PEDIATRIC ENDOCRINOLOGY AND DIABETES

2022 UPDATE

Editors:

Iulian P. VELEA
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EDITURA MIRTON

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Preface

The increasing prevalence of endocrine diseases, obesity and diabetes, as well as their impact on the health of the population from a young age, requires the continuous training of both pediatric endocrinology and diabetes specialists, pediatricians and even family doctors.

After two years of restrictions in which we had to organize the congress in an “online” format, we are happy to return to the organization in a physical format and to meet all of us again in Timișoara.

Respecting the purpose of the "ENDOPED" society of involvement in the professional training of doctors who are in contact with the pediatric patient, we offer all participants of the 9th National Congress of Diabetes, Nutrition and Pediatric Endocrinology a new volume "Pediatric Endocrinology and Diabetes - 2022 Update".

The concept of these annual "update" volumes, we hope, will meet your expectations.

The materials contained in this year's volume, as in previous years, we hope will succeed at least sensitizing the reader to the diversity and difficulty of endocrinology and pediatric diabetes problems that can be faced in current practice, becoming a competent provider of medical services even if he is not a specialist in endocrinology and pediatric diabetes.

Professor Iulian P.Velea MD, PhD
President of Romanian Society of
Diabetes, Nutrition and Pediatric Endocrinology.

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DOWN SYNDROME: GENERAL HEALTH AND ENDOCRINE ISSUES UPDATE

Stuart J. Brink, MD, PhD (Hon)

Down Syndrome (DS)[1,2] is the most common genetic birth defect associated with mental retardation[3] and one of the genetic disorders that can be identified clinically and verified genetically.[4]

DS was first described by John Down in 1866 and took almost 100 years until the cause of DS was identified.[5] DS occurs across all races and levels of society throughout the world. 95% of DS is caused by trisomy 21 thought to result from nondisjunction during maternal meiosis so that two copies of chromosome 21 do not separate and end up together in the same oocyte.[2]

About 3-4% of DS is caused by translocations of genetic material and about 1-2% caused by mosaicisms.[6] As such, antenatal or neonatal diagnosis in many parts of the world is feasible with alpha-fetoprotein screening (low levels), direct analysis of karyotypes or with FISH analysis of chromatin from chorionic villus sampling or amniocentesis.[7] [*Figure 1* (karyotype) and *Figure 2* (fluorescent trisomy blue spots)].

In many parts of the world where such technologies are not available or are too expensive, then physical characteristics of the newborn often readily identifies a neonate with DS. Such characteristics include downward slanting eyes (what used to be called “Mongolism”), protruding tongue, short hands, feet and trunk, wide spacing between the first and second toes (sandal-gap toes) and a single

palmar crease (simian crease) and some suspicions of congenital heart disease (see below).

Figure 1.

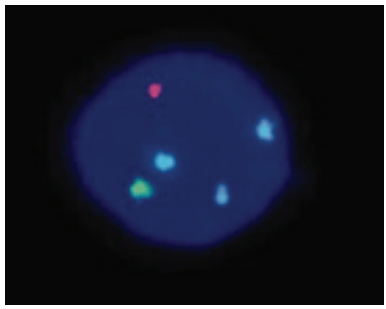

Figure 2.

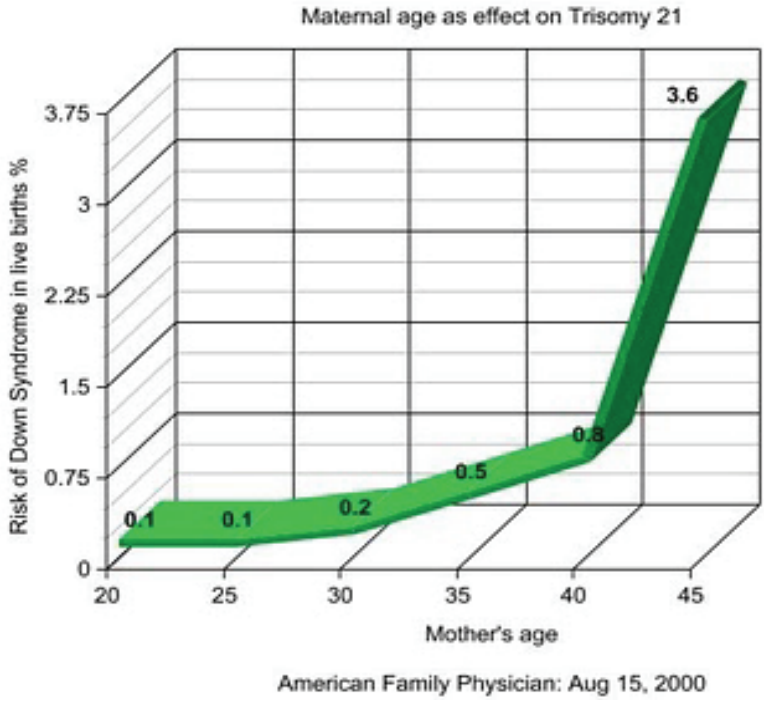

Figure 3. - Maternal incidence curve

Average incidence of DS is approximately 1:800 live births.[8] Incidence of DS increases with increasing maternal age: <1:1000 incidence if mother is less than 30 years old but steadily rising through about maternal age 40-45 where the DS risk is 1:35 live births. Some research suggests that 25% of DS genetic errors may, in fact, be of paternal and not maternal origin with rising paternal age also a factor in such genetic errors.[1]

Heart Disease[1]

About 50% of DS patients will have congenital heart disease with endocardial cushion defects, atrioventricular canal problems, atrial septal defects (ASD) or ventricular septal defects (VSD) all more common than the general population. Congenital heart disease occurs in some infants, however, who have normal cardiac physical examinations[7] so that screening tests (echocardiography) and cardiology consultation should be done on all DS infants in the nursery.

DS Guidelines recommend periodic cardiology followup screening as well in later life. Many of these are serious enough to cause cardiac symptoms and require not only specialty cardiology care and ultimately require surgical correction. These are risky procedures often in sick babies and toddlers. Originally, those with DS were “denied” cardiac surgery[9] because of concerns about the seriousness of their heart defects as well as their postoperative morbidity and mortality.

