electronic records and computerized programs are also available to assist in this record keeping process but paper records work quite well as long as they are being plotted several times each year and data obtained with proper technique. Electronic notes should also specifically require

comment on growth data obtained and plotted since it reflects so importantly on treatment as well as quality of care.

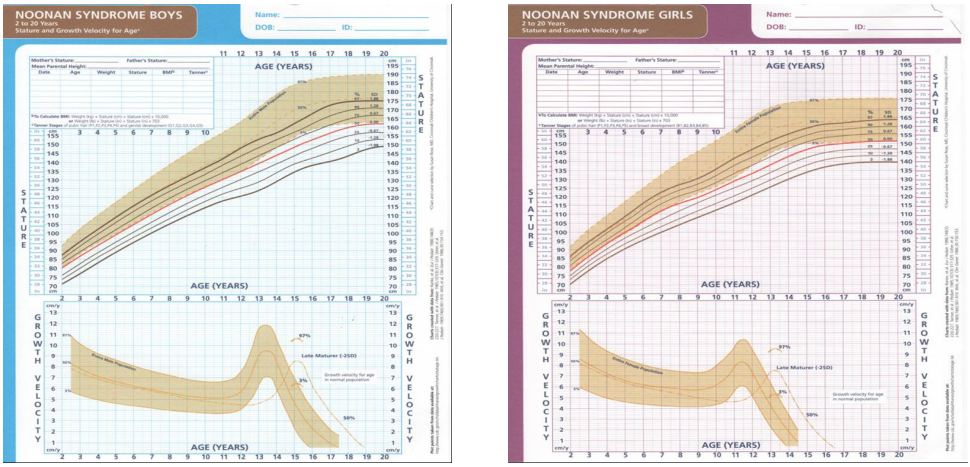


Figure 3. Noonan boys and girls growth charts

While country specific norms would be ideal, these are not always available but those available from the United States (www.cdc.gov/growthcharts for free downloads), Canada, Australia, Japan and many parts of the European Union can be used as surrogates since the pattern may be more important than the absolute percentile placement on the grids for identifying potential serious abnormalities of growth.

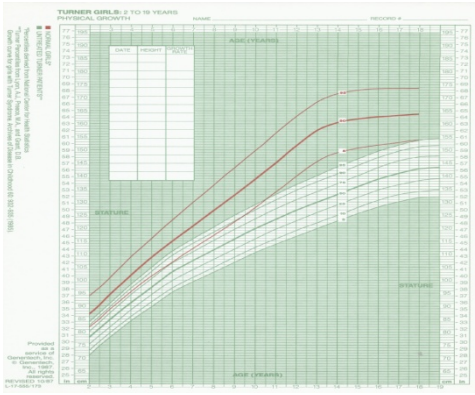


Figure 4. Turner Syndrome

Standard general pediatric as well as pediatric endocrinology textbooks describe normative growth data for infants, children and adolescents and should be referred for such information as needed for the novice or for refresher purposes.[2,3,4,5]

So-called "Tanner charts" also are available that incorporate timing of puberty in comparison with broader, normative growth data over time to highlight how the individual with either significant early or delayed pubertal timing compares.[6]

Aberrations of growth can occur if there is "crossing of percentiles", ie. acceleration or deceleration as well as when there is marked deviation from the normative data, ie. tracking along at a normal velocity but at a substandard (or superstandard) percentile. For instance, investigation may be warranted for a child staying and tracking 3 or 4 standard deviations below the normative charts particularly if this is significantly different from other members of the family.

Normal crossing of channels may occur in an infant who is rather large postnatally but then moves over the first 9-18 months towards genetic length percentiles. This is a normal and common occurrence. Similarly, over the first 3-4 years of age, there often is some worrisome height deceleration towards genetic patterns compared to standard annualized height velocities approximate 5-6 cm (~2 – 2½ inches) as the child moves toward the familial and expected percentiles but this should at least be noted by providers. Specific male and female height velocity charts are also available (*Figure 5*) to help plot and track such changes but height velocity data is a bit more "noisy" than straight height and weight plotting and can show more variability so may be more difficult for definitive interpretations.

Steady decreasing height velocity information (persistent deceleration) is worrisome and also warrants further detailed investigation and questioning as well as comment in the medical record.

Depending upon the age and timing of puberty, the expected accelerated growth phase would then be identifiable

as the adolescent hormone changes take place except for those showing constitutional pubertal delay; this often occurs on a familial basis so that appropriate questioning of family members should be considered when pre-pubertal slower height tracking continues but looks dramatically different from the rest of the age-matched population unless corrected for Tanner staging, family history and bone age.

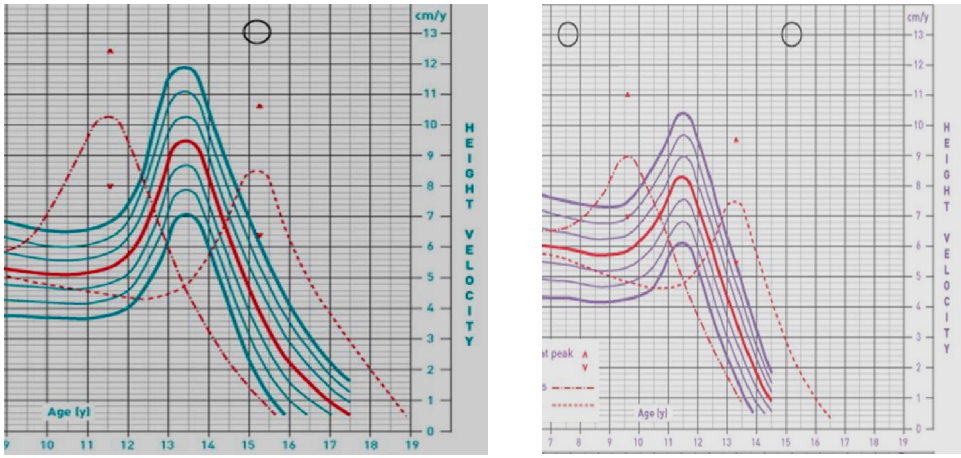


Figure 5. Height velocity chart

Adolescent height velocity may increase up to 10-15 cm (5-6 inches) annualized for a period of time with girls generally entering this more rapid growth phase about 2 years, on average, earlier than boys. Because girls' puberty occurs usually earlier than boys by overt actual age, boys continue to grow for a relatively longer period of time before epiphyseal closure and thus boys, in general, end up on average 13 cm taller (5 inches) than do girls at final height. Of course, individual variability is enormous and influenced as well by general nutrition, infectious disease exposure, well cared for or poorly cared for chronic illness effects and familial, genetic influences.

Throughout the world, under-nutrition and infectious diseases remain the major cause of poor growth but in richer parts of the world with better hygiene, water supply, immunizations and medical care, such causes of significant poor growth/stunted growth are rather rare except for diseases of the gastrointestinal tract where subtle malabsorption (ie. celiac[7]) may be a factor.

Seasonal variation in growth also is well known so that sequential measurements several times a year at regular followup visits with plotting in a standard fashion optimizes the ability to interpret progress that is normal or potentially abnormal.

Early detection of a growth disorder or a condition which affects growth requires appreciation of subtle changes in actual height and weight and especially in growth velocity. Experience is needed to identify when subtle divergence from the normal range is deviant for that individual child or adolescent.

Bone Age Skeletal Maturation.

A key component of growth evaluation, involves taking a plain film xray of the left hand and wrist to obtain a bone age assessment to allow assessment of the skeletal maturation and epiphyseal status of the growth plate of the growing child.[8]

Growth hormone and IGF-1, thyroid hormone and sex hormones, especially estrogen, play key roles in skeletal maturation as do familial, genetic factors which are mostly unknown.

Ossification of the many bones of the fingers, knuckles, hand and wrists (see figure) occur in a predictable fashion and with the use of age-identified standards[9,10] that have stood the clinical test of time; these too can be used across different ethnic and geographic groups when local standards are (often) not available.

The standards were done many decades ago predominantly in Caucasian populations but still demonstrate appropriate progression over time and with adolescence as well.

Comparison bone age data can be assessed and compared for longitudinal changes as well as used for predicting adult height standard estimations. (several are listed in *Table 1*).

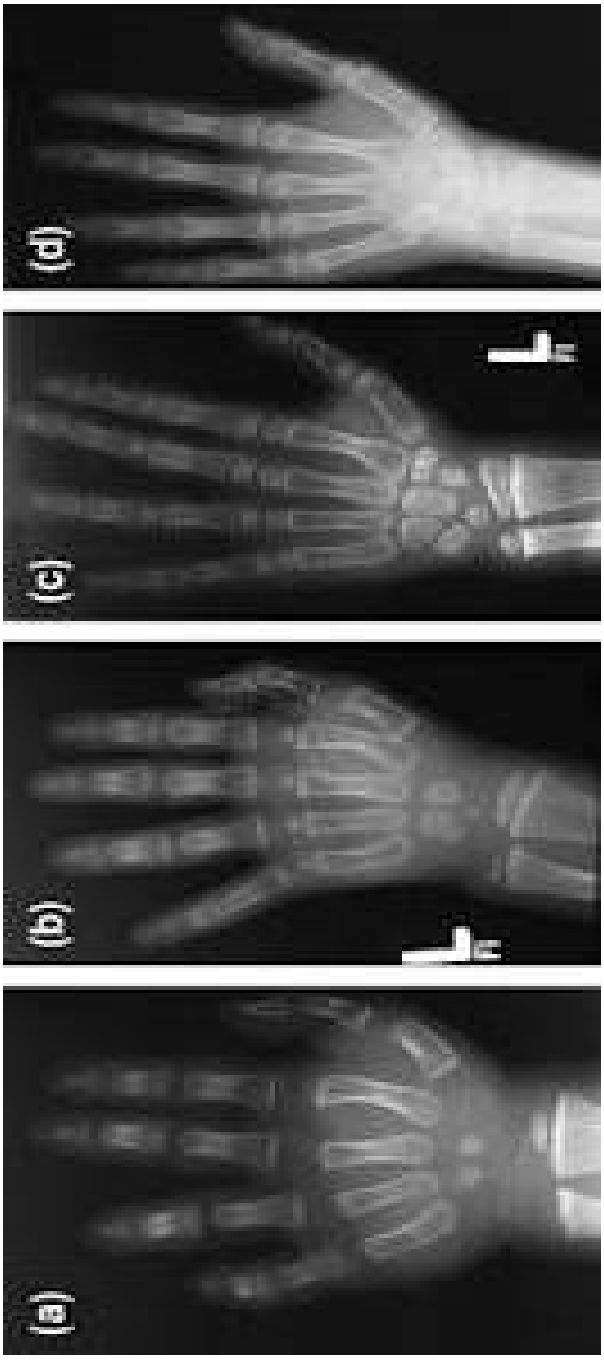


Figure 6. - Bone Age Skeletal Maturation.

Generally, bone age films are obtained annually when questions about growth and puberty are raised so comparisons can be made longitudinally.

The extent of skeletal maturation can be assessed by these various methodologies. More recently simple hand-held "calculators" as well as computer models have become available to predict final adult height with reasonable accuracy in non-Caucasian based populations compared to those studies by Bayley-Pinneau in the USA and by Tanner-Whitehouse in Europe.

As bone age advances, the prediction of final height becomes more accurate and such estimates are based on data from normal children even though now also commonly applied also to those with chronic illnesses, hormone deficiencies of various kinds and those treated for such disorders.

Most recently radiologists working with computer programmers, mathematicians and digital image specialists[11] have proposed more modern computerized assessment programs.

Mid-parent height is also a useful tool to estimate the genetic potential for the child or adolescent and is obtained by averaging the mother and the father's heights with an adjustment of about 13 cm (~5 inches) for the average height differences between the sexes. 13 cm is either "subtracted" from the father's actual height before it is averaged with the mother's actual height for a female or 13 cm is "added" to the mother's height before averaging with the father's height for a male.

The mid-parental height or mid-parental height percentiles so derived can be useful for looking at disparities or similarities with current height attainment and expectations of final height since the more similar, the less likely there will be to discover abnormalities requiring intervention or even expensive laboratory and radiographic testing.

The more dissimilar the current height percentiles and projections, the more important may be the possibilities to investigate potential diagnoses/explanations. When there are large differences in parental heights, however, the averaging of the parents' heights in this fashion, may be less useful and, of course, one parent may have a greater or lesser "genetic" influence on the individual child even if larger population-

based studies confirm the validity of the construct of mid-parental height under such circumstances.[1,3,4,5]

Table 1: Predicting final adult height

- Bayley-Pinneau[1] charts using chronologic age, actual height and bone age
- Roche, Wainer, Thissen (RWT) method[1] using chronologic age, actual height, bone age and mean parental heights
- Tanner-Whitehouse[1] assessment utilizing chronologic age, actual height, bone age, pubertal height and pubertal bone age incremental changes
- Khamis-Roche[1] multiple regression analysis using weight, height, birth measurement and mid-parental height data

Family history

As with any practice of medicine, detailed family history can be invaluable when assessing growth and short stature differential diagnoses. Height not only of mother and father with calculation of mid-parent heights and mid-parental height percentiles can provide a "genetic target height" from which similarities or discrepancies can be assessed for the individual child. As indicated above, big differences in mom and dad's heights may provide false security under such circumstances but this serves at least as a starting point for such assessments.

Heights of siblings, aunts, uncles, grandparents as well as first cousins may also provide some knowledge about such familial "genetic" contribution. This does not exclude a diagnosis such as growth hormone deficiency since there certainly can be familial clusterings of the same idiopathic growth hormone deficiency that occur (see below).

Similarly for other conditions that may have large genetic components, ie. celiac disease, diabetes, early puberty or late puberty.

Endocrine Growth Regulation.[1,3,4,5]

Growth is an incredibly complicated process uniquely useful for pediatricians and any health care professional providing care for infants, children and adolescents since so many factors can affect growth progression. Growth involves not only growth hormone but also its control by growth hormone releasing hormone and somatostatin, its mediation via growth hormone binding proteins (GHBP) and growth hormone related effects of insulin-like growth factor-1 (IGF-1) and IGF-binding proteins especially IGF-BP3.

Thyroid hormone and estrogen as well as testosterone are also required for optimal growth and when hypothyroidism or hypogonadal states exist, growth may be affected negatively. During fetal life, insulin effects on growth appear to be more important than growth hormone, per se. IGF-2 is also an important factor in controlling fetal growth. Estrogen directly or via aromatizable testosterone play increasing roles in the peri-pubertal, pubertal and immediate post-pubertal phase of growth particularly in the timing of the epiphyseal growth plate changes and ultimate closure. Facilitation of such growth homeostasis involves calcium, phosphate, vitamin D and parathyroid hormone as well as adrenal hormone factors. Delivery of adequate amounts of glucose, proteins and fats to cells as well as appropriate amounts of minerals and other nutrients are all necessary to optimize overall metabolic balance and insulin, cortisol and leptin as well as catecholamines all are needed to allow appropriate fuel homeostasis for growth to occur. The interbalance of all these factors is incredibly complex and intertwined, difficult to assess and measure. Growth deviations may serve as the initial clue to investigate deficiencies, excesses or variations of how the entire endocrine and metabolic systems are functioning.