More recent ethical, social and legal considerations changed in the 1970s with improved technologies and outcomes. Geneticists like Dr Murray Feingold suggested that children with DS did poorly because they did not receive prompt surgical repairs and not directly because of their DS.[10] Many different factors involved with care of DS patients continued to improve as exemplified in the American Academy of Pediatrics Committee of Genetics treatment guidelines.[11]

In the hands of skilled pediatric intensivists, cardiologists and cardiothoracic surgeons and associated specialized personnel such as nurses and respiratory

therapists, outcomes have improved dramatically in the past few decades.

Leukemia[12]

Leukemia risk in DS patient is approximately 1% and DS diagnosis is associated with a 20 fold increased risk of leukemia [13] compared to the general population.

DS seem to be younger at diagnosis and have earlier deaths in comparison in comparison to non-DS leukemia patients. Again, improved treatment protocols and improved outcomes over the past two decades have greatly reduced morbidity and mortality in places where such high technology medical care is available.

Mental retardation[14]

99% of DS patients have moderate to severe mental retardation but with some extraordinary exceptions such as one American television actor in the 1990s who was the focus of a television show about a family with a DS child (himself) as the star. Other DS patients have also been musically talented as performers and even orchestra conductors.

Several decades ago, most health professionals counseled families to place DS patients in institutions where they were not treated very well nor were their individual skills highlighted and supported. In parts of the world where resources are not available, this is still the case. However, more recently, DS patients tend to remain at home with professional education, guidance and family support all contributing to more normal family and patient quality of life, improved screening and awareness of co-morbidities and their treatment so that specific and general outcomes are improved.[15]

DS patients can mainstream in schools with individualized education plans providing aides and assistance for parts of the day but allowing socialization with peers for other parts of the school day including specialty sports involvement. Specific work skills can be taught and mastered according to the individualized needs of a particular child or

adolescent and then transitions occur to allow some work skills as teenagers and adults in either sheltered workshops or in special placements in the general workplace.

Many DS patient[16] continue to live with their parents, with siblings or other relatives into adulthood while some move into group living homes sponsored either by local governments and/or private foundations.

Early intervention programs also have been enormously helpful [17] not only to identify needs but also to support families remaining intact and promoting the same type of positive attitudes and behaviors that allow for the child or teen to stay together with the rest of the family.

Brain function in DS patients also shows some unusual and unexplained aspects which suggest a premature aging process not only physically but also mentally. Now that longevity is, in general, increased in recent decades, this has become more obvious with better overall medical care and facilities as well as identification of such changes within families who can make better observations over time. An Alzheimer-like brain tissue change has been described[18] with forms of senile dementia in middle-aged and older DS patients.[19] 80% of DS children reach 60 years of age or older where resources are consistently available for DS patients and their families.[2]

Eye and ear problems

DS patients have more frequent poor vision, often need to wear eyeglasses, have more cataracts, strabismus and also more early nystagmus than the general population. Eye screening is part of routine health supervision by the primary health care provider as well as genetics consultant; as such an ophthalmologist is often a key part of the treatment team for DS patients.[9] An unusual manifestation in DS patients are streaks in the iris which do not seem to cause any physical or ocular problems specifically except that they are noticeable on examination, the so-called Brushfield spots.

More frequent chronic serous otitis media or recurrent otitis media occur in DS patients when they are young. [20]

Classical treatment with antibiotics and consultation with ear-nose-and-throat specialists including early placement of drainage tubes when appropriate has also helped solve some of these problems. In addition, hearing problems[14] are also more common and such hearing difficulties contribute to more difficult speech and language acquisition and comprehensibility. Early intervention when hearing problems occur has helped with identification and treatment consideration such as use of sign language.

Growth

Poor growth often already exists antenatally with many DS neonates demonstrating small for gestational age (SGA) characteristics.[1]

Postnatal growth problems are common but may be attributed to chronic aspiration, pulmonary or ear infections, sinus infections or various feeding/GI difficulties. Serous cardiac disease may also contribute to poor growth. Even without such obvious explanation, however, poor postnatal growth can persist that seems not directly related to growth hormone deficiency although low IGF-1 levels are reported. Some research studies have suggested abnormalities in the GHRH–GH-IGF-1 axis including classic abnormalities on growth hormone stimulation testing.[21,22]

Growth hormone treatment under such circumstances has produced similar increases in growth velocity compared to other populations including those with classical growth hormone deficiency, Turner and Noonan's Syndromes and post-SGA children. Specifically, results of growth hormone stimulation testing when carried out suggest hypothalamic[23] rather than pituitary abnormalities in the axis with normal post-GHRH test results but some DS patients also demonstrate abnormal clonidine, dopa, arginine, insulin and glucagon stimulation test results.

Separate Down Syndrome growth charts[24] are available and should be used in addition to standardized population charting to track and identify deviations from the norm, look for other conditions that are common in DS (celiac, type 1

diabetes, thyroid dysfunction) and begin proper therapeutic interventions. As a general rule for both boys and girls, DS patients are shorter as infants and remain shorter as children with further deviation and less of a prepubertal and pubertal growth spurt compared to non-DS patients.

Of note on the charts is also the increased degree of excess weight for height that becomes apparent in childhood and is often exaggerated in the adolescent years while persisting or even worsening in adulthood adding to metabolic syndrome and cardiovascular compromise.

In general, Down Syndrome without documented growth hormone deficiency is not an accepted treatment rationale for giving growth hormone injections and there has been some reluctance to test as well as treat growth hormone deficiency, if it can be documented. The potential concerns include not only high costs of growth hormone itself but the necessity for injection therapy on a daily basis (although now there are weekly GH injections available) and quality of life issues that make such treatment problematic for some.[25] Risks of slipped capital femoral epiphysis, cerebral edema, exacerbation of glucose intolerance or frank increased diabetes risk as well as increased leukemia risks in DS patients remains unknown but also potential barriers to GH treatment consideration.[26] While adult height gain estimates of 5-10 cm may be possible, how may this change the quality of life of someone with DS as an adult remains a difficult question not yet answerable especially considering the persistent high costs of potential growth hormone treatment added to many other costs usually required. Most pediatric endocrinologists as well as geneticists involved with DS care have not recommended such difficult evaluations or treatment protocols for DS patients coming to them for consultation.[27]

Gastrointestinal abnormalities

DS patients have an increased risk of several different kinds of anatomic and functional gastrointestinal disease as well as celiac disease. This would include gastroesophageal reflux (GERD) and hiatal hernias, chronic aspiration,

dysmotility disorders severe enough to warrant gastric or jejunal tube feeding for many years, duodenal atresia[28] and Hirschsprung disease[29] as well as chronic severe functional constipation.

Duodenal atresia and Hirschprung disease require surgical correction following appropriate GI, radiologic and surgical consultations.

Celiac disease also seems to be more common in DS patients with reported estimates in the 4-15% range[30] and is another indication of increased autoimmunopathy just like type 1 diabetes mellitus and Hashimoto's thyroiditis are more common in DS patients (and even more common if one of these three exists).[31] Some authors have suggested routine testing not only for screening celiac antibody (usually transglutaminase antibody) levels but also HLA-DQ2/8 testing since negative human leukocyte antigen testing would provide some reassurance to families and health care providers that celiac disease is significantly less likely than in those testing positive.[32]

Celiac disease, as in non-DS patients, may be asymptomatic or present with nonspecific gastrointestinal complaints or even constipation although malabsorption related to gluten sensitivity usually produces loose, malodorous bowel movement with or without iron deficiency, low vitamin D and calcium absorption, osteopenia or osteoporosis and other vitamin and mineral deficiencies. Positive transglutaminase antibodies, positive endomysial antibodies, positive antigliadin IgG and antigliadin IgA antibodies all occur with celiac disease.[28] Most gastroenterologists[33] continue to advise intestinal biopsy to confirm such positive antibodies with or without gastrointestinal symptoms but such recommendations may change in the near future as experience with antibody measurement increases. With confirmation of positive antibodies by consistent biopsy abnormalities, strict gluten free dietary counseling works just as in others with celiac disease but may be more challenging because of DS associated behavioral issues (see below). Any growth

compromise and abnormalities of vitamin and mineral absorption usually respond to such strict avoidance of wheat and gluten. Confirmation of such dietary elimination can occur by normalization of positive antibodies with accidental or purposeful exposure documented by resumption of positive antibodies on follow-up evaluations. Whether or not long term gut lymphoma risks are the same for DS patients as for those without DS is unknown. Most guidelines for DS include routine and periodic screening with transglutaminase or similar antibodies even in asymptomatic DS patients every 2-3 years.[9]

Sleep Disturbances

Chronic low-level aspiration, obstructive sleep apnea including restless sleep and snoring all seem to be more common in DS patients.[34] Appropriate specialty consultation should be considered if found positive on systems review.

Skin problems

Problems with the extremely dry skin may raise questions of hypothyroidism but they usually remain unexplained yet require special attention and topical lotions as well as dermatology consultation.

Neck vertebrae

Abnormalities of cervical vertebrae causing atlantoaxial instability and/or subluxation are not rare. This requires some screening radiography especially when sports participation is either anticipated or occurring in the adolescent age group. Appropriate orthopedic consultation should occur to minimize or prevent spinal compromise if an abnormality is suspected or confirmed.

Hypovitaminosis D, Osteopenia and Osteoporosis

Low vitamin D levels may be related to undiagnosed celiac disease or its variants and is also more common when type 1 or type 2 occurs, any thyroid disorder occurs or with GI diseases. However, in many parts of the world and especially

in the USA, decreased dietary intake of calcium and vitamin D in dairy (milk, cheese, yogurt, ice cream) coupled with lack of sun exposure, use of suntan preparations to protect the skin from skin cancer risks, more indoor activities such as television, computer and video game time and more high phosphate cola intake as well as general obesity or just being overweight all contribute to a generally higher incidence and prevalence of abnormalities of calcium as well as vitamin D.[35,36] Whether or not there is a separate and higher risk of osteopenia and osteoporosis even without celiac disease or other gastrointestinal abnormalities in DS patients is unknown. In association with type 1 or type 2 diabetes as well as Hashimoto's thyroiditis and celiac disease, more people are being diagnosed with hypovitaminosis D as well as bone mineralization abnormalities that respond to improved calcium and vitamin D supplementation.[37]

Dietary history can provide a diagnostic clue to the need for further evaluation, and this would include actual sequential measurements of total vitamin D levels using more and more reliable assays. If such vitamin D deficiency or insufficiency is diagnosed, then appropriate vitamin D supplementation either with vitamin D3 or vitamin D2 can be made available in small softgels, tablets and/or liquid vitamin D preparations to optimize blood vitamin D levels.[38]

Baseline bone density assessments compared to appropriate pediatric and adolescent as well as adult standards are also now available to look for osteopenia and osteoporosis and then allow future comparisons of treatment efficacy and compliance.[39]

Long term data of hypovitaminosis D, osteopenia and osteoporosis do not exist for those with or without DS when diagnosis occurs in childhood, adolescence or in adulthood but with our understanding of bone mineralization, it would seem reasonable to assume that correction of such abnormalities when detected and in an earlier than usual fashion, should improve short and long term bone mineralization outcomes. Some research[40] also suggests that identification and treatment of hypovitaminosis D may also

decrease risks of type 1 and type 2 diabetes, autoimmunopathies such as thyroiditis, respiratory infections and various types of cancers; there is no reason to expect that this would be less important in the DS population than in the general population.

Hashimoto's thyroiditis, acquired hypothyroidism, hyperthyroidism

It has long been known that patients with DS have an increased risk of a variety of thyroid dysfunctions [41,42,43] where variable thyroid functions have been detected in DS reports.[44,45]

Studies in Italy following natural history of thyroid problems in children with DS indicated an increase in acquired thyroid dysfunction from 30% at birth to 49% by 10 years of age ($p<0.001$).[35] These authors emphasized the importance of not only recognizing this fact but of careful monitoring with annual screening to allow early identification and treatment options and this has appeared in DS treatment guidelines for some time.

Follow-up assessments[46] have sometimes produced conflicting data with some intermittent abnormal findings, compensated hypothyroidism (normal T4 but elevated TSH) or inconsistencies between total and free T4, total T3 and TSH levels as well as non-persistence of such abnormalities even if not treated but just followed in an otherwise asymptomatic DS patient. Explanations for such discrepancies generally have been lacking except for hypothetical abnormal feedback loops and/or resistance syndromes. Whether or not such abnormalities should be treated is difficult to know since there are often few if any symptoms associated with these abnormalities yet subtle hypothyroidism has its own set of comorbidities associated and these can potentially cause further problems in DS patients otherwise easily treated and monitored.