Detailed Patient History and Physical Examination including Genital Exam and Tanner Staging and Screening Laboratory Examinations.

Frequently, initial history and physical exam point the way to certain types of problems and a differential diagnosis can be established. When this is not so obvious, certain screening laboratory tests may indicate hematologic status and possibilities of infections (blood count and differential count), inflammation (sedimentation rate or c-reactive protein), general chemistry profile (electrolytes, kidney and liver functions, calcium and phosphate levels), urinalysis and specific gravity.

Nonspecific evaluation of growth would often also include measurement of IGF-1 and IGF-BP3, as well as T4, free T4 and TSH. For adolescents, LH, FSH, prolactin, DHEA-sulfate and either testosterone for boys or estradiol for girls should be considered for baseline testing and sequential followup.

Because celiac disease (see below) can often be asymptomatic except for poor growth, celiac screening is often included in a first pass of screening tests with a transglutaminase antibody assessment when this is available and affordable. With this array of information as a baseline, sequential future assessments can occur and either reassurance of more specific investigations can take place accordingly.

Baseline bone age xray almost all of the time should be obtained and sometimes, depending upon diagnostic suspicions raised, lateral skull xray to assess pituitary and hypothalamic region (ie. calcifications, cysts, tumors), more specific CT scans or brain MRI imaging if possible (ie. head trauma, neurologic symptoms or signs, mass lesions) with some examples presented in *Figure 7*.

Karyotyping if available and affordable for Turner's Syndrome in short females (see case example below) and specific genetic testing, if available and affordable, for Noonan's Syndrome (see case example below) as well as other genetic disorders that may often be missed by simple exam

and history unless health care provider knowledge and suspicions are appropriately raised around the world. Specific genetic testing for SHOX mutations or abnormalities also can be considered, although expensive, and often nonspecific even when such rarer mutations are identified. Particularly when conditions such as idiopathic short stature are diagnosed and considerations for growth hormone treatment entertained, abnormalities in SHOX genes, may help with decisions to wait and watch vs begin GH treatment.

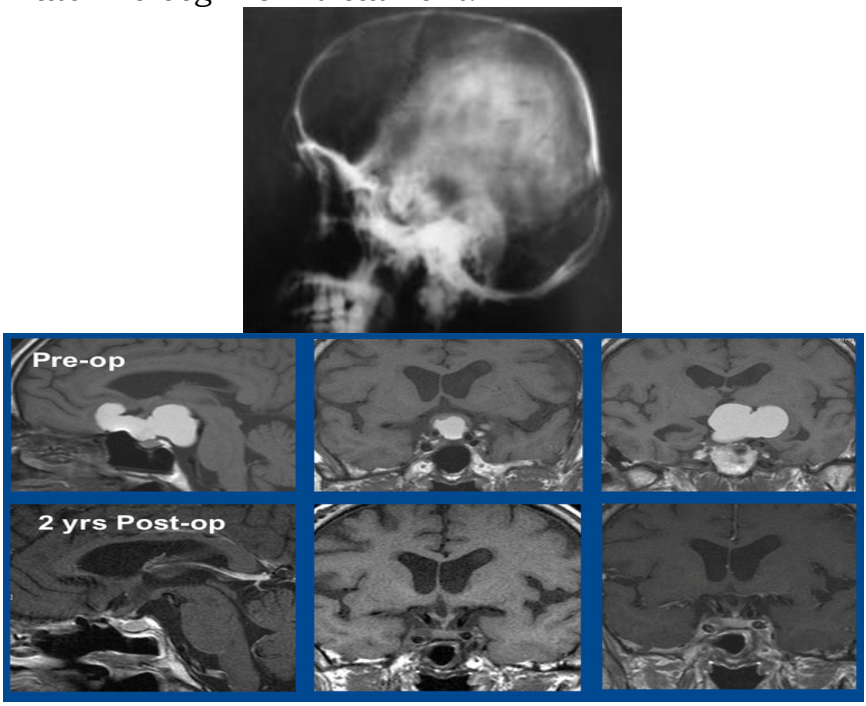


Figure 7. Pituitary/hypothalamic imaging: initial plain film showing previously undiagnosed craniopharyngioma calcifications on left; three preoperative non-calcified pituitary tumor views on the upper panel and then the same patient 2 years postoperatively with similar comparative views

Other imaging and more detailed testing would then be carried out depending upon initial results and diagnostic suspicions. Over time and with more definitive research endeavors, it is expected by many growth specialists that

some of what is now considered "idiopathic" may be elucidated and hopefully more specific treatment designed.

Growth Regulation via GH-IGF1 Axis as Basis for GH Testing Protocols.[1 3 4 5]

Growth hormone (GH) is a neuropeptide single chain 191 amino acid protein created in the hypothalamic/pituitary region stimulated by growth hormone releasing hormone (GHRH) from the hypothalamus.

GHRH then enters the portal system of the pituitary stalk and stimulates a protein kinase A activation pathway causing influx of calcium ions into the somatatrophs to stimulate synthesis and release of GH itself.

Somatostatin (also called somatropin release inhibitory hormone, SRIH) is produced by the hypothalamic paraventricular nuclei and released into the same system. SRIH acts on the somatotroph potassium channels preventing outflow of potassium ions which accommodate the influx of the calcium ions and therefore blunt the release of GH.

The balance between SRIH and GHRH determine the pulsatile release of GH with negative feedback loops of the entire system. IGF-1, cortisol and thyroxine, physical activity sleep, fasting metabolic condition and dopamine agonists all influence SRIH and GHRH and thus GH production.

Growth hormone stimulation testing takes into account this fact with normative data available for attempting to determine GH sufficiency (values above 10-15 ng/ml) or deficiency and insufficiency (values below 10 ng/ml).

Nocturnal pulses of GHRH persist during stage IV sleep while SRIH activity is low and these nocturnal pulses are felt to be the major time period for GH stimulation physiologically. (Grandmas all around the world were right that "good sleep helps growth!"). The basis of testing overnight GH levels (*figure 8*)[12] reflects this knowledge that "deep sleep" might allow identification of GH deficiency but too much variability from one night to the next or from one patient to another caused such expensive overnight testing to drop out of favor after some initial enthusiasm.

In some parts of the world, synthetic GHRH is still available and can be used for distinguishing hypothalamic vs pituitary GH deficiency as part of routine GH stimulation testing protocols.

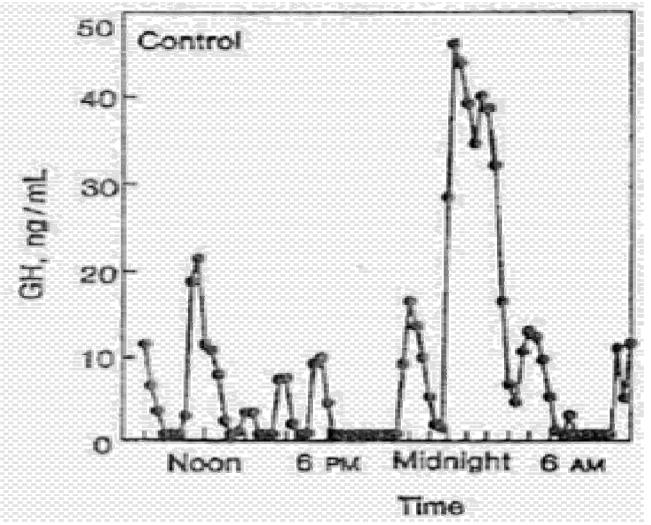


Figure 8. Overnight GH data

Exercise also is known to stimulate growth hormone secretion and so in years past, a 15 minute early morning exercise burst was often used as a GH screening test of sorts. Failure to see any GH rise following exercise was then suggestive of the need for more extensive testing of the GH axis whereas higher GH responses suggested that GH deficiency or insufficiency was significantly less likely. His has fallen out of favor in recent years, however.

During puberty, with increased sex steroids, especially estrogen in both girls and boys, these pulses increase in amplitude as well as frequency.

Ghrelin, primarily secreted from the stomach during fasting, as well as triiodothyronine also can stimulate GHRH secretion. Prolonged cortisol excess[13] as in Cushing's disease or Cushing's syndrome as well as when corticosteroids are provided for medicinal purposes (ie. appropriate treatment of

inflammatory conditions such as arthritis, inflammatory bowel disorders or part of cancer therapeutic protocols) inhibit GHRH and augment SRIH thus decreasing GH production. Brain stem catecholaminergic factors also stimulate GHRH and, as with using dopa stimulation testing, clonidine can also be used as a stimulating agent with the same somewhat arbitrary normal/abnormal response cutoffs of below 10 ng/ml GH levels suggesting deficiency or insufficiency and values above 10-15 ng/ml suggesting sufficiency (committee consensus definitions).

Insulin induced hypoglycemia, arginine and glucagon have also been utilized in stimulation testing and such GH stimulation testing protocols are summarized in *Table 2*. While insulin is often considered the premier GH stimulation agent, it has the distinct disadvantage of sometimes causing severe, convulsive hypoglycemia and/ loss of consciousness and seizures, and requires a continuous intravenous infusion as well as ability to provide medical rescue with intravenous glucose and constant medical or nursing attendance throughout a 2-3 hour time period of GH testing.

This author no longer uses insulin induced hypoglycemia as a GH stimulation test agent because of such risks and while we previously used GHRH stimulation testing in the panel, GHRH is no longer available in the USA.

The testing is done with these three tests in this order so minimize side effects from each agent: (1) clonidine GH testing, (2) levodopa or carbodopa GH testing and if a third stimulation tests is required, then (3) glucagon GH testing.

Levodopa and carbodopa as well as glucagon stimuli also have an added advantage of concomitantly stimulating cortisol responses as well so that information about the hypothalamic-pituitary-adrenal axis may be obtained simultaneously when thinking about hypothalamic and pituitary functions vis-à-vis growth issues. Possible side effects with each stimulation test agent are also listed as are dose recommendations based upon weight categories. If TRH is available, it too can be combined with other stimulation agents to verify TSH status.

Table 2. GH Stimulation Testing [1,3,4,5]

Stimulus	Dose	Timing of GH Samples	Testing side effects
exercise	climb steps or use exercycle steadily for 10 minutes	0, 10, 20, 30 minutes	fatigue
clonidine	5-15 kg: 50 ugm 15-25 kg: 100 ugm 25-35 kg: 150 ugm 35-50 kg: 200 ugm >50 kg: 250 ugm	0, 30, 60, 90 minutes for GH with fasting glucose as well	fatigue, sleepiness, postural hypotension
GHRH	1 gm/kg intravenously	0, 15, 30, 45, 60, 90, 120 minutes for GH with fasting glucose as well	flushing, metallic taste
Dopa	<15 kg: 125 mg 10-30 kg: 250 mg >30 kg: 500 mg	0, 30, 60, 90 minutes for GH as well as cortisol with fasting glucose as well	nausea, vomiting
Glucagon	0.03 mg/kg up to 1 mg maximum intramuscularly.	0, 30, 60, 90, 120, 150, 180 minutes for glucose & cortisol as well as GH	nausea, sometimes emesis
Arginine	0.5 gm/kg up to max 30 gm of 10% arginine HCl in normal saline infused IV over 30 minutes	0, 15, 30, 45, 60 minutes for glucose and GH	
Insulin	0.05-0.1 u/kg intravenously with IV infusion of saline maintained for potential glucose rescue	0, 15, 30, 45, 60, 75, 90, 120 minutes for glucose and GH	mild, moderate or severe hypoglycemia. IV glucose & glucagon must be available for rescue PRN

Some specialists prefer arginine stimulation testing for GH responsivity but this too requires more personnel, time,

supervision and does not seem to provide any benefit of the easier stimulation testing protocols.

Most such testing can be carried out in an ambulatory fashion in the office or clinic and hospital admission usually is not required with such protocols.

Local skin anesthetic creams such as those containing lidocaine (EMLA ®) can minimize pain and discomfort so that such testing can be done with indwelling infusion lines or with multiple intravenous venipunctures about every half hour for 2-3 hours depending upon the expected known GH peak responses in normal child and adolescent populations. Some clinicians prefer combination testing, although this is a longer test protocol, ie. clonidine then glucagon, insulin then arginine or augmentation with propranolol, ie. propranolol-glucagon. Some also suggest adding a small dose of estrogen prior to the stimulation testing if there also is concomitant pubertal delay but this too is controversial and this author does not routinely do this.

Problems with interpretation of these results include the frequent nonreproducibility from one day to the next even with the same stimuli, the somewhat arbitrary cutoff points for interpreting sufficiency, insufficiency and deficiency which more often involve financial and cost decisions of how many people can society, an insurance company or the government "afford" to receive an expensive treatment like GH at any one time. Science and economics of medication costs may compete because of the continued enormous expense of GH treatment and this would likely not be the case were GH available in a significantly lower-cost generic product.[14,15,16]

GH in serum exists in a free form but also in a bound form to GH-binding protein (GHBP) derived from the extracellular portion of the GH receptor. GHBP reduces glomerular filtration and modulates GH binding to the GH receptor and GHBP concentrations vary with age, estrogen levels, body mass index and feeding states. Changes in GH receptor, interactions with Janis kinase 2 (JAK2), changes in phosphorylation all can change IGF-1 effects. GH receptor changes especially in the liver influence production of IGF-1

binding protein 3 (IGB-BP3) as well as the acid-labile subunit (ALS) and these components combine to transport IGF-1 in the blood and have some influence on the anabolic and metabolic actions of GH itself.

Most measurable IGF-1 comes from the liver influenced greatly by GH itself. But GH can also have known effects independent of the hepatic production of IGF-1 since there are GH receptors found in the epiphyses and bone marrow as well as other body tissues. GH alone or via IGF-1 has body composition effects promoting lean mass accretion, insulin counter-regulation, increased lipolysis and decreased lipogenesis as well as muscle nitrogen retention among other effects. Such effects may be very important in conditions such as Prader-Willi syndrome[33] and likely influence the illegal use of growth hormone in athletes and muscle builders since GH, particularly when given in supra-physiologic dosage, increases muscle mass and strength.[17]

Whether or not the frequent very high doses of GH abused by athletes/body builders around the world also add to future malignancy and cardiovascular problems, also remains suspect and pediatric and adult endocrinologists must participate in discussions about such risks to education everyone in appropriate fashion.[18] Linear growth occurs with both increased epiphyseal growth and increased bone mass also through effects of GH as well as IGF-1.