Recommendations for routine thyroid function test screening also have produced similar dilemmas for the clinician whether it be the primary care provider, family

doctor, pediatrician, geneticist or endocrinologist. Nevertheless, it is also known that there is more autoimmunopathy in a DS patient population and especially more Hashimoto's thyroiditis.[47,48] Such Hashimoto's thyroiditis is known to be associated with either compensated hypothyroidism or full-fledged acquired hypothyroidism as well as hyperthyroidism. Whether it is more reasonable, cost efficient and efficacious to screen all DS patients just with sensitive TSH assays alone or to also include thyroid antibodies in the screening process is unknown since comparison studies are few and without sufficient long-term follow-up to know if there is any difference in short or long term outcome. This author usually recommends total T4, free T4, TSH for initial screen plus thyroglobulin and microsomal thyroid antibody levels; if antibody levels are positive, then periodic (every 6-12 month) total T4, free T4 and TSH should be monitored and with rising TSH and/or falling T4 values, levothyroxine begun. With negative thyroid antibodies, less screening would be reasonable but still should be continued since change in thyroid function can occur at any time.

In one study[49] congenital hypothyroidism was considered more commonly seen in an already existing congenital hypothyroidism registry study comparing incidence of 1:50 in DS neonates compared to 1:4000 in the non-DS neonate population, an approximately 25x increase in incidence. In older children, adolescents and young adults, goiter may or may not be present but is often small, nontender and without any respiratory compromise. This is not necessarily related to presence or absence of positive thyroid antibodies or to degree of compensated or acquired hypothyroidism itself. Asymptomatic thyroid disease exists in DS populations just as it does in the non-DS population quite commonly or only with mild findings.

If compensated hypothyroidism occurs (normal T4 and/or free T4 associated with elevated TSH levels), then some would suggest follow-up assessments assuming that no symptoms exist and treatment with levothyroxine to normalize all thyroid function tests if either the abnormalities persist on

sequential follow-up or there is a change in either subtle symptoms or size in the thyroid gland itself. Assessment with thyroid antibodies would be recommended with those having persistent and/or higher antibody titers more likely to require levothyroxine treatment and such decisions would not be any different for the non-DS population.

Full-fledged acquired hypothyroidism can occur with or without symptoms. Symptoms might include lethargy, thickened hair or hair and nails slowly growing, dry skin, cold intolerance, constipation with signs including slowed height velocity, increased weight, slowed pulse and low blood pressure, goiter as well as decreased or absent deep tendon reflexes. Some patients do not have an obvious goiter.

T4 would be decreased as would be free T4 elevated TSH levels. Total T3 could be low if there was sufficiently long duration hypothyroidism but sometimes Total T3 levels would still be normal.

Thyroid antibodies most of the time would be positive assuming that Hashimoto's thyroiditis is the most common underlying cause for such acquired hypothyroidism in DS patients. Of the two commonly available antibody assays, microsomal or peroxidase antibodies compared to thyroglobulin are most often positive if only one of the two antibodies is abnormal.

Thyroid ultrasonography is rarely necessary in acquired hypothyroidism as it does not add anything to the clinical diagnosis not apparent by history and physical exam as well as the above listed laboratory tests. If ultrasonography is done, it often will show evidence of chronic Hashimoto's thyroiditis.

Treatment of hypothyroidism[50] involves taking once-a-day levothyroxine tablets and titrating to normalize and sustain normal thyroid functions especially TSH levels. Abnormal signs and symptoms would then slowly improve and remain normal as long as compliance with levothyroxine was maintained and confirmed with follow-up thyroid function tests. Thyroid antibodies usually remain positive but sometimes become negative months or years after institution

of treatment but the status of thyroid antibodies does not predict exact dosage needed or whether or not any goiter present in association with hypothyroidism would decrease. Such goiters get smaller and disappear over several weeks or months of levothyroxine treatment. Sometimes combined treatment with triiodothyronine (T3) as well as levothyroxine (T4) is needed to completely normalize all thyroid function abnormalities even though symptoms abate.

Euthyroid Hashimoto's thyroiditis with or without a goiter but with completely normal thyroid functions can also occur especially if screening programs pick up just positive antibodies. No specific treatment is needed and there is not much clinical evidence to suggest that treating such euthyroid Hashimoto's thyroiditis would do anything to the natural history of the inflammatory process or change ultimate need for levothyroxine treatment. Sequential follow-up of the size of the thyroid gland may provide evidence for instituting levothyroxine treatment just as sequential evaluation of thyroid functions may allow early identification (decreasing free and/or total T4 as well as increasing TSH or just increasing TSH while the free and/or total T4 remain okay) rather than waiting for signs and symptoms to actually develop. There is no evidence in DS patients compared to the general population as to what should be done except for sequential follow-up assessments following typical endocrine guidelines as discussed yet even subtle hypothyroidism that might ameliorate some other DS-related issues raise some potential concerns.

An unusual presentation of thyroid dysfunction has been called Hashitoxicosis. This exists when hyperthyroidism is the first presenting finding with or without a goiter and with or without proptosis or exophthalmos.

Usually such Hashitoxicosis involves hyperthyroid symptoms and signs as well as elevated total and free T4, elevated total T3 and suppressed TSH with positive thyroglobulin or peroxidase/microsomal antibodies. Sometimes there is also positive thyroid stimulating

immunoglobulin (TSI) as well as thyroid binding immunoglobulin (TBII).

Thyroid ultrasonography still is not needed and if done would likely show only patchy Hashimoto's thyroiditis changes if anything.

Standard treatment for hyperthyroidism then should be commenced but in Hashitoxicosis, response to such treatment can be rather brisk, and then the thyroid functions test results convert to either a euthyroid state or to a hypothyroid state. When hypothyroidism occurs following hyperthyroidism, then the treatment of hypothyroidism is dictated by thyroid function test results as well as physical findings and levothyroxine treatment is needed while the antithyroid medication is tapered away.

Hyperthyroidism (Graves' Disease)[51,39] when it occurs in DS patients also is rather similar to non-DS patients but often not associated with proptosis or exophthalmos. Graves may be milder than in the general population perhaps because DS patients see medical personnel because of their other medical problems more often than general pediatric or adolescent patients so this has the potential for earlier recognition. Goiters are usually but not always present but may not be recognized by the patient or his/her family on their own.

Symptoms include increased appetite associated with otherwise unexplained weight loss, thinning hair, palpitations and tachycardia, loose bowel movements, skipped or otherwise abnormal menses, heat intolerance, sleep disturbances, anxiety and nervousness. Physical findings aside from eye changes (proptosis) and thyroid gland changes itself would include tachycardia, mild hypertension, tremors and brisk reflexes.

Classical abnormalities of TFTs[52] include elevated total T4, total T3 and free T4 in association with suppressed TSH. Often there are positive thyroglobulin and/or thyroid microsomal/peroxidase antibodies as well as thyroid stimulating immunoglobulin (TSI) and thyroid binding immunoglobulin (TBII).

Thyroid ultrasonography is not needed unless there is a question of a solitary hyperfunctioning nodule. Iodine or technetium thyroid scanning often is done but often does not do anything more than confirm a hyperfunctioning nodule, if that is the cause; in usual cases of hyperthyroidism, such diagnostic scans show generalized hyperactivity throughout the thyroid gland. Often there is a mild leukopenia or neutropenia as well as modest elevation of liver enzymes at diagnosis of hyperthyroidism. It is usually thought to be important to get baseline blood count, differential count and liver function tests because side effects of treatment may also include changes in these parameters.

Hyperthyroidism treatment for DS patients is the same as that for non-DS patients.[38,53] If the tachycardia, palpitations, hypertension, nervousness and tremors are bothersome enough, oral beta blockers such as propranolol or atenolol may be used for several weeks to provide relief.

A thyroid blocking agent such as methimazole once or twice-a-day is used to normalize TFTs and titrated to achieve this goal. Carbimazole is a drug that is biologically converted to methimazole and is available as an alternative in some countries. Previously propylthiouracil was also another thyroid blocking agent that was used with some research data suggesting propylthiouracil was slightly better at inducing a remission of the hyperthyroidism. More recently, in the USA, propylthiouracil has been phased out because of concerns about increased liver abnormalities and liver failure.[54] Most hyperthyroid patients respond to such thyroid blockade within several weeks and as the previously created excess thyroid hormones are metabolized by the body, symptoms slowly resolve.

There are two approaches to dosing called by some “titrate” and “block-and-replace.”[38,39]

“Titrate” can be defined as adjusting the anti-thyroid medication dose to achieve euthyroidism clinically and biochemically with follow-up and lab hormone levels about every 2-3 months.

"Block-and-replace" is defined as using progressively higher doses of anti-thyroid treatment plus adding levothyroxine to achieve euthyroidism in an attempt to achieve remission more readily. No prospective randomized trials have been done in any patients with these two approaches and both seem to work reasonably well from a clinical perspective. Non-DS remission rates are reported in the 25-65% range[38,39] but relapse is common varying from 35-50%.[38,39]

Over the course of the first few months of treatment, one option for treatment is to continue methimazole for at least two years while watching TFTs as well as TSI and TBII sequentially not only to titrate the dose of methimazole needed but to see if the underlying inflammatory process itself may abate. With full normalization of TFTs and with TSI and TBII becoming negative, a tapering trial off methimazole to see if a prolonged remission would occur is reasonable. Sometimes, with positive TSI and TBII (as well as persistent suppressed TSH ("block-and-replace" treatment variant) higher doses of methimazole are used in conjunction with levothyroxine simultaneously. This may occur in as many as 25-30% of hyperthyroid patients. Such combination treatment can be continued indefinitely or, if a sustained remission occurs, tapering off the methimazole first and then the levothyroxine thereafter can be attempted.

With either clinical course, if an allergy to methimazole occurs, or if there are significant side effects such as elevated liver transaminase enzymes or worrisome neutropenia, then an alternative is to use radioactive iodine I^{131} to chemically ablate the hyperthyroid gland. If there is noncompliance with methimazole treatment or if there is one or more relapses of hyperthyroidism, then radioiodine treatment is also a reasonable option.[38]

Most pediatric and adult endocrinologists follow such treatment protocols for hyperthyroidism with oral blocking agents used as first line of treatment but there are many US adult endocrinology referral centers and a few US pediatric endocrinology centers (ie. Massachusetts General Hospital

and Yale University) where radioiodine is considered as primary preferred treatment for hyperthyroidism.[55]

Such I^{131} treatment is provided orally with standard dosages estimated by the degree of hyperthyroidism and the size of the thyroid gland.[38,39]

The patient is allowed to become modestly hyperthyroid with some tapering or decrease of the initial blocking medication prior to provision of the radioiodine dose and then the radioiodine provides sufficient iodine to the thyroid tissue to chemically ablate the hyperfunctioning gland.

Almost always, hypothyroidism results that requires levothyroxine treatment indefinitely. There do not appear to be any long term side effects nor increased malignancy in patients so treated with I^{131} but long term follow-up data are not available in large cohorts either in the pediatric and adolescent non-DS or DS patients so treated.

In DS patients with some increased risk of malignancy, there are no known long term studies confirming the specific long term safety of radioiodine in the treatment of hyperthyroidism under such circumstances but it may be reasonable to offer radioiodine if there are side effects or allergic problems as well as medication noncompliance. Similarly, when there is recurrence of hyperthyroidism, radioiodine should be considered for a definitive cure.

In the past, surgical removal of the hyperthyroid goiter (or an isolated hyperfunctioning thyroid nodule) was also an alternative treatment. This is utilized less frequently because of the excellent results from methimazole or propylthiouracil and/or radioiodine. If the thyroid gland is large enough, then consideration of surgical “cure” is also reasonable.