IGF-1.[1,3,4,5,19]

IGF-1 and IGF-2 are small peptides called insulin-like growth factors (IGFs) and have about 50% homology with insulin. There are IGF receptors which bind both these proteins and through which the mitogenic and metabolic actions of IGF protein are mediated. Expression occurs in many body tissues. GH through its binding of the growth hormone receptors and pathways involve JAK2, Stats, cytokine suppressor signals and eventually STAT5b induced DNA production in the nucleus and as well as IGF-1 production. IGF-1 is fundamentally involved with linear growth and these actions are mediated through at least six

IGF-binding proteins which transport the IGFs to target cells and modulate interactions with cell surface receptors. Measurement of IGF-1 and IGF-BP3 is available and can serve as a surrogate for GH assessments on random blood sampling since these two hormones are not altered in an immediate sense by fasting or food intake nor time of day/night. Sequential measurement of IGF-1 can be used to assess and estimate growth hormone levels indirectly. IGF-1 levels can also be used to titrate against GH dosage in those receiving GH treatment with an aim to use sufficient GH to bring and sustain IGF-1 values into the mid-normal range for sex and age with the assumption that this will optimize growth promoting effects and minimize potential side effects of growth hormone so dosage can be increased or decreased based on IGF-1 response. These are reasonable clinical assumptions but hard scientific evidence for justification remains lacking.

Growth hormone related genetics.

A variety of genetic mutations [20] have been defined which result in GH deficiency including HESX-1 linked with septo-optic dysplasia, combined pituitary hormone deficiency syndromes, idiopathic GH deficiency and ectopic posterior pituitary; LHX-3 and 4 linked with pituitary hypoplasia (GH, TSH, LH, FSH); Pit-1 or PROP-1 linked with combined pituitary hormone deficiency, (GH, TSH, prolactin, ACTH, LH, FSH); GH1 linked with isolated GH deficiency; SOX2 linked with LH, FSH deficiencies, anterior pituitary hypoplasia, anophthalmia/micropthalmia as well as learning problems; SOX3 linked with isolated GH deficiency, MR and midline abnormalities. Also important to recognize is the marvelous story of the extremely

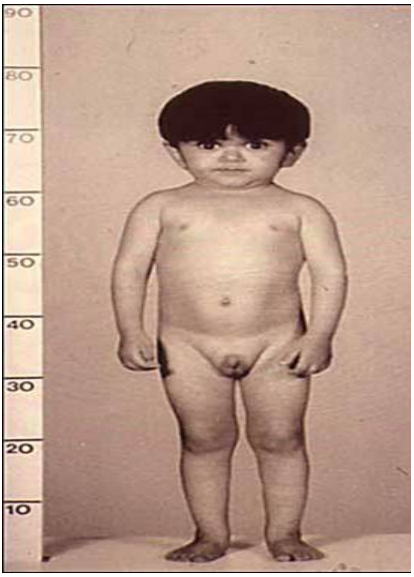


Figure 8

rare Laron dwarf in whom GH resistance occurs and the gene has been identified, the treatment identified and epidemiologic studies around the world have confirmed the utility and benefit of IGF-1 treatment to restore health and improve quality of life. (see *Figure 8*) [21]

Assessment of SS and Illustrative Case Vignettes

Short stature, therefore, is a rather common clinical problem. It is a symptom not a disease and, in fact, may represent a variant of normal growth, so called constitutional short-stature. It can occur on a familial basis presumably with a strong genetic component or may occur discordant from other members' growth patterns in the family. However, short stature may represent a pathologic state sometimes with concomitant other symptoms and signs but sometimes as the prime parameter to which attention should be addressed in order to make a more definitive diagnosis. New information over the past several decades of research suggests that what used to be clinically ignored as "familial short stature" with no treatment possibilities may represent variants of growth hormone insufficiency or deficiency that respond to growth hormone treatment exactly the same as classical growth hormone deficiency states.

General physicians, family physicians, pediatricians and nurses must be taught this "new paradigm" since their counseling to children and parents must change to acknowledge this new set of medical facts.

Pertinent investigations would then be considered rather than dismissed just as growth hormone treatment itself, previously thought to be not possible to succeed when familial short stature was the diagnosis, now can be considered as well. As with all conditions of growth and short stature, earlier diagnosis leads to earlier treatment possibilities and usually greater final adult height. Future biochemical and genetic specific testing is expected to better define such conditions and perhaps even help individualize not only which patients should be considered for GH treatment but also potentially assist with helping decide about

dosing considerations as well. Even when such conditions are diagnosed relatively late, ie. late childhood or early adolescence, significant height may accrue with standard growth hormone therapy if epiphyses remain open/delayed compared to chronologic age.

Familial Isolated GH Deficiency Case Vignette.

Gustavo B., came from a very poor immigrant family and for many years his parents were told that he was "just like them, short because they and many members of their family were short. So, there was nothing to be tested and nothing to be done." However, he presented at age 14 with significant short stature to our office for another consultation. He seemed destined to fulfill this family history except when he was actually evaluated, he had significantly low IGF-1 levels and stimulation testing demonstrated classical and severe isolated growth hormone deficiency on two separate stimulation tests (presumably just like his dad and paternal grandfather). He responded quite nicely to a combination of standard dose growth hormone treatment plus leuprolide to temporarily delay epiphyseal closure/puberty and thus allow the growth hormone to produce acceleration of height ("catch-up growth"). This combination treatment approach lasted for about 4 years and he ended up approximately 20 cm (about 8 inches) taller than pre-treatment predictions (and 20 cm taller than his dad!): initial height predictions 152 cm and actual final height at age 20 of 172 cm. A year later his first cousin also presented - but at a younger age - with the same history and also had similar isolated growth hormone deficiency treated successfully because his family knew another option existed.

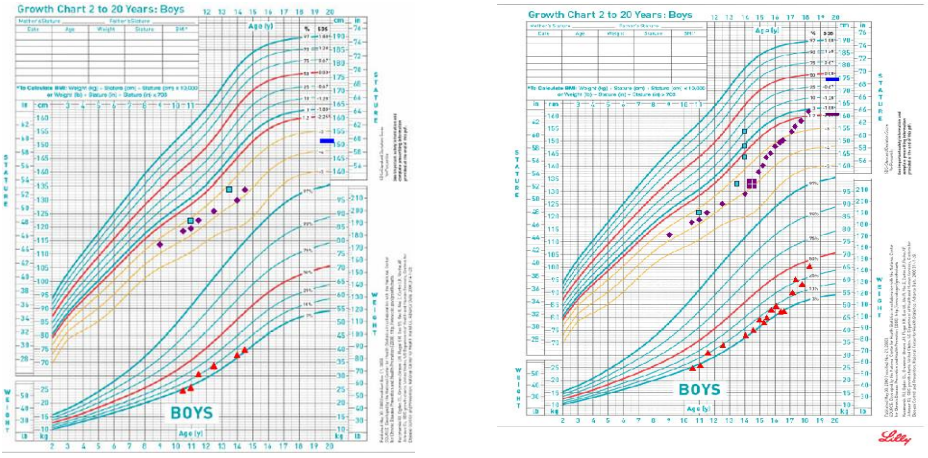


Figure 9. Gustavo B. Growth chart at dx and then at end of tx

Table 3. Short stature classification scheme

- Normal variant short stature
  - Familial short stature: short as a growing child and remain short as an adult like others in the family
  - Constitutional short stature: short as a growing child but eventually grow faster and catch-up to normal adult heights; often familial pattern as well
- Pathologic short stature
  - *Disproportionate short stature*
    - Achondroplasia and dyschondroplasia
    - Known genetic disorders
      - Turner Syndrome
      - Noonan Syndrome
      - Down Syndrome
      - Prader-Willi Syndrome
      - Russell-Silver Syndrome
      - SHOX deficiency syndromes
    - Excess steroid syndromes
      - Steroid treatment of: inflammatory bowel disease, JRA or other inflammatory conditions, malignancies, chronic renal disease
      - Cushing's syndrome or disease
  - *Proportionate short stature*
    - Rare genetic syndromes with or without midline defects or significant central nervous system dysfunction
      - Seckel's
      - Pierre Robin
      - Septo-optic dysplasia
    - Hypothyroidism
      - Unrecognized/untreated especially where no neonatal thyroid screening occurs
      - Acquired hypothyroidism (ie. most commonly Hashimoto's thyroiditis but can be post-radiation, post-thyroidectomy for cysts or thyroid malignancies, primary vs secondary (pituitary) vs tertiary (hypothalamic) induced hypothyroidism)
    - GI disorders
      - Cystic fibrosis
      - Celiac disease- symptomatic or asymptomatic
      - Inflammatory bowel disorders
      - Poverty-related malnutrition/caloric deprivation
    - Adrenal insufficiency (ie. Addison's adrenalitis, other more rare genetic conditions, post-operative adrenalectomy)

- Hyperandrogenism or precocious puberty (with initial accelerated growth and puberty but then ultimately short stature with early epiphyseal closure)l
  - Congenital adrenal hyperplasia
  - Precocious puberty conditions
- Hypogonadism- primary, secondary or tertiary
- Hypoparathyroidism
- Psychological/maternal deprivation syndromes
- Mauriac syndrome/insulin omission/deficiency
- Short stature associated with Attention Deficit Hyperactivity Disorders &/or Tx
- Post-renal transplant and other renal disorders
- GHRH-GH-IGF-1 axis disorders
- SHOX deficiencies
- Laron Dwarf
- Specific genetic mutations: PROP-1, PIT-1,LHX-3,LHX-4,GH1,SOX2,SOX3 etc.
- Hypothalamic or pituitary GH related problems
  - Malformed hypothalamic/pituitary anatomic abnormalities
  - Craniopharyngioma
  - Pituitary/hypothalamic microadenomas, dysgerminomas, prolactinomas
  - Post-hypothalamic-pituitary tumor treatment (ie. surgery, chemotherapy or irradiation)
  - Post-hypothalamic-pituitary trauma / surgery
  - Neurofibromatosis involving hypothalamus or pituitary region
  - Infectious diseases involving hypothalamus or pituitary region (ie. tuberculosis, histiocytosis)
  - Autoimmune hypopituitarism ("hypophysitis")
  - Idiopathic isolated growth hormone or axis abnormalities
    - Autosomal dominant isolated GH deficiency (neonatal hypoglycemia)
    - Autosomal recessive isolated GH deficiency
      - Familial version (w/severe neonatal hypoglycemia)
      - Non-familial
- Neurosecretory growth hormone deficiency or insufficiency

- *Post-Small for Gestational Age infants* who do not spontaneously "catch-up"

Acquired Hypothyroidism and Myxedema secondary to Hashimoto's Thyroiditis Case Vignette.

Jasmin L. stopped growing in height nearly completely between ages 3 and 4 while weight stayed at a normal velocity. Nobody seemed to recognize that she became edematous, was very lethargic and not eating very well instead of the being the energetic toddler that she had been. She was referred for poor growth but she looked classically ill and myxedematous as one can see from the initial pretreatment (*Figure 10.a*). She had no goiter but had decreased reflexes with a relatively slow pulse, thickened hair and dry skin. T4 levels were unmeasurable (<1) and TSH levels 748 with positive thyroglobulin as well as thyroid peroxidase antibodies confirming our clinical impression of severe, acquired hypothyroidism secondary to Hashimoto's thyroiditis. She was slowly started on replacement levothyroxine orally once each morning and the dose increased every few weeks until all her thyroid functions were normalized. Within 2 weeks she was back to her energetic self and all her symptoms disappeared; within 4 months she started showing height acceleration. She returned very close to her premorbid height and weight percentiles and maintained normal growth with only minor levothyroxine dose increases based upon periodic thyroid function testing aimed to keep her TSH in the completely normal range.

The *Figure 10b* shows her as a normal preschooler one year after diagnosis and maintaining her euthyroid state on replacement therapy. *Figure 11* shows growth chart tracking very close to familial expectations.

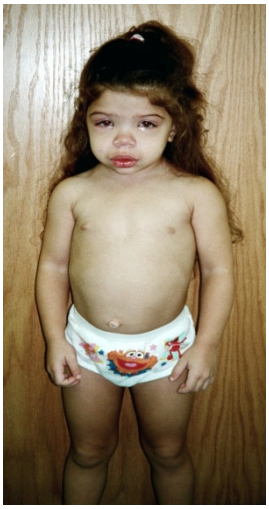


Figure 10.a. Jasmin L Pretreatment

Figure 10.b. Jasmin L. 1 year Post-Treatment

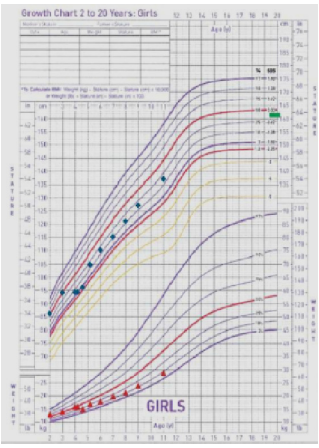


Figure 11. Acquired Hypothyroidism & T4 Treatment Response.

Growth failure unrecognized between ages 3 & 4 then catch-up growth with proper diagnosis & thyroxine treatment

Celiac Disease Case Vignette Presenting with Poor Growth rather than GI symptoms.

Jennifer M. presented for consultation as an 8 year old poorly growing with a 2 year history of height deceleration that had been noted by her pediatrician but without any detailed evaluation.

The growth data from the pediatrician suggested a slowdown in height after age 2 that was likely artifactual and based upon plotting length at age 2 on a height chart, a common error in making the transition from infantile lengths before age 2 to heights at around age 2-3 years of age (when kids stand reasonably still enough for accurate measurements). Systems review was negative and initial screening laboratory results also negative except for slightly low IGF-1 levels with normal IGF-BP3 levels. Included in the screening laboratory tests was a transglutaminase antibody and this was extremely positive, +148 (normal range <15). On follow-up, the results were similar with positive antigliadin antibody and positive endomysial antibody as well as low ferritin levels and low vitamin D levels. In retrospect, her parents reported some mild episodic constipation but no flatus, bloating, abdominal pains or diarrhea of any kind.

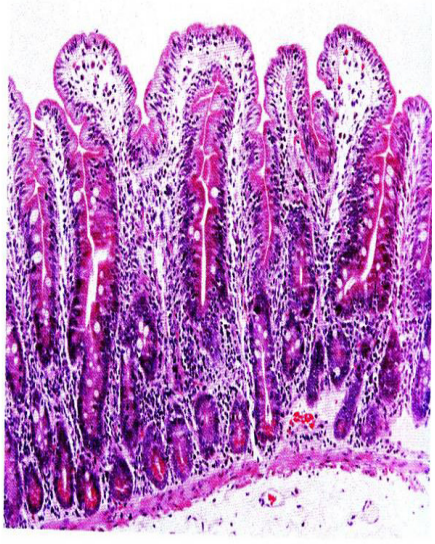


Figure 12. Typical Celiac

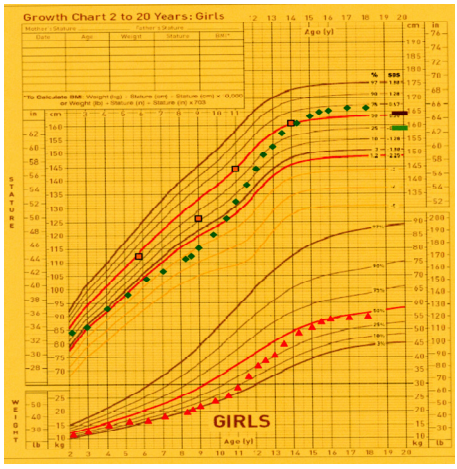


Figure 13. Celiac growth chart. Diagnosis made without any GI symptoms by screening with transglutaminase antibody.

Figure 12 shows a classical positive celiac duodenal biopsy with loss of villi and round cell infiltrates present. She was treated with a strict gluten-free meal plan and also lactose-free products because of concomitant lactose intolerance which did not clear as she was maintained gluten-free. Antibody levels slowly and steadily decreased and on follow-up

visit she and her family acknowledged that, in retrospect, she really had been complaining of stomach discomfort and looser bowel movements as well as gasiness prior to diagnosis but that this was just not recognized until she became gluten free and she noted less gasiness, less malodorous flatus and not only no longer being constipated but also more energy, better sleep, better mood and improved school performance. Height took about 18 months to show definitive growth (chart, Figure 13). Weight showed a similar improvement pattern and she had normal puberty and ended up slightly taller than her mid-parental height predictions.

Mauriac Syndrome Case Vignette.

Severe DKA at diagnosis of classical type 1 diabetes mellitus at age 10 with chronic poor control, poor parental supervision of blood glucose monitoring, meal planning and insulin administration despite efforts at education, psychosocial interventions and counseling. Complicated by both parents having untreated and undiagnosed attention deficit disorder and the child also having the same condition. All poorly compliant with treatment afterwards. Persistent elevated hemoglobin A1c levels but no actual recurrent ketoacidosis. Hyperlipidemia as well. Both height and weight deceleration evident throughout with some pubertal delay but otherwise normal pubertal progression clinically. No retinopathy but limited joint mobility first noted at age 13 with progression to stage IV limited joint mobility by age 14-15. Early nonproliferative background retinopathy as well as hepatomegaly, elevated liver enzymes and persistent hyperlipidemia all reflecting omitted insulin, monitoring, dietary issues and inappropriate adult supervision despite counseling and education efforts. With early microalbuminuria at approximately age 20, treatment with angiotensin converting enzyme inhibitors was recommended but compliance with this was also problematic.

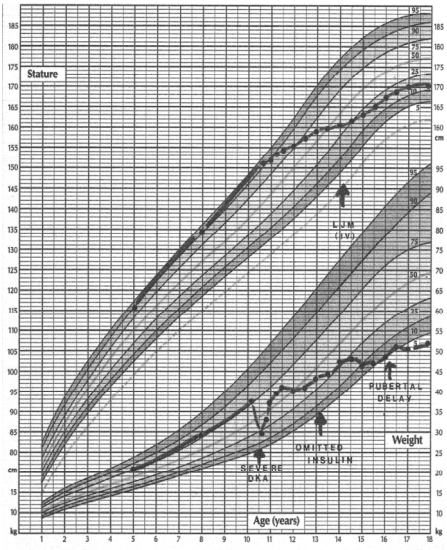


Figure 14.
Mauriac growth chart

Congenital Panhypopituitarism Case Vignette.

James S., male born at term without any known maternal difficulties or any other problems.

Significant neonatal hypoglycemia associated with small phallus recognized day 2. Diagnosed by absent growth hormone levels and suppressed insulin levels as well as absent cortisol levels during a witnessed hypoglycemic episode in the NICU.

GH stimulation testing confirmed absent GH levels.

Concomitant low TSH, low T4, low cortisol, low ACTH documented panhypopituitarism. Begun on GH as well as thyroxine and cortisol daily replacement at standard doses as a newborn with prompt resolution of the hypoglycemia. Cranial imaging unremarkable. Subsequently while GH therapy was continued had obesity and greater than expected height acceleration with intermittent mild episodes of hypoglycemia throughout early childhood. Never developed posterior pituitary deficiencies (ie. no diabetes insipidus) and had thyroxine and cortisol replacement continued and adjusted according to lab parameters and clinical findings while GH continued. Never any severe hypoglycemic seizures or other events. Never any adrenal insufficiency crisis. Normal mentation and development. Eventually testosterone added as a teenager to allow virilization and final aspects of growth (see *Figure 15*). Both parents tall and obese with his final height and weight both consistent with parental stature expectations. Continued to receive adult growth hormone replacement when a trial off GH treatment documented expected low IGF-1 levels. Also continued normal adult dosage of thyroxine, hydrocortisone and testosterone with dosage decisions based upon actual IGF-1 levels, free and total T4 levels and circulating levels; hydrocortisone levels were dosed based on typical weight and adult needs with booster doses during intercurrent illness and occasional blood glucose measurements during such illnesses.

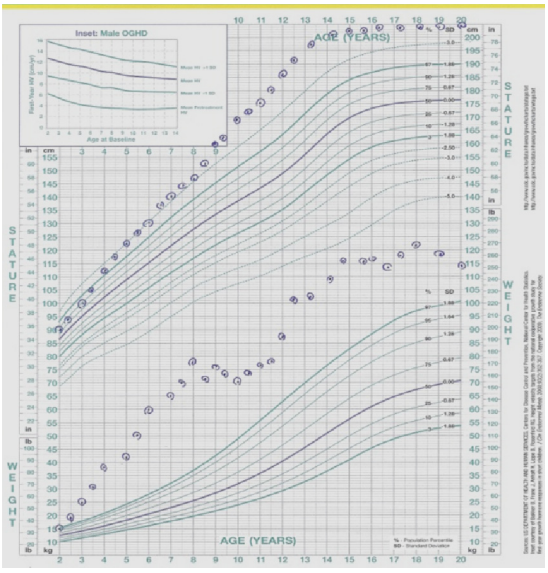


Figure 15. James S.
Congenital Panhypopituitarism

Acquired Craniopharyngioma with Post-Treatment Anterior and Posterior Panhypopituitarism Case Vignette.

Michelle D. Presented as a previously well 7 year old girl to her pediatrician because of unremitting headaches lasting 2 weeks associated with nausea and vomiting. No history of head trauma or illness. Completely normal examination and well hydrated but with papilledema bilaterally. Plain film skull xrays showed suprasellar calcifications with extension of a solid mass into the third ventricle and erosion of the dorsum sella and floor of the pituitary fossa. This was confirmed on CT scan with biventricular hydrocephaly. Emergency neurosurgical evaluation concluded with biventricular shunting. Headaches, nausea and vomiting resolved. Dexamethasone was given pre- and post-operatively and then subsequently tapered off. She received cranial irradiation to the tumor with excellent shrinkage over the ensuing weeks and endocrine follow-up documented normal adrenal and thyroid functions as well as normal urinary concentrating ability but growth deceleration occurred associated with low IGF-1 levels as demonstrated in her growth charting, *Figure 16* for height and weight and *Figure 17* for height velocity. GH stimulation testing was abnormal and growth hormone was begun with cadaveric GH available at the time. After initial successful treatment and because of Jacob-Creutzfeld fears from cadaveric GH sources, GH was discontinued for about a year. Growth cessation again documented still without any other hormone deficiencies clinically or biochemically except for nonspecific learning disabilities presumed secondary to the cranial irradiation. Stable shunt function.

A year later, synthetic GH became available and GH was restarted with repeat growth catch-up (see figures) but, now as an early adolescent, no thelarche or pubarche. During this second GH treatment phase, hypothyroidism developed clinically and was confirmed with good response to standard thyroxine replacement protocols while GH was continued.

Bone age remained delayed compared to chronologic age consistent with absent gonadotropins and her hypogonadism. Primary amenorrhea as expected associated with low estradiol, LH and FSH levels. Estradiol and then oxandrolone were added to her replacement regimen with documented thelarche, adrenarche and eventually menarche. Never any clinical adrenal crises or insufficiency despite low-normal cortisol levels and absent ACTH levels. Progesterone was added and eventually cyclical estrogen and progesterone were provided while continuing her GH and thyroxine with normal menses thereafter.

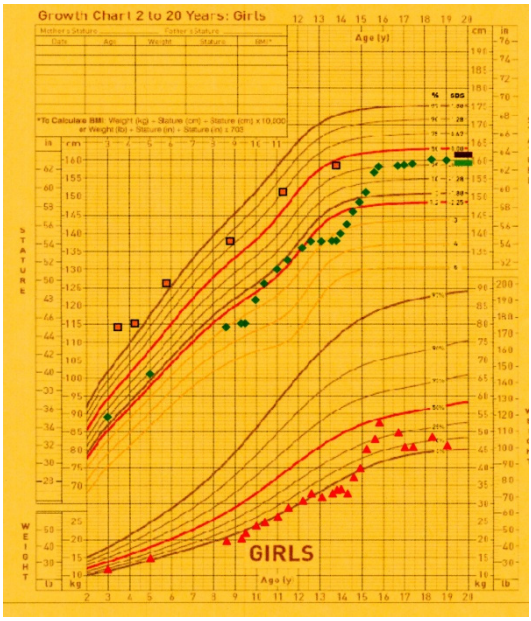


Figure 16. Michelle G.
Craniopharyngioma pre and post treatment growth chart

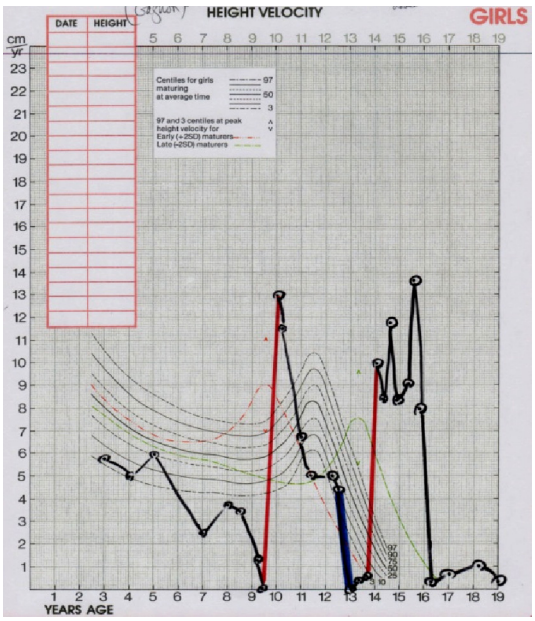


Figure 17. Michelle G - Craniopharyngioma.
Height velocity Pre, During and Post Treatment.

She ended up at a similar height to mid-parental expectations and then GH was discontinued while thyroxine and combination estrogen/progesterone were maintained. IGF-1 levels decreased significantly off GH and several years later as a young adult she had continuing deterioration of her memory and the same or worse learning problems with executive dysfunction. Adult persistent GH deficiency was documented on stimulation testing and GH treatment resumed titrating dosage to mid-adult normal IGF-1 levels. Two years later she complained of worsening fatigue with low-normal blood pressure. Cortisol levels were similarly low. Thyroid hormone and growth hormone biochemical parameters all remained stable and at target range. Replacement hydrocortisone was provided and full replacement hormone therapy for all aspects of her post-craniopharyngioma pan-anterior-hypopituitarism resolved her fatigue problems.

Initial growth deceleration from unrecognized and relatively asymptomatic craniopharyngioma. Slight acceleration post-operatively and then further deceleration. Initial acceleration from GH Treatment initially. Then cessation of growth with discontinuation of cadaveric GH with concerns about Creutzfeldt-Jacob disease before synthetic GH became available. Then acceleration once again in association with resumption of GH and addition of estrogen to complete puberty.

Post-Head Trauma Isolated GH Deficiency Case Vignette.

Lisa P. Familial short stature with height and weight proportionate and both tracking at normal annualized height velocity but significantly below the standard growth percentiles. On consultation by her primary physician, advised nothing problematic about such growth. Hit by car while riding her bicycle with growth deceleration and, in retrospect, this fact and the association of her growth slowdown with her head injury, was missed by pediatrician's office as well as family and school nursing staff despite well documented and charted growth data. Never had broken bones or skull fracture and never had

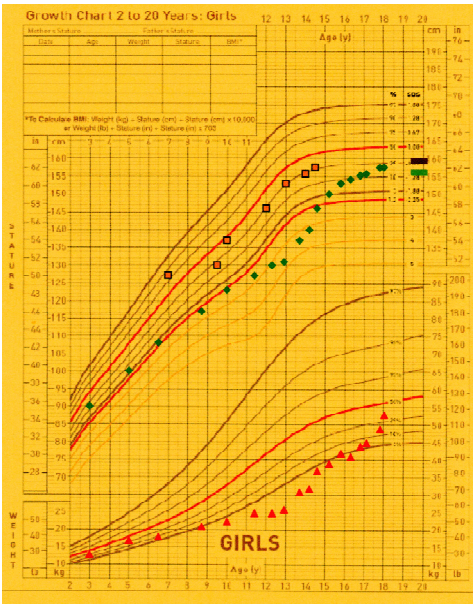


Figure 18. Lisa P.
Post-Head Trauma Growth Chart

subtle or clinically significant neurologic findings post-injury or thereafter. Three years later, referred to endocrinology because of her poor growth without any clinical suspicion of any other pituitary issues and with normal examination. IGF-1 levels low and SHOX testing as well as karyotype normal in a prepubertal female. GH stimulation testing was abnormal and GH treatment begun with excellent catch-up height and IGF-1 response.

All other endocrine functions remained normal and she had normal spontaneous puberty and menarche. Estimated total height gain on GH treatment 17 cm (~7 inches) and slightly taller than mid-parental height estimates at conclusion of GH treatment. No adult GH deficiency documented but IGF-1 levels modestly low off GH.

GH dosing.[22]

Most European pediatric endocrinologists start GH treatment at doses approximately 1/3-1/2 of their North American counterparts without very good scientific studies to support one or the other dose regimens. Registry studies suggest that the American children seem to grow at a faster pace with the relatively higher doses being used and reach somewhat taller final heights but again, direct prospective studies have not been definitive in this regard except for noting that the Europeans achieved relatively shorter stature than the Americans. The more absolute the GH deficiency, the less actual GH dosage needed to boost IGF-1 levels, and this is reflected in dose response data around the world. Daily dosing with synthetic GH seems to be more effective than the earlier historical doses of only 2 or 3 injections of cadaveric GH each week.