If medical treatment of hyperthyroidism fails (or is unavailable), chronic noncompliance occurs or if there is unavailability of radioiodine treatment, then surgical treatment of Grave’s Disease – as in those without DS – is also an option.[38,39]

Type 1 diabetes mellitus; Type 2 diabetes mellitus, obesity and metabolic syndrome, hyperlipidemia, hyperuricemia

Type 1 diabetes mellitus (T1DM) is another of the autoimmunopathies as a co-morbidity in DS patients.[56,57] Sometimes, T1DM coexists with thyroid disease and also celiac disease in DS patients just as this relationship occurs in the non-DS patients.[58 59] It is thought that there is about a 7x increase in T1DM in DS but exact reasons are not known.[60]

Presentation of T1DM is the same as for those without DS including polyuria, polydipsia, nocturia, enuresis and unexplained weight loss. With missed or late diagnosis increasing the risk of diabetic ketoacidosis, severe dehydration, coma and death may occur if the diagnosis of T1DM is not recognized or treated appropriately.

General treatment goals of T1DM in DS are the same as with other young patients but with DS patients more dependent on parents, other family members and other caretakers because of their other limitations. Supervision needs are high and persist even into adolescence and adulthood, of course, reflecting the compromised mental status of DS patients. Specific treatment goals always include optimizing glucose control, decreasing symptomatic hyperglycemia and, most importantly, reducing the risks of hypoglycemia as much as possible. All such goals are difficult in non-DS patients but some compromise in glucose targets may be required in DS patients. Frequent blood glucose monitoring, intensified basal-bolus insulin treatment regimens with multidose injections, carbohydrate counting and multidisciplinary team care all work in similar fashion to optimize DS T1DM care.

More recent advances in artificial intelligence combining insulin pump communicating directly with continuous subcutaneous glucose monitors and utilizing automatic low glucose suspend protocols as well as addressing hyperglycemic surges automatically may offer some excellent treatment modalities to help with the DS patients who also

has classical T1DM since they also will allow parents, other family members and anyone supervising the DS patient to simultaneously monitor with a cell phone or other monitor device attached to the computerized BG and insulin delivery modules. DS patients can participate in summer and weekend camp programs to help provide support and education as well as family respite. Monitoring of hemoglobin A1c, screening and monitoring for lipid and kidney abnormalities as well as thyroid functions[61] and celiac disease as well as early detection and treatment of retinopathy are the same for all T1DM patients.[62]

The metabolic syndrome in all its permutations beginning from simple obesity through insulin resistance, hepatic steatosis, hyperuricemia, hyperlipidemia, intermittent and then more persistent glucose intolerance and finally frank type 2 diabetes mellitus all seem to be more commonly seen in DS patients.[63]

It is reasonable to provide DS patients and their families with guidance about all these issues and especially focusing on ways to minimize and prevent as well as reverse obesity to the extent that this is possible – even if difficult. Whether or not this can be accomplished is not known and whether or not attempts to postpone such obesity changes in DS will help ameliorate or prevent any or all aspects of the metabolic syndrome is also unknown; yet is reasonable to make such attempts a high priority and to support medical team efforts as well as family efforts to understand these risks and goals. As with T1DM in DS patients, metabolic syndrome and T2DM treatment goals are not so different than in other children, teenagers and adults.[64]

Blood glucose monitoring can be taught to many DS patients and their families as well as their caretakers to provide guidance coupled with hemoglobin A1c determinations. Metformin remains the main medical treatment of T2DM once more persistent hyperglycemia occurs. Hyperlipidemia is treated either with medications such as CholestOff (plant sterols and stanols), bile acid sequestrants (cholestyramine) or high dose niacin as well as

fibrates and statins in much the same way that hyperlipidemia is treated in the non-DS population after attempts at weight loss, increased activity and dietary changes are made. Hyperuricemia is likewise treated with non-medication options first and then with allopurinol to stave off clinical gout. Hypertension is treated as well in a manner identical and in stepwise fashion as with other patients who do not have DS with beta blockers, diuretics and newer medications aimed to lower high BP values safely and perhaps even help if there is concomitant hyperglycemia by using newer therapeutic agents if needed. Exact progression of metabolic syndrome through glucose intolerance and finally to T2DM after metformin does not work is not known exactly for the DS population compared to the non-DS population but standard treatment protocols should be similarly followed moving through secondary oral medication and finally to insulin with the same types of modifications needed because of intellectual capacity and supervision needs of the DS adolescent, young adult and adult. Additional screening and follow-up for kidney complications of T2DM as well as eye complications are also similar. Most guidelines for DS as well as general associations of obesity and the metabolic syndrome [65] now suggest routine and periodic screening for diabetes, lipid, blood pressure and uric acid abnormalities usually in adolescent and adulthood.

Hypogonadism[66]

Relative hypogonadism often with small testes prepubertally as well as in adolescence for the boys and small breasts for the girls as they progress through puberty is common. Usually, however, there are no hormonal abnormalities, ie. no gonadotropin abnormalities or specific low androgens or estrogens nor any specific abnormalities of adrenal function apparent in most young DS patients. Menses are usually normal but sometimes slightly delayed and sexual interest also blossoms in both males and females as they move into and through puberty and into adulthood.[67]

By mid-late puberty and into adulthood, there is modest hypogonadism in some DS patients but often there is not much need for hormonal gonadal replacement.[68]

If menses are abnormal, as with non-DS patients, use of cyclical estrogen-progesterone hormone treatment should be considered; similarly for dysmenorrhea.

Because of the MR issues, sexuality and potential need for contraception also pose some difficult issues to discuss with family members.

There is some theoretical consideration for androgen treatment for males with poor bone mineralization and for females for the same reason but short and long term data are lacking to provide therapeutic guidance.

Behavioral problems, Anxiety, depression, ODD and OCD

As DS patients get older, sometimes in adolescence and sometimes in adulthood, not only is there evidence of some dementia, but there is also an increased incidence of anxiety and depression[69] and perhaps also more oppositional defiant disorders (ODD) and obsessive compulsive disorders (OCD).

Often such issues become a source of major emotional upheaval in the family particularly if they occur in adolescent or adult DS patients since their parents, often then are also quite elderly themselves. Behavioral therapy and medications may be necessary and some studies have documented an increased prevalence of these types of issues with DS patients.[70]

Male sex and more severe mental disabilities were associated with more behavioral problems.

Medications for such issues including anti-anxiety medications and selective serotonin reuptake inhibitors (SSRIs) and these frequently produce or exacerbate obesity, glucose intolerance, hyperlipidemias or produce liver enzyme abnormalities.[71]

Combinations of such psychotropic medications often are prescribed and side effects of such combinations may be additive in all these realms.