American starting GH doses are usually 0.043 mg/kg/day, usually given in the evening but with slightly higher doses of 0.05 mg/kg/day for Turner, Noonan and post-SGA and ISS patients. The effect of GH seems to decrease over treatment duration even when efforts to titrate against sequential IGF-1 levels are well maintained. Thus, best height acceleration is usually seen in the first year with somewhat lower annualized height velocities thereafter.

Following the protocols proposed by Cohen and Rosenfeld, pubertal dose increases have been studied and seem to increase annualized height velocity in ways that

mimic and maintain adolescent-related higher IGF-1 levels thus further promoting ongoing catch-up and maintaining such catch-up heights. Registry studies have documented such an effect[23] and it is common with some pediatric endocrinologists, including this author, to routinely boost GH doses when clinical signs of puberty begin, or when there is chemical adrenarche (increasing DHEAS), from initial doses maintained at 0.043 mg/kg/day or 0.05 mg/kg/day (depending upon individual initial protocol being followed) to "pubertal doses" of 0.1 mg/kg/day. Under such circumstances it is common to see further increases in follow-up IGF-1 levels and further height acceleration. This also allows pubertal hormone replacement, in those patients who do not produce pubertal hormone responses on their own (ie. Turner or panhpopituitary patients) to occur sooner rather than later. In some cases, when puberty starts on its own but somewhat earlier than family history or with peers, temporary pubertal blockade with gonadotropin-releasing hormone antagonists such as leuprolide in its injectable form (Lupron ®) once or twice-a-month) or subcutaneously implanted histrelin (Supprelin ®) have been very helpful.[24] Two such examples are presented in Figure 19 for patients considered to have isolated GH deficiency, the first with a SHOX mutation and the second with normal SHOX genetic studies. Both boys entered puberty somewhat earlier than expected and did well clinically with three years of pubertal blockade while pubertal doses of GH were maintained. Excellent growth was documented for both and then normal puberty occurred at the end of the pubertal blockade treatment phase.

GH side effects/registries.

GH is a relatively expensive but relatively safe medication with a host of diagnosis to be considered where treatment with GH shows favorable responses. Most information about side effects of growth hormone treatment came originally from studies like the US National Pituitary Agency Registry as well as similar cooperative research programs in several other parts of the world when cadaveric

growth hormone was being used. Expanded information became available when commercially produced recombinant DNA growth received approval for use as several different pharmaceutical companies created their own synthetic recombinant DNA growth hormones on a daily subcutaneous injection basis.

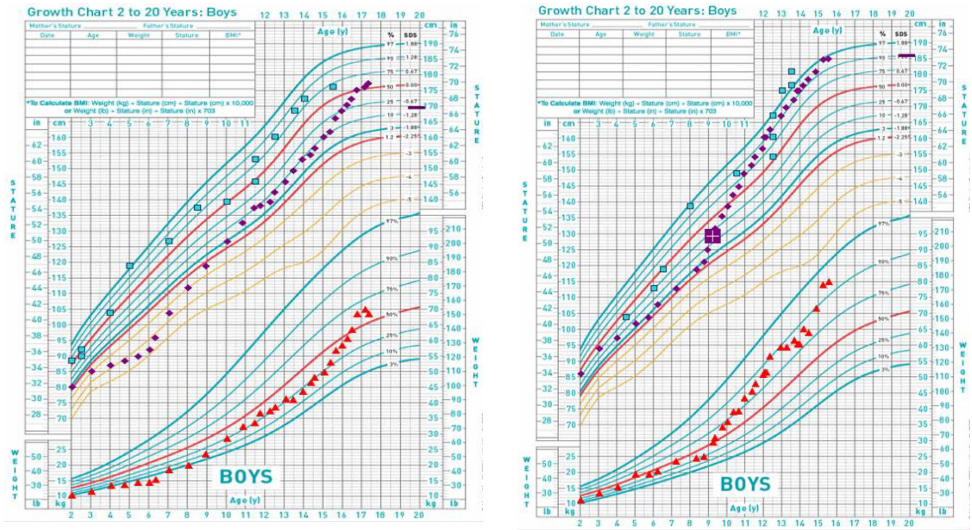


Figure 19A. Samuel S and Figure 19B. Chris R.
Isolated GH Deficiency with Increased GH Pubertal Dosing plus Pubertal Blockade in Combination

No direct independent comparison research studies have ever been conducted to determine if one or another growth hormone product is equivalent or more beneficial/harmful than another but clinically there has not been any evidence for superiority or inferiority. However, there are differences in manner of administration of growth hormone that may be more or less acceptable and beneficial as well as easier to provide GH for individual families and patients. For instance, several companies only have vial and syringe administration preparations while many have manual or semi-automatic pen systems for administration using small subcutaneous 4 mm – 12 mm disposable needle tips. These

offer convenience as well as decrease the fear of syringes and needles. Some companies offer devices which allow less wastage of the growth hormone through semi-mechanical pressure injectors and some offer injection pressure devices which minimize local injection discomfort. For the past several decades, numerous surveillance registries sponsored and organized by the GH producing pharmaceutical companies with medical advisory boards consisting of pediatric endocrinologists who supervise the academic and intellectual questions posed, organization and retrieval of data working closely with medical research statisticians. Sponsored symposia and numerous research articles have been presented at national and international meetings as well as prepared, peer-reviewed and accepted studies published in international medical journals looking not only at safety and efficacy of GH treatment but also helping to ascertain benefit and risk factors of treatment. As a model of good pharmaceutical interrelationships with supervisory bodies such as the US FDA and the European Union as well as many other national oversight bodies, this has been an excellent collaboration with a wealth of information because of the large numbers of patient years of data collected coupled with the ability to obtain sequential, longitudinal data.

GH Adverse Effects/Events.[1]

Recombinant biosynthetic GH preparations are highly purified and free of contaminants. Storage is relatively easy with simple refrigeration although this remains problematic in places around the world with limited resources as well as high-cost barriers in general. The possibility of infectious transmission such as became evident with cadaveric pituitary preparations and Jacob-Creutzfeld disease has been eliminated. Need to harvest and transport of pituitary glands for purification also has been eliminated. Antigenicity of recombinant biosynthetic GH preparation has also been low although antibodies against GH can be detected in up to ~1/3 of patients so treated. This does not seem to interfere with dose requirements or efficacy of the GH clinically in any way

apparent, however. Some preparations have a more acidic base and so sting a bit more than others but generally such problems have been rather minimal.

Similarly, allergic reactions to the diluent or the GH itself has also been rather rare. Switching from one brand to another usually solves the problem.

Table 4: Post-marketing surveillance databases monitor the safety of GH treatment around the world with more than 100,000 patients enrolled in more than 400 centers

- US: National Cooperative Growth Study (NCGS)
  - Established 1985
  - www. www.clinicaltrialsgps.com/search-clinical-trials/trial-8895/?
  - More than 50,000 Genentech pediatric patients enrolled
  - 372 research centers in the US and Canada
  - Over 600 clinical investigators
  - ~170,000 patient years of statistical data
  - Dataset closed
- Europe and North America: Pfizer International Growth Database (KIGS)
  - Originally established by Pharmacia in 1987 as Kabi International Growth Study
  - Data investigating GH treatment in children and adolescents with short stature
  - More than 60,000 patients from more than 50 countries
  - Separate registry: KIMS includes data on adult patients with GHD
  - Dataset closed
- Australian and New Zealand Growth Database (OZGROW)
  - Established 1989 following the introduction of synthetic human GH to Australia
  - www.ozgrow.com
  - More than 5,000 children from Australia and New Zealand registered and followed
- Serono Growth Hormone Registry
  - Established 1998
  - www.endserono.com
  - Dataset closed
- Europe and North America: NovoNordisk Answer Registry
  - Established 2002
  - www. www.novonordisk-trials.com/Website/…/registry
  - Dataset closed
- Americas, Asia, Middle East and Europe Lilly Genesis Study
  - Established 2002

During treatment, **monitoring for thyroid dysfunction and for adrenal insufficiency** is important as are following

bone mineralization issues with sequential vitamin D and bone density DXA scans for hypovitaminosis D, osteopenia and osteoporosis. It is felt that sometimes when GH is administered particularly when the diagnosis seems initially to be isolated GH deficiency, thyroid functions deteriorate and hypothalamic and/or hypopituitary hypothyroidism shows up over time. This may not show up until the teenage years or even the young adult years so that prolonged endocrine followup is needed in such patients as well as awareness of subtle signs and symptoms to heighten earlier diagnosis before symptoms show up. Similarly, secondary or tertiary adrenal insufficiency also may become apparent only after GH sufficiency is established during GH treatment so here too, awareness makes it possible to make the diagnosis before an adrenal crisis or death occurs. What starts out and appears to be isolated GH deficiency may, in fact, be more subtle or partial hypothalamic or hypopituitary insufficiency or deficiency. Therefore, periodic assessment by interval history and physical examination as well as periodic laboratory reassessment of thyroid function and adrenal functions is important to optimize health, perhaps indefinitely. Assessment for lipid abnormalities, cardiac problems, other neurologic abnormalities as well as osteopenia and osteoporosis also are important to be part of the advice provided to patients and family members periodically to promote such appropriate long-term endocrine assessment and followup, optimize health, address problems early rather than late and potentially prevent severe long-term associated consequences of missed diagnoses/treatment opportunities.

During GH treatment, increases in T3 values and decreases in free T4 values may occur[1] even without invoking subtle abnormalities of the hypothalamus or pituitary system. More rapid conversion from T4 to T3 also may suggest hypothyroidism and such patients may benefit from adding thyroxine to GH treatment even without any overt clinical symptoms or signs although this remains somewhat controversial. Routine thyroid hormone treatment, however, is not needed but ongoing monitoring would be prudent.[25]

Similarly, changes in serum cortisol values [26] usually without concomitant rise in ACTH levels may indicate subtle hypoadrenalism and subtle symptoms such as fatigue or sleep disturbance as well as mild hypotension may be reversed with addition of cortisone as part of the replacement protocols. Caution is especially important if any anesthesia is being considered for any other reason (ie. dental procedures, appendectomy) so that stress doses of cortisone can be provided and health care personnel made aware of the potential for hypotension and/or hypoglycemia. Depending upon the primary diagnosis and initial assessment of need for GH treatment in the first place, some conditions have a natural history where years later, hypothyroidism or hypoadrenalism become apparent even when there is no ongoing need for GH per se. Specific questions concerning learning difficulties and neurocognitive issues should be more routine in such patients especially when children and teenagers or young adults are still in school. This author suggests not only baseline thyroid functions and adrenal functions but at least annual assessment of sequential thyroid functions and adrenal functions to be sure that no subtle abnormalities arise and using such a monitoring protocol, no hypothyroidism or hypoadrenalism has gone undetected in our practice. We too have witnessed the late need for either thyroid and/or adrenal hormone replacement as well as common need for addressing lipid and hypovitaminosis D situations to promote optimal cardiac health as well as optimal bone mineralization. While osteoporosis has been diagnosed more than would have originally been suspected, many of our GH treated patients have had significant osteopenia, but without early fractures documented, so we are hopeful that correcting the low calcium and mineral intake, as well as low vitamin D intake coupled with tracking DXA scans every few years into the adolescent and young adult years will help us identify and ameliorate/treat such problems effectively.

Metabolic syndrome and **glucose intolerance** as well as **hyperlipidemias**[24] also may be more common in those with GH insufficiency or deficiency. Depending upon primary diagnosis and rationale for GH treatment, similar to thyroid and adrenal issues discussed above, some such conditions are known to be associated with obesity or with the metabolic syndrome itself. This author's practice has been to document initial fasting glucose levels as well as fasting lipid baseline levels as part of the pre-GH treatment phase of investigations, often when the GH stimulation testing is done. If there is already glucose intolerance and/or positive family history of metabolic syndrome or its component parts, usually asymptomatic, and especially if there is associated weight excess/obesity, then such patients should also be monitored periodically for changes in glucose tolerance since this may represent a pre-diabetes situation with or without insulin resistance. During GH treatment, usually excess weight reverts with successful height acceleration. Higher GH doses can contribute to glucose intolerance *per se* during therapy so efforts to avoid undertreatment as well as overtreatment both are important to consider by the treatment team. If lipid abnormalities persist and there is no specific hormone insufficiency attributable, then consideration for physical exercise recommendations, dietary recommendations and/or standard lipid lowering medications should be considered.

Disproportionate growth has been a theoretical concern of using GH therapeutically.

Titration against IGF-1 levels periodically has been a method of trying to minimize such "iatrogenic acromegaly" and are also actually quite rare.

Acromegaloid features such as large hands and feet occasionally are seen even when no elevated IGF-1 levels or excessive dosage is used and such "side effects" are sometimes disturbing enough that patients will opt to discontinue successful GH treatment as a result. Usually such effects are bilaterally and usually occur with both hands and feet simultaneously but may be more noticeable in the

hands. Such effects do not seem to regress, however, once they occur and the exact explanation is rarely elucidated.

A separate problem has arisen in the previous decade with IGF-1 measurements utilized for titration dosing of GH. In some laboratory methodologies, falsely elevated IGF-1 have occurred because of interference with the heterophile antibodies used in the testing and measurement process. This group of patients has not been studied very well, don't usually have any physical stigmata (ie. not larger hands or feet, not disproportionate or acromegaloid features) but it makes it difficult to move ahead with higher GH doses based on trying to maintain IGF-1 levels in the 50-80th %ile for age and pubertal status rather than just on a weight based dosing protocol. Changing laboratories and duplicate testing in different laboratories using different methodologies sometimes suggests this laboratory dilemma is occurring.

Pseudotumor cerebri seems to occur in about 1:1000 GH treated patients.

This is not related to higher or lower dosage or to compliance issues and all the registries seem to confirm similar occurrence rates. Adolescents and those who are obese seem to be at higher risk than thinner and younger patients. Cerebral edema and fluid retention are likely reflected by the antidiuretic effects of GH and/or IGF-1 perhaps with some changes in renin and aldosterone. When fluid accumulates, benign intracerebral pressure increases occur and such symptoms as new and unexplained headaches, subtle neurologic findings, vision loss, nausea and vomiting as well as clinical papilledema may occur. Patients with pre-existing chronic renal disease and those with Prader Willi Syndrome may be at more risk and those with more severe GH deficiency also may be at more risk than those with neurosecretory GH deficiency or milder insufficiency syndromes in some studies. There does not seem to be any particular genetic subset of individuals yet identified at higher

risk, however, aside from those with Prader Willi. Patents and their family members should be advised of such risks of cerebral edema, when to contact the health care team for evaluation of such new symptoms and that cessation of GH usually resolves the problem. Sometimes diuretics or even neurosurgical shunt and steroid treatment is needed for severe cases of pseudotumor cerebri. Fundoscopic examination should be done at diagnosis, at start of GH treatment and periodically (at least annually) in all GH treated patients and especially anytime new symptoms arise with neuroimaging and neurosurgical consultation as appropriate and available.

Slipped capital femoral epiphyses (SCFE).

GH treatment causes changes in the epiphyses and these changes may be associated with increased risk for SCFE just as any time of increased/rapid growth in or around adolescence poses similar increased risks. This is thought to be related to increase in growth plate proliferation and hypertrophy. SCFE is also associated with obesity and also associated with untreated GH deficiency as well as hypothyroidism. Those with the most severe GH deficiencies and who seem to respond the best of all GH treated patients, often with the lowest GH replacement doses, are also more at risk of SCFE than other patients. As with cerebral edema, such issues should be openly discussed prior to starting GH treatment. Periodically, questions about limping, hip or knee pain should be ascertained with a reminder to notify the health care team should conditions change or new concerns arise between follow-up visits. Efforts to reduce obesity would be expected to be helpful and to reduce SCFE risks. SCFE is thought to occur based on registry data in about 1:1000 GH treated patients.

Malignancy.

The most worrisome concern with GH therapy has always been the fear that providing increased GH would facilitate the development of cancer since GH could be

mitogenic especially if supraphysiologic doses are given, or periodic increases in IGF-1 levels after pharmacologic administration of GH may produce similar effects. Some GH patients are treated because initially they had a malignancy and either the malignancy itself, its anatomic position or the treatment for the malignancy induced the GH lack. Such patients, have been studied on numerous occasions in various centers around the world, including specifically specialty cancer centers and, with the help of the GH registries, it does not appear that there are more primary cancers or secondary/recurrence of cancers in those treated with GH. Some studies have documented concerns about increased leukemia but other studies have refuted such findings.[1,27]
Long term health issues for those treated with GH have also been unknown and some studies have suggested potential problems but research continues to track such issues.[28,29] The most recent safety review from the society position papers and long term registry reports[30,31,32,33,34,35,36,37,38,39,40] continue to report some increase in type 2 diabetes mellitus incidence compared to the general population but most cases had other diabetes risk factors. There also was no increase in hemorrhagic strokes and risk of death or primary cancer was not elevated in GH-treated children.

Prader-Willi syndrome(PWS) [41]

PWS is the most common known genetic cause of significant obesity in children. It is associated with abnormalities on the 15th chromosome, occurs in both boys and girls equally and appears in all racial groups. Estimated prevalence is highly variable and in some studies as low as 1:8,000 and in others as rare as 1:25,000.

In infancy, there is unexplained hypotonia, sometimes also poor sucking and there may be low birth weight for gestational age. Slow developmental landmarks and sometimes frank failure to thrive and poor weight gain persist for the first few years. Later in childhood, the food situation changes without obvious explanation and there is significant

lack of satiety, overeating and overt frank obesity. The hypotonia persists and there is also often poor growth, short stature and then lack of sexual development.

The food compulsions and unsatisfied appetite can be very significant and often become a source of family stress as parents are advised to restrict calories and increase daily activity only to be faced with seeming noncompliance and even hoarding food behaviors. These food issues generally last all the rest of the lifetime. Weight control sometimes requires locking the kitchen or cabinets where food is stored.

Caloric restrictions and increased activity/exercise energy expenditure can be successful but strict and consistent behavioral approaches are often needed. Levels of ghrelin in those with PWS are elevated and may play a role in the orexigenic factor driving their often insatiable appetites.

GH treatment has not only helped with achieving genetic height potential but seems also to help counter-balance the metabolic disadvantage in PWS with sometimes dramatic weight loss and weight maintenance while continuing GH treatment. (see pre and post GH treatment *Figure 20*).

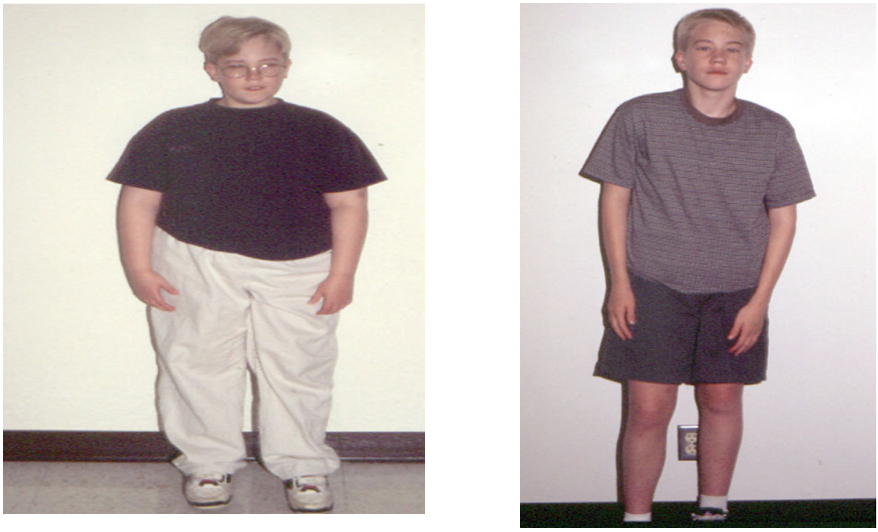


Figure 20A & 20B. PWS Pre-GH Treatment and 2 years later

Average IQ is 70, but even those with normal IQs almost all have some type of learning differences. Social interactions are affected and muscle weakness and generalized hypotonia persist.

The genetic cause of PWS is loss of paternal genes occurring from three main genetic errors with about 70% having a deletion in the paternally contributed chromosome 15. 25% have maternal uniparental disomy (UPD) with no paternal chromosome 15 but two maternal 15s. About 2-5% have an error in the "imprinting" process that makes the paternal chromosome 15 nonfunctional. Distinct facial features in a hypotonic infant poorly feeding can lead to the diagnosis in infancy whereas voracious and uncontrollable eating and persistent weight gain and frank obesity in a child who is hypotonic with behavioral or learning problems should cause some suspicion of PWS. Specific DNA and FISH genetic testing allow proper diagnosis and, in the future, may provide some more specific immunotherapy to address some of these significant problems.

Hypogonadism usually from 3^{o} hypothalamic or 2^{o} hypopituitary hypogonadism is associated with small phallus, small testicles and poor or absent pubertal progression spontaneously in older children and adolescents/adults and can contribute to otherwise unexplained short stature.

GH can be deficient in an absolute sense, relatively deficient and suggesting insufficiency or neurosecretory GH deficiency or may be normal but often with unexplained lower IGF-1 levels than stimulation testing would otherwise suggests. Treatment with GH has been successful (unrelated to absolute or relative GH deficiency) in normalizing height progression and allowing final adult height to be similar to mid-parental height ranges if treatment is started early enough. Testosterone treatment for males and estrogen treatment for females helps normalize pubertal secondary sexual characteristics as well as helps complete and mimic the normal pubertal final steps of growth and development. However, sometimes testosterone treatment significantly worsens behaviors especially if there is depression or anxiety

as well as aggressiveness and anger management issues. OCD-like behaviors, worsening aggressive behaviors, temper dysregulation dysphoria all may increase even without gonadal hormone treatment and behavioral issues may worsen in the teenage and adult years. Family awareness, early addition of psychologists and social workers skilled with such difficult multifactorial problems can be extremely helpful.

GH treatment is especially interesting since it helps correct some of the obesity and metabolic syndrome issues associated with the uncontrolled satiety while also optimizing height. BMI decreases, body fat percentages are decreased and lean boy mass increases with GH treatment.

Osteoporosis is also more common and treatment with appropriate calcium, mineral and vitamin D supplements often required; some studies of GH treatment have suggested that this may help as will appropriate sex steroid replacement since both GH and testosterone/estrogen are needed for optimum bone mineralization.

Sleep apnea is also present and there have been some concerns that GH may worsen such apnea or even contribute to cardiorespiratory death[42] in PWS patients so that some endocrinologists have been reluctant to institute or continue GH treatment when such studies became better known and acknowledged. More research into such risk factors needs to occur to answer such questions about GH treatment to try to determine if the obesity and neuropsychiatric as well as sleep abnormalities are the primary risk factor and whether or not GH treatment adds to or decreases such risks.[43] Numerous other physical and behavioral issues also occur in association with PWS and these too require coordinated ongoing care via dental, genetics, ophthalmology, gastrointestinal, orthopedic, cardiac, neurologic, psychiatric, psychologic, educational and endocrinological consultations.

Down Syndrome[44]

Small size already is present with most Down Syndrome patients at birth and Down Syndrome growth charts are

available for comparison with normal boys and girls data. While lower GH and IGF-1 levels have been documented in Down Syndrome patients as a possible explanation for their relative short stature and obesity, results with GH treatment have not been as robust as with other conditions.

Concerns about leukemia risks and metabolic syndrome/diabetes risks with GH have limited enthusiasm for DS GH treatment.[45]

Autoimmune Hashimoto's thyroiditis with hypothyroidism and hyperthyroidism are more common in Down Syndrome patients as is celiac disease and both, of course, can have a major impact on growth parameters. Treatment of thyroid dysfunction and celiac disease follows standard protocols and many, including this author, suggest yearly thyroid and celiac screening tests as well as assessment of glucose intolerance and vitamin D levels but not routine GH testing or GH treatment. Early and periodic DXA scans looking for osteoporosis and osteopenia in Down Syndrome patients also seems to be worthwhile because of higher abnormalities detected that may help prevent future actual fractures.

Turner Syndrome[46, 47, 48.]

Resulting from a complete or partial absence of one X chromosome, Turner Syndrome (TS) is the most common occurring chromosomal abnormality in females. TS was first described in 1930 by Ullrich and then "re-described" by Turner in 1938. Numerous problems present in the neonatal period but usually are not diagnosed unless there has been prenatal chromosomal amniocentesis on the fetus, usually for other reasons (ie. older maternal age). Thereafter, problems include not only significant short stature but also multiple birth anomalies, cardiac and gastrointestinal problems including celiac disease and inflammatory bowel disorders as well as renal problems and hypertension. Primary gonadal failure is a hallmark of TS and combination treatment with GH, estrogen, and progesterone have produced significant improvement in quality of life and final height as well as ways

to mimic more normal pubertal development itself. Psychosocial and learning problems add to the complexities of TS as do eye, ear and orthopedic issues. Much is known about these issues and yet good pediatricians and general practitioners as well as nurses most of the time still fail to even consider TS as a diagnosis even when numerous problems associated with TS are readily apparent and dealt with individually.

About 50-60% of TS patients have a single X, 45XO karyotype while chromosomal mosaicism occurs in about 15%, structural anomalies of the X chromosome (isochromosomes, partial deletions or ring chromosomes) and 15% have other combination abnormalities and mosaicisms of the X chromosome. Overall TS occurs in about 1:2500 girls in the US and remains markedly underdiagnosed despite being well known for nearly the past 90 years.

Growth failure in TS begins in utero, is significant by mid-gestation and birth length is usually below the mean for female infants. Thereafter, growth is progressively slower than normal girls but with some overlap for the tallest of the TS patients with the shortest of the general female child and adolescent population. As the girl moves into her pre-teen and teenage years, however, if the diagnosis is not already made, then primary hypogonadism becomes apparent with lack of significant thelarche and lack of menarche. This is most apparent in the classical 45XO TS patients whereas those with mosaicisms and structural abnormalities of the X chromosome, some will have relatively normal thelarche, pubarche and menarche while others will initiate puberty but seem to stall before full completion with lots of individual variability in such details. Early growth failure, however, occurs with all karyotypes of TS. On average, height is below the 5th percentile for 5 years before diagnosis of TS suggesting that attention to growth charts, once again, might allow earlier diagnosis and therefore earlier start of treatment with better ultimate final height outcomes. This is true in all parts of the world and follows the same pattern in relatively tall Scandinavia and Germany as in parts of the world where

there are shorter adult women. Average TS height untreated is about 20 cm below mean for mid-parental height. As with Down Syndrome patients, attention to higher risk of celiac disease and thyroid dysfunction is important and may interact with height achievement particularly if subtle and not fully symptomatic so that recognition takes longer before treatment is begun.

Multiple international clinical studies document relatively normal GH stimulation testing but low-normal or normal IGF-1 levels when trying to elucidate causes for the short stature associated with TS. TS specific growth charts (*Figure 4*) are available from www.magicfoundation.org as well as the Turner Syndrome Society and the CDC websites among others. TS patients who fall further away from the standards on the TS charts themselves should be investigated for other co-morbidities that impact on growth. There is a classical dose response when prescribing GH in TS and earlier diagnosis allows for earlier institution of treatment with GH resulting in improved height velocity as well as final adult height achieved.[49] Combining oxandrolone with GH can be used in a combination treatment protocol to augment growth.[50] Earlier diagnosis and earlier start of GH treatment in TS also allows for the possibility of earlier institution of estrogen treatment and therefore allowing TS girls to move into puberty closer to peers.[51] Early or late estrogen provision does not seem to have a major effect on final adult height although there are some studies suggesting that slightly delaying initiation of estrogen therapy shows some benefit in final height achieved. Oxandrolone is given at a dose of 0.0625 mg/kg/day orally at about age 8-10 and GH given at an initial dose of 0.05 mg/kg/day with consideration for pubertal dose increases to 0.1 mg/kg/day based upon clinical pubertal status, IGF-1 levels, height achieved and annualized height velocities documented.

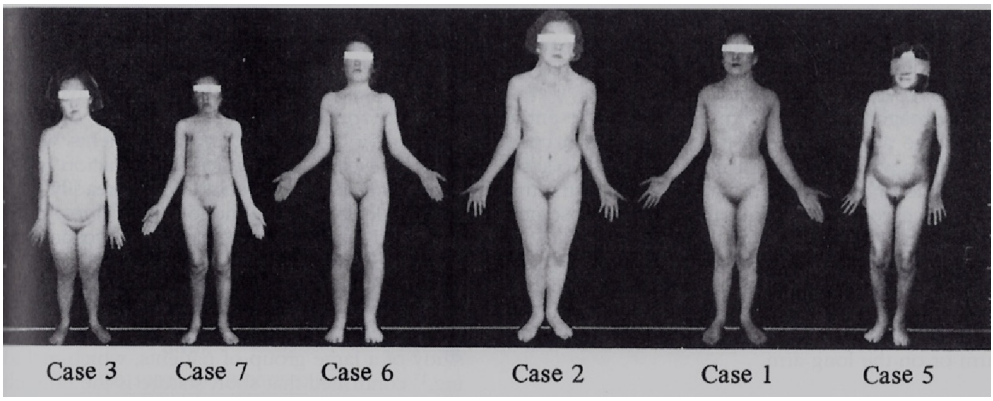


Figure 21. Original Turner patient photographs with web neck, short stature, cubitus valgus.