Summary

Down Syndrome is a relatively common genetic condition which can have enormous complexities and require numerous specialty health care providers to address such issues. Endocrine disturbances are more common in DS patients but offer the possibilities of screening and early identification with potential for decreasing morbidity with optimized institution of such early diagnosis and treatment. Pediatric endocrinologists should consider working very closely with geneticists as well as primary health care providers to coordinate such screening, early intervention and care.[72,73,74,75]

Thyroid disorders and celiac disease as well as growth abnormalities, type 1 and type 2 diabetes, glucose intolerance and the metabolic syndrome, hypertension, obesity and hyperlipidemias, hyperuricemia and vitamin D and bone mineralization disorders as well as the milder hypogonadal states all are increased in DS patients and these can clearly have direct impacts of some of the many other comorbidities in the DS patient. Awareness of such difficulties by health care providers remains an important educational goal around the world.[76]

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CHALLENGES IN THE MANAGEMENT OF GRAVES DISEASE IN ADOLESCENTS

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1. BACKGROUND

Graves' disease (GD) represents the most frequent cause of hyperthyroidism in children, although its prevalence is quite rare in the pediatric population. With a vast predominance in females compared to males, 2% compared to 0.2%, children represent only 1-5% of all patients with Graves' disease, the prevalence being 1:5000.[1,2] The proclivity to affect the female sex carries up in children as well, with girls being affected 5-8 times more than boys.[3,4] Graves' disease can occur at any age, but its frequency increases with age, reaching a peak in adolescence (3:100.000 adolescents).[3] However, recent reports show that the condition has a variable incidence: between 1/10.000 in the USA and 1/100.000 cases/year in the UK and Ireland, in the age group 0-15 years.[5]

An important aspect to keep in mind is that Graves' disease occurs more frequently in patients who associate other autoimmune diseases (type 1 diabetes, vitiligo, celiac disease, rheumatoid arthritis, lupus erythematosus) or genetic syndromes (Down syndrome, Turner syndrome, Di George syndrome).[6-8]

1.1. Etiology and pathogenesis

Although the pathogenesis of Graves' disease is not fully understood, it is known to be the result of a complex

interaction between genetic predisposition, environmental factors, and alterations of the immune system. Studies on twins and the observed higher prevalence of GD in first-degree relatives of GD patients suggest that the genetic predisposition is involved in up to 80% of the disease, while environmental factors account for only up to 20% %. [9,10]

The genetic predisposition to develop GD is thought to be polygenic. It is associated with the HLA DR3, DQ2 and, DQ A1*0501 antigens, the PTPN22 gene on chromosome 1p13 and, the cytotoxic T lymphocyte antigen 4 (CTLA-4) gene on chromosome 2q33.[3]

The imbalances of the immune system in GD occur between the pathogenic and regulatory T lymphocytes, which are responsible for the development and the severity of the disease. The reduction in the number and function of suppressor T lymphocytes causes the hyper-production of auto-antibodies, ultimately stimulating the thyroid function. They bind to the TSH receptor on the thyroid cell membrane - which represents the most important auto-antigen in this autoimmune process - and cause its stimulation, through adenyl cyclase and phospholipase A2. Consequently, follicular cell enlargement, increased thyroid vasculature, and excessive thyroid hormone synthesis/secretion occur. Morphologically, the thyroid gland shows lymphocytic infiltrates and T-lymphocyte abnormalities, without the destruction of thyroid follicles. T lymphocytes cause local inflammation and tissue remodeling, through the production and release of cytokines, which also leads to the involvement of B lymphocytes, with increased production of antibodies.[3,11]

From a functional point of view, the antibodies mimic the actions of TSH. However, there are also antibodies that bind to the receptor, without causing its stimulation, preventing TSH from binding to the receptor and exerting an inhibitory effect, these being known as thyroid stimulation-blocking antibodies. The secretion of thyroid hormones will therefore depend on the balance between the two types of actions (stimulation/blocking), a fact that could explain the

hormonal oscillations, frequently found in patients with BG.[9,10,12,13]

As mentioned before, the triggers of the autoimmune process in Graves' disease are not fully understood. There are some arguments that suggest the involvement of viral infections or Yersinia enterocolitica infection in the onset of the disease. [14-16]

1.2. Clinical aspects

The manifestation of Graves' disease is largely the result of the effects exerted by excess thyroid hormones on target tissues.

At the onset, the symptomatology is most often non-specific and, therefore, rarely associated with the real diagnosis: behavioral changes, the child's inability to concentrate at school, restlessness, irritability, nervousness, emotional lability, sleep disorders up to insomnia, and fatigue. Palpitations, tremors, and excessive sweating are associated with stagnation or, more often, with weight loss, despite an increased appetite and adequate caloric intake. Intestinal transit is accelerated, and the child frequently presents with diarrhea. This diversity of non-specific signs makes the patient end up in various other pediatric services (child neuropsychiatry, cardiology, or pediatric gastroenterology) before being consulted by the pediatric endocrinologist.

Goiter is often present, the thyroid gland is enlarged, usually symmetrical, firm, smooth, and painless to palpation. A murmur may be heard in the region of the gland, which reflects increased blood flow at this level. If the goiter is more voluminous, it can cause symptoms due to the compression of the cervical organs: dyspnea, dysphagia, and cough. In some patients, the thyroid is only slightly enlarged, which is why the goiter may not be noticed by the examiner.

Infiltrative ophthalmopathy is rare in pediatric patients. There are, however, ocular changes with soft tissue involvement. The patient presents a "surprised", bright look, proptosis, retraction of the upper eyelid, and wide palpebral

opening.[17] Sometimes the child also shows photophobia, abundant lacrimation, and rare blinking.

Among the major clinical signs present in Graves' disease in children, cardiovascular ones occupy an important place. Sinus tachycardia, increased blood pressure (HT), and systolic ejection murmur due to functional mitral insufficiency are present in varying degrees, and sometimes, in severe forms, heart failure may occur.