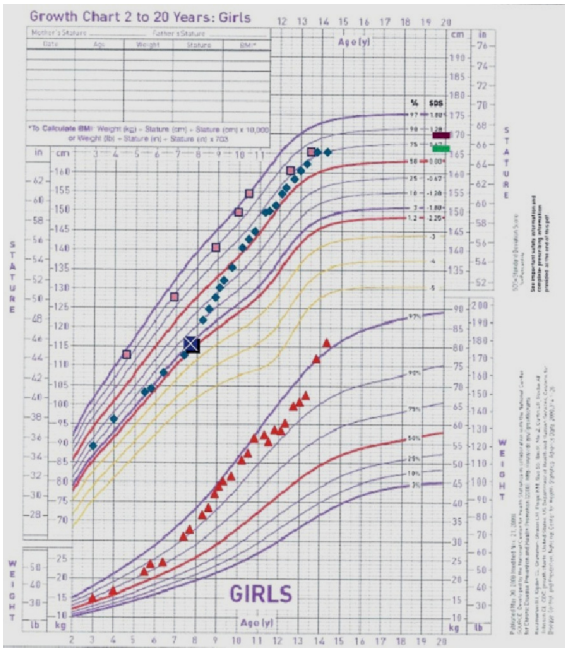


Figure 22. Turner growth chart with missed growth deceleration for several years prior to diagnosis and then post-treatment with growth hormone and then with estradiol added resulting in final height near mid-parental expectations.

Noonan Syndrome [52] [53]

Originally described by Flavell "incorrectly" in 1943 as "male Turner's Syndrome," but redescribed by Noonan in 1963 with Ehmke and then in a more expanded fashion in 1968, Noonan Syndrome affects between 1:1000-1:2500 live births so is somewhat more common than Turner Syndrome although even less likely to be thought about or diagnosed by general physicians or general pediatricians !

As with TS, Noonan patients have rather distinct problems that should allow the possibility of diagnosis much more often than takes place so one would assume that these problems in an active practice or clinic are more subtle than expected. Males and females are affected and Noonan Syndrome is thought to be an autosomal dominant or recessive condition with short stature, right sided (rather than left side heart problems in TS), early feeding problems and characteristic face and body habitus including web neck, clinodactyly, nonspecific learning and intellectual difficulties. Mental retardation may be present in 25-50% of Noonan patients.

New mutations occur in about 80% of Noonan patients but 20% seem to reflect a family pattern where especially distinct facial and ear appearance can provide another diagnostic clue (pictures of parent and child). Short stature is present in about 80% of Noonan patients and cryptorchidism in about 60% of male Noonan patients. Delayed puberty can occur in both sexes. Low set ears, broad nose, low posterior hairline, high forehead, small triangular jaw or micrognathia, hypertelorism, ptosis, strabismus and nystagmus as well as pectus (both excavatum and carinatum) are some of the distinct physical features that might provide a clue for considering this diagnosis.

A subset of Noonan patients also have bleeding difficulties especially problematic after tooth extraction or postpartum. Easy bruising associated with low platelet counts and blood clotting problems exist in this subset. As in most genetic conditions, not all abnormalities are present in every patient.

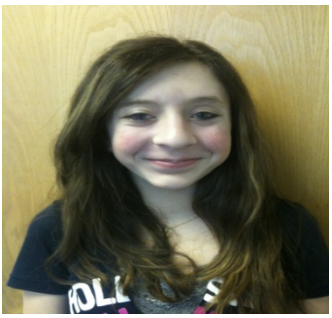
Pediatric cardiologists, hematologists, gastroenterologists, neurologists, psychologists as well as learning specialists should be particularly attentive to considering Noonan Syndrome as a diagnosis once they familiarize themselves with these striking features yet this too does not seem to happen anyplace in the world.

The most common genetic mutation is called PTPN11, a protein tyrosine phosphatase mutation occurring on the long arm of chromosome 12q24. This mutation explains about 50% of Noonan patients and especially those with pulmonary valve stenosis, cardiac septa problems, facial dysmorphology and short stature. KRAS mutations (Kirsten Rat sarcoma) explain another ~3-5% of Noonan phenotypes with somewhat more extensive dysmorphology than the PTPN11 group. RAF1 mutations (v-raf-1 murine leukemia viral oncogene homolog 1) add another ~3-17% prevalence and especially in the subset with hypertrophic cardiomyopathy. SOS1 (Son of Sevenless 1) mutation explain another ~17% of Noonan patients with less common growth disorders but more cardiac issues and facial dysmorphology. This leaves about 20% of Noonan patients who do not have a genetic mutation identified (yet) but whose clinical features seem to fit the clinical diagnosis including short stature. Noonan syndrome growth charts are now available (*figure 3*) and are particularly helpful since they include normative data on the same charts for ease of comparison.

Untreated Noonan adult male patients average 162.5 cm (63.9 inches) and adult female patients average 152.7 cm (60.1 inches) in Caucasian populations studied to date. About 50% of Noonan patients if untreated will be significantly short as adults. Research studies suggest that Noonan patients are not classically growth hormone deficient, do not have consistently low IGF-1 levels and have inconsistent results following GH stimulation testing so that there is no consensus among researchers or clinicians to date. Some studies suggest GH insensitivity rather than a true GH resistant state. In many parts of the world, Noonan Syndrome diagnosis *per se* is sufficient to offer GH treatment because research findings

when treatment has been provided have been very successful in improving growth velocity and final adult height. Most of the studies were nonrandomized but one study sponsored by NovoNordisk was a prospective, randomized lower and higher dose study of Noonan patients for two years and then finished to final height. Height velocity increased from 9-10 cm in the first year and 7-8 cm in the second year with significant improvement in final height standard deviation with ongoing GH treatment as well.[54] [55] Androgen therapy sometimes is also needed as adjunct therapy in the Noonan subset with significant clinical cryptorchidism and hypogonadism based upon standard LH, FSH, testosterone and Tanner staging criteria. Usual Noonan Syndrome GH dosing starts at 0.05 mg/kg/day, as in Turner Syndrome, and can be increased in puberty to 0.1 mg/kg/day to titrate and optimize IGF-1 levels in standard protocol fashion. No cardiac patients with Noonan Syndrome have shown any cardiac deterioration in any of these studies. Earlier diagnosis and beginning treatment seem to show greater promise than later start of treatment, as with all examples of short stature responsive to GH treatment. Follow-up cardiac echocardiography and collaborative evaluations by pediatric endocrinologists and cardiologists seems prudent to identify subtle problems that so far have not shown up. Attention to vitamin D status and osteopenia/osteoporosis is important in Noonan Syndrome and treatment should facilitate optimizing final height as well as bone mineralization.

Figure 23. Typical Noonan patient photograph with high forehead, mildly underdeveloped nasal bridge, widely spaced eyes, low set posteriorly rotated ears, web neck, slight pectus excavatum, pulmonary stenosis and short stature



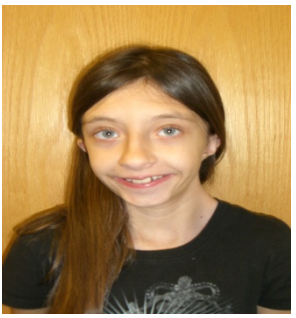


Figure 24. Katlin S and Marissa B Photographs.
Typical Noonan facial features but negative genetic studies and no significant cardiac problems but unexplained short stature with low IGF-1 levels but normal GH stimulation testing. Both responded in excellent fashion to GH treatment.

Brandon R.
Noonan Syndrome Case Vignette.

Brandon presented with short stature associated with known and genetically confirmed PTPN11 Noonan Syndrome. He had some neonatal feeding difficulties requiring gastrostomy tube feeding for the first year or so of life, easily diagnosed and surgically corrected pulmonary stenosis and some nonspecific mild learning difficulties as well as classical facial features including web neck, ptosis, hypertelorism, pectus excavatum, clinodactyly of fifth fingers bilaterally and was referred not by his pediatrician but by his pediatric genetics physicians after a Noonan Syndrome GH lecture delivered by this author. Baseline lab work was okay with low-normal IGF-1 but no stimulation testing was done and he was started on standard protocol 0.05 mg/kg/night GH

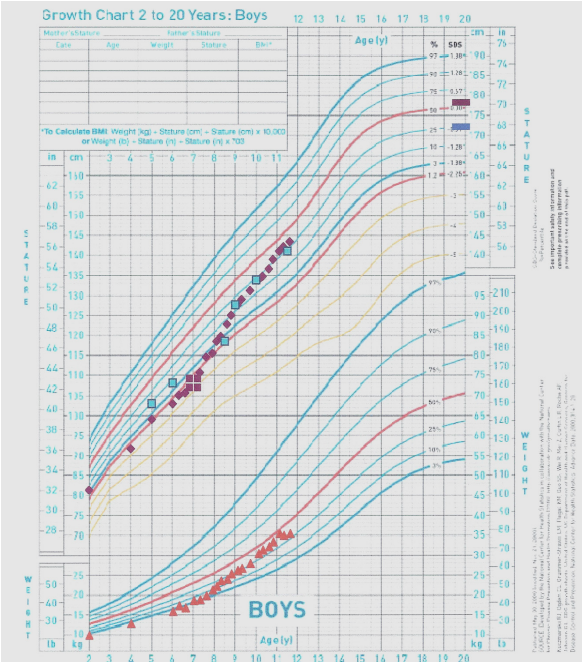


Fig 25. Brandon R.-
Noonan Dx as newborn with pulmonary stenosis

injections with an excellent and almost immediate height acceleration that has continued over the past 5 years. With the recent onset of testicular enlargement and increasing DHEAS levels, dosage has been increased to 0.1 mg/kg/night following the Cohen/Rosenfeld pubertal protocols and to be titrated to achieve mid-range IGF-1 levels if possible.

Post-SGA without spontaneous catch-up [56] [57]

Children born small for gestational age (SGA) are defined as having a birth weight and/or length less than 2 standard deviations below the mean for their sex and gestational age (ie.<3rd%iles).

Intrauterine growth retardation/restriction (IUGR) is a synonym. About 10-15% of SGA children fail to show spontaneous catch-up growth postnatally by 2-3 years of age and likely constitute a relatively large population of short stature children who consequently end up with significant adult short stature. In children born SGA, the greater the birth length, the greater the chance of spontaneous catch-up growth. Catch-up growth is not associated with sex, gestational age at birth or multiple births.

Bone age in SGA children does not accurately predict final height because of the association of earlier than expected puberty (possibly premature adrenarche) and therefore relatively shorter duration pubertal growth spurt.

Tests of the GH-IGF-1 axis have been unremarkable although low levels of IGF-1 and IGF-BP3 in utero have been postulated. Insensitivity to GH and IGF-1 also has been studied as an explanation since higher GH and IGF-1 levels have also been seen in some SGA studies.

Premature adrenarche, insulin resistance, ovarian hyperandrogenism, reduced pubertal growth, metabolic syndrome including glucose intolerance and hyperlipidemia and finally type 2 diabetes, hypertension and more cardiovascular disease in adults s/p SGA have all been observed and perhaps linked to the initial insults of fetal malnutrition/undergrowth[58] with metabolic “memory” playing some role.

GH treatment studies have been positive and approval for GH treatment in North America as well as the European Union

and other parts of the world have occurred with research studies documenting improved height velocity, increased height standard deviation scores, better response with higher rather than lower GH dosage (as in Turner and Noonan patients) and no adverse effects vis-à-vis lipids, glucose tolerance, weight, blood pressure or lipid profiles but some concerns vis-à-vis insulin resistance, glucose tolerance, metabolic syndrome, pre-diabetes mostly in youngsters who already have or who develop other comorbidities (ie. obesity) and/or high risk family or by history (ie. SGA) known topredispose to diabetes and its forerunners. If earlier than desired adrenarche or full puberty occurs in such SGA patients, as is common, then addition of GNRH analogs used to inhibit gonadotropins and thus delay pubertal progress has also been shown to be helpful to maintain the height gain that occurred prior to the early puberty by keeping epiphyses open for several more years while GH effects continue. [1]

ISS: **familial vs nonfamilial** [59 60 61]

Idiopathic short stature (ISS) is defined as a condition in which the height of the child or adolescent is more than 2 standard deviations scores (SDS) below the corresponding mean height for a given age, sex and population group without evidence of any systemic, nutritional, endocrine or chromosomal explanation.

ISS is a diagnosis of exclusion. Usually ISS children have a history of normal birth weight and length and are growth hormone sufficient by virtue of normal IGF-1 levels, normal IGF-BP3 levels and normal growth hormone following stimulation tests. This is a markedly heterogeneous group of children and adolescents and this category of ISS may include as many as 2/3 of all short children by some estimates. Those with constitutional delay of growth and puberty as well as familial short stature may fit into this diagnosis of ISS.

Frequency of referral of such children depends upon local politics and health care coverage and costs, socioeconomic status and whether or not society perceives short stature as a possible “disability” worth investigating and

potentially treating or not. The whole concept of ISS has stirred enormous medical, ethical and economic debates both within and outside of the pediatric endocrinology community without definitive research and scientific based studies to answer such questions yet. Big problems exist in defining ISS and in predicting whether or not a child, even one with delayed bone age, will actually continue to be delayed in pubertal timing and pubertal growth achieved, whether or not such a child as a future adolescent will have a shorter or more prolonged pubertal growth phase and whether or not such a child will, as a teenager reach the mid-parental height expectations estimated, follow one or another parent's height percentile to the exclusion of the other etc.[62]

Predictions prospectively, of course, are much more nonspecific compared to retrospective analysis of how the child concludes his or her growth trajectory and where that child as a young adult winds up. So the key question medically (and perhaps also ethically and economically) is to what degree ISS should be considered a normal, biologic variant and under what situations is treatment with GH justified and not just "cosmetic".[63] Such decisions are based upon how short the child is at presentation (SDS), likelihood for an "acceptable" final adult height (greater than ~150 cm, ~59" for females and greater than ~160 cm, ~63" for males), psychological stress associated with short stature (teasing, bullying, family dysharmony and parental guilt), convincing-enough scientific treatment evidence that growth can be accelerated safely and that quality of life will also improve. As with most treatment strategies with GH, earlier onset of GH treatment seems to be associated with taller final height outcomes and boys seem to benefit more than girls (perhaps reflecting later diagnosis of short girls, in general, than boys and relatively earlier puberty in girls vs boys). As with other conditions treated with GH, temporarily blocking puberty to keep epiphyses open with gonadotropin blockade seems also to be a helpful adjunct. It is expected that future genetic studies will identify subsets of this ISS population in which treatment options and treatment response may be better

classified than is currently possible. SHOX genetic testing is currently available in many parts of the world and, although expensive, may detect mutations of the SHOX gene that would potentially explain otherwise idiopathic short stature and thus also facilitate GH treatment decisions. GH treatment is generally using a protocol of 0.033 -0.067 ugm/kg/day, most commonly 0.05 ugm/kg/day. Study data and registry data suggest positive responses to such GH treatment protocols and is at least as efficacious as its use in other non-GH conditions for which GH therapy already has been approved and is utilized.[64]

Brian T - Case Vignette.

Brian presented with both weight and height deceleration between ages 2-3 which did not persist but also did not spontaneously self-correct. Screening tests all negative including normal SHOX testing and normal GH stimulation testing. Because of his expected final adult height significantly below both parents' height percentiles and their mid-parental values, he met criteria for ISS and was begun on GH treatment accordingly with a significant, positive therapeutic "challenge" (see growth chart in *Figure 26*). He continued to respond nicely reaching the 50th %ile for height and weight and maintaining this response until bone age began to advance spontaneously with slightly earlier than expected adrenarche. At this point, pubertal blockade was added with subcutaneous histrelin and this successfully delayed puberty and help delay epiphyseal advancement for several more years while GH treatment continued. Growth thereafter continued along the 50th %tiles until pubertal blockade was discontinued as planned and puberty allowed to proceed. Excellent final height results as documented in the growth chart in Figure 26. GH treatment discontinued without problems and no evidence of any ongoing hormone issues seen except for well treated hypovitaminosis D and osteopenia even off all other treatments.

Brent S.

Case vignette.

ISS not yet "allowed" by health insurance or governmental authorities and with evaluation totally negative at age 7-8 years, returned to pediatrician's care and follow-up. Shortly later, ISS diagnostic categories were approved for consideration for GH treatment and repeat consultation took place with decision to offer a one year GH therapeutic trial on followup consultation. Successful response moved Brent from approximately 3-4 SDS

below the mean to nearly the 10th percentile, allowed him to participate more fully in desired sports activities with peers without teasing or bullying and with improved quality of life reported. Current expectation is that he will reach approximately his mid-parental height percentiles or slightly higher if he continues on the same trajectory following standard ISS GH treatment protocols.

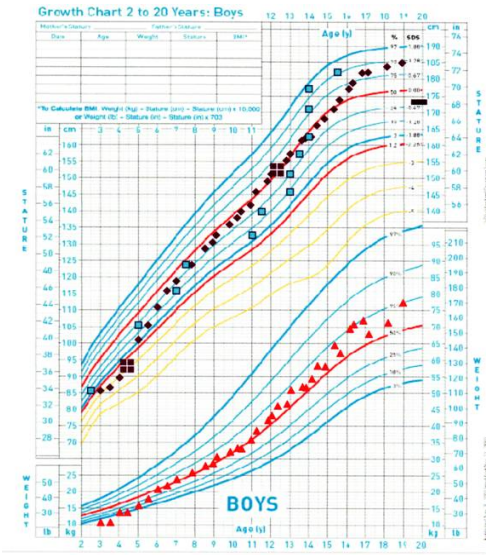


Figure 26. Brian T.
ISS patient growth chart w/GH treatment since age 4½ years, supprelin added from age 14-16½ years and GH discontinued at age 17 years.

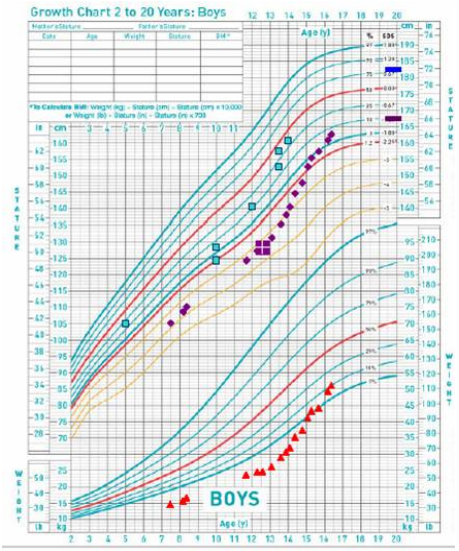


Figure 27. Brent S. ISS patient growth chart

Support:

Around the world there are several support groups that are excellent for family and patient information, blogs and chat-rooms. Many have local city, regional or national chapters. Some are listed here:

- Human Growth Foundation: www.hgfound.org
- Magic Foundation for Childrens' Growth: www.magicfoundation.org

- Turner Syndrome Society: www.turnersyndrome.org
- Noonan Syndrome Support Group: www.noonansyndrome.org
- Prader Willi Syndrome Association: www.pwsausa.org

Future directions.

More work on the genetics of short stature patients, growth hormone and IGF-1 and its axis needs to continue with the expectation that more specific genes and mutations will be elucidated, and as with Noonan Syndrome as a perfect example, different genetic markers will facilitate diagnosis and perhaps even help determine higher or lower GH dosage, which conditions would benefit (or not) from consideration for GH treatment etc. Work also continues on ways to make GH available for use by the body in non-injectable format and in reducing the very high costs of current GH preparations as well. Educational efforts aimed at parents and the public as well as nurses in clinics and offices and nurses at schools, general pediatricians and general practitioner physicians to remind them of these new discoveries and new initiatives so that they may become better clinicians, consider better ways to identify short stature and introduce the possible consideration for such evaluations and treatment also needs to continue. More recent pharmaceutical preparations offering long-duration GH products to potentially replace the usual need for daily subcutaneous GH injections look promising if expense barriers can be overcome. Scientific studies with these longer-acting growth hormone injections all suggest good efficacy, no different safety concerns and good acceptance by patients and families.

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ROHHAD SYNDROME

A RARE DISEASE WITH SEVERE OUTCOME

Cecilia Lazea

Introduction

ROHHAD (rapid-onset obesity with hypoventilation, hypothalamic, autonomic dysregulation) syndrome is a rare disease characterized by disorder of respiratory failure and autonomic dysregulation with endocrine abnormalities. Neuroendocrine tumours can be associated in more than half of cases. The condition is a rare disease and have a severe outcome because of high morbidity and mortality.

Definition

Rapid onset obesity with hypoventilation, hypothalamic dysfunction and autonomic dysregulation (ROHHAD) syndrome is a rare disease first described by Fishman et all[1] and renamed ROHHAD by Ize-Ludlow et al in 2007.[2] The acronym ROHHAD describes the typical sequence of symptoms in the order of their appearance.

This disease is characterized by early and rapid onset of obesity associated with hypoventilation, autonomic dysregulation and endocrine abnormalities. Several reports

described additional clinical manifestations and neuroendocrine tumours (NET) as ROHHADNET.[3]

The diagnosis of ROHHAD syndrome is challenging due to unknown etiology, absence of confirmatory tests and is made based on clinical presentation. The clinical presentation is heterogenous, there are cases with marked endocrine involvement, while others exhibit marked behavioural disturbances or neural crest tumours. The condition is characterized by high morbidity and mortality rates.[4, 5]

Incidence

ROHHAD syndrome is a very rare disorder, about 100 cases being reported to date and it is considered a relatively new disease. Because of the explosion of the exogenous obesity in children worldwide, ROHHAD syndrome have to be considered for differential diagnosis in these cases.[6]

Etiopathogenesis

The genetic basis for ROHHAD has not been established, there are studies which have ruled out the mutations in several candidate genes, including *PHOX2B* (causative for central hypoventilation syndrome), *BDNF, TRKB, NECDIN, ASCLI, HTR1A, OTP, PACAP* (responsible for development and function of the hypothalamic, neuroendocrine and autonomic systems).[7-12]

A nonsense mutation was reported in the retinoic acid-induced 1 (*RAI1*) gene known to cause Smith-Magenis syndrome, in a patient with morbid obesity and clinical diagnosis of ROHHAD syndrome.[13]

Nevertheless, familial cases have been reported, suggesting that it may be a monogenic condition, but this assertion was not demonstrated.

Further evidence for immune-mediated etiology in the pathogenesis of ROHHAD syndrome was suggested in some cases.[14,15]

Clinical presentation

The onset of this disease ranges from 0 to 9 years, but the most common onset is in early childhood, at ages between 2 and 4 years, with hyperphagia and rapid weight gain. Children with ROHHAD syndrome usually have normal growth, development and general health prior to onset of symptoms. Clinical presentation of these patients is variable in severity and timing.[16]

Rapid obesity is often the first recognizable sign and is followed by hypothalamic disorders, autonomic dysfunction and alveolar hypoventilation.

Hypothalamic dysfunction may manifest as growth hormone deficiency, diabetes insipidus, central precocious puberty, hypogonadotropic hypogonadism, hyperprolactinemia, hypothyroidism, corticotrophin deficiency. These manifestations appear from months to years following the rapid-onset obesity.

Autonomic dysregulation may present as ophthalmologic abnormality, such as blurred vision, altered pupil response to light, strabismus, altered perception of pain, gastrointestinal dysmotility with chromic constipation or diarrhea, cold extremity, bradycardia, neurogenic bladder, excessive sweating, thermal dysregulation, syncope, urinary incontinence.

Behavioural disorders

Behavioural change is the most common form of cognitive dysfunction and the symptoms include mood changes such as irritability and aggression, fatigue, social withdrawal, poor school performance, intellectual disability, flat affect, hallucination, major depressive disorder, attention deficit disorder and psychosis.

Neurologic abnormalities consist in seizure, blurring of consciousness, sleep disturbance, developmental delay, gait disturbance, nystagmus, general weakness. Seizures may be related to episodes of hypoxemia due to inadequate ventilator support. Enlargement of the pituitary gland and generalized brain atrophy were also reported.[17]

Other clinical manifestations may be fever, rash, enuresis, headache, edema, pulmonary hypertension, cough, renal failure.

Hypoventilation is the most life-threatening feature of ROHHAD syndrome and can lead to cardiorespiratory arrest. Most of children with ROHHAD syndrome will have obstructive sleep apnea at early ages, but because this feature is often present in obese children, the connection with ROHHAD phenotype can be delayed. Other sleep disorders breathing described are central sleep apnea, abnormal ventilatory response to carbon dioxide and nocturnal hypoventilation. Hypoxemia and hypercapnia are present during sleep, but in more severe cases hypoventilation may also occur while awake. Early recognition of the spectrum of respiratory abnormalities can raise the index of suspicion of ROHHAD syndrome.[5]

Hypothyroidism, one of the most common associated endocrine disorders can influence the central ventilatory control based on decrease of oxygen consumption.[16]

Approximately 40% of the patients with ROHHAD syndrome will develop tumours of neural crest origin such as ganglioneuroma and ganglioneuroblastoma localized in the chest, abdomen or along the sympathetic nervous system chain. Hamartomatous masses with neural elements were also reported in one case.[16]

Diagnosis

The diagnosis of ROHHAD syndrome is based on clinical presentation and clinical course and involves a cooperative consultation by specialists in the fields of pneumology, endocrinology, oncology, psychiatry, ENT, cardiology, surgery, nutrition and psychology. There is no genetic testing available to diagnose this disorder.

The diagnosis is made based on the presence of following features:

(1) rapid-onset obesity starting in early childhood and alveolar hypoventilation during sleep;

(2) signs and symptoms of hypothalamic dysfunction,

(3) exclusion of other condition causing similar features, such as congenital central hypoventilation syndrome.

Rapid onset obesity and the most common endocrine disorders such as precocious puberty and hypothyroidism are very often the early recognizable signs.

Workup

Sequential comprehensive evaluation is recommended for children with ROHHAD syndrome as the clinical presentation is very variable.

Overnight polysomnography is used to evaluate the signs of obstructive sleep apnea and hypoventilation.

Imaging of chest and abdomen (CT, MRI) is used for neural crest tumour screening.

Echocardiography, cycle ergometry and 24-hour Holter monitoring provide a comprehensive cardiac evaluation.

A head up tilt test can be performed to assess the autonomic response to positional changes.

Neurocognitive testing is used for tracking the intellectual function.

Gastrointestinal motility studies should be performed in cases with severe constipation.

Complete evaluation of the endocrine function includes antidiuretic hormone secretion, IGF-1 secretion, thyroid function, prolactin secretion, gonadotropic function, corticotropic function.

Ophthalmologic findings should be evaluated by a paediatric ophthalmologist.[16]

Laboratory findings

The most common findings are hypoxemia, hypercapnia, dysnatremia (hypernatremia and hyponatremia), hyperprolactinemia, hypothyroidism, low or normal IGF1 level. Dysnatremia is linked with impaired water balancing

such as polydipsia or diabetes insipidus due to hypothalamic dysfunction.[16, 18]

Complications

Insulin resistance, diabetes mellitus, hypertrygliceridemia, progressive fatty liver disease, bradycardia, cor pulmonale, right ventricular hypertrophy, pulmonary hypertension, heart failure and scoliosis can be present. [7, 19, 20]

Mortality rate is high at 50-60%, due to hypoventilation, cardiopulmonary failure and cardiopulmonary arrest/.[5]

Treatment

Multidisciplinary care characterizes this condition and is very important for management of these patients for optimize the care and quality of life. This team includes pulmonologists, endocrinologists, cardiologists, intensivists, otolaryngologists, surgeons, gastroenterologists, neurologists, ophthalmologists, psychologists, psychiatrists, respiratory therapists, nurses, social workers. The family is another very important member of these multidisciplinary team. Early diagnosis and adequate conservative intervention are critical to optimizing the quality of life and neurocognitive outcome.

The treatment of ROHHAD syndrome is based on the clinical features.

The obesity control with diet and exercise is difficult to control and requires the intervention of a nutritionist.
Moderate exertion is recommended and pulse oximetry monitoring is required during exercise.

Hypothalamic dysfunction is variable and the treatment may include a strict fluid intake regimen and hormone replacement.

Hypoventilation may need artificial ventilation during sleep in the first years of evolution with progressive need for continuous ventilatory support (mask ventilation, bilevel positive airway pressure, continuous positive airway pressure,

mechanical ventilation and tracheostomy). These procedures may improve the quality of life and prevent sudden death and they must be available at home. [5, 16]

Early recognition of sleep disorders breathing and targeted therapeutic interventions will limit morbidity and mortality associated with ROHHAD syndrome.[5]

Regulation of ambient temperature is required in children with thermal dysregulation.

Stool softeners are indicated in children with constipation.

Antiepileptics and antipsychotics are indicated in children with neurologic disorders.

Antihypertensive medication can be also be useful.

Surgical removal is indicated in patients with neural crest tumours.[16]

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