Linear growth is rapid (accelerated growth rate) and the bone age is advanced, directly influenced by the period of exposure to excess thyroid hormones. Similar to adults, children show a reduction in bone mass - due to the imbalance between resorption and bone formation. This normalizes after approximately 2 years of euthyroid status obtained through treatment with synthetic antithyroid drugs (ATS).[18]

Neurological symptoms (chorea) are rare in children.[19]

Other clinical signs, which may be present especially in adolescents with Graves' disease, include temporal alopecia, hyperpigmentation of the dermis, pruritus friable, and muscle weakness associated especially with reduced proximal muscle mass. Pretibial edema is a rarity in children. Secondary amenorrhea in girls, respectively gynecomastia in boys, can occur due to excess estrogens caused by the increase in the metabolism of steroid hormones and their aromatization to estrogens.

Thyrotoxic crisis is extremely rare in children.

1.3. Laboratory and imaging findings

The laboratory diagnosis is easy to establish. Serum levels of free thyroxine (FT4) and free triiodothyronine (FT3) are elevated, and TSH is low. However, in some patients, a normal level of FT4 and an increased level of FT3 (T3 toxicosis) can be identified, a situation that can be present at the onset or during relapses, which occur during the course of the disease.

The diagnosis of Graves' disease is confirmed by the presence of TSH anti-receptor antibodies (TRAb) titers in

significant titer, which is pathognomonic for the diagnosis. TRAb antibodies are present in the serum of most patients with Graves' disease, in highly variable titers, with a positive correlation between TRAb and FT4 levels.[11]

The TRAb antibody titer is higher in young children (≤ 5 years) compared to older children (>5 years), as well as in those with a more severe clinical picture at the onset, compared to those with a milder clinical picture at the onset easily.[20]

Demonstration of a positive titer of antithyroxine peroxidase (anti-TPO) and antithyroglobulin (antiTg) antibodies is useful for confirming the diagnosis of autoimmune thyroid disease.[11]

Biological investigations also reveal a favorable lipid profile with low serum levels of total cholesterol and the HDL fraction, with serum triglycerides at the lower limit of the normal range. Carbohydrate metabolism is characterized by increased insulin requirements, due to increased hepatic glucose production and reduced insulin sensitivity. Protein metabolism is accelerated, with an increase in excretion products.[21]

The imaging evaluation of the thyroid in Graves' disease is done by thyroid ultrasound, which allows both the assessment of the volume of the gland and the highlighting of structural changes and thyroid vascularization (through the Echo Doppler method) in the context of the disease.

Sonographically, the thyroid appears enlarged, to varying degrees (10% of patients have a normal thyroid volume),[11] the structure is usually homogeneous but can also be inhomogeneous, with a pseudonodular appearance (*Figure 1*). The appearance is usually hypoechoic, similar to the appearance of thyroiditis, less often with normal echogenicity, the vascularization is accentuated, often with the specific appearance of "thyroid inferno" (through the opening of the arteriovenous shunts at the level of the gland) (*Figure 2*).

Other imaging investigations, such as thyroid scintigraphy, MRI, and CT, are not necessary to establish the diagnosis of the disease.

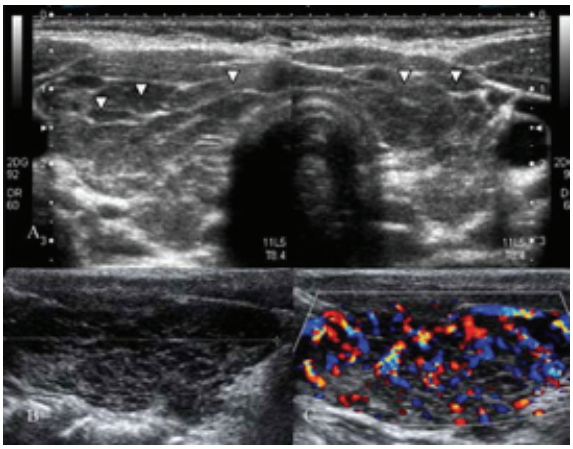

Figure 1.
An ultrasonographic aspect of Graves' disease in a child: *inhomogeneous structure, with a pseudonodular appearance*

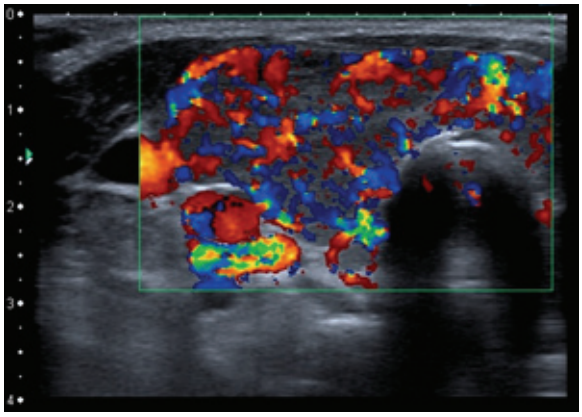

Figure 2.
An ultrasonographic aspect of Graves' disease in a child: *accentuated vascularization, the specific appearance of "thyroid inferno"*

1.4. Positive diagnosis

The positive diagnosis is established relatively easily, based on the *anamnestic data* (possible family history of autoimmune thyroid disease or other autoimmune pathology), the *symptoms,* and the *ultrasound appearance*, correlated with the *biological investigations, with the presence of specific antibodies (TRAb) in significant titer.*

2. TREATMENT AND MANAGEMENT OF PEDIATRIC GRAVES' DISEASE – THE EUROPEAN THYROID ASSOCIATION 2022 GUIDELINE [22]

2.1. Medical treatment

Patients with GD need to be treated promptly.

Young people with GD should be treated with either carbimazole (CBZ) or its active metabolite methimazole (MMI). The use of propylthiouracil is not advised in children, due to the risk of hepatic failure.[22]

The starting dose of an antithyroid medication (ATD) is 0.15 to 0.5 mg/kg of MMI or 0.25 to 0.75 mg/kg of CBZ each day. Each medication can be administered once daily, or in 2-3 doses.[22]

The dose titration (DT) method will normalize thyroid hormone concentrations in the majority of patients within the first 4-6 weeks with a starting dose of 0.15-0.3 mg/kg MMI or 0.25-0.5 mg/kg CBZ. After ward, the dose is decreased by 25–50% in accordance with the most recent thyroid function tests. In more severe, symptomatic instances, higher dosages of ATD up to 0.5 mg/kg MMI or 0.75 mg/kg CBZ can be given.[22]

If FT4 and/or FT3 are relatively high but TSH is normal, the medication regimen might not need to be adjusted.

To maximize compliance, education on GD, particularly its treatment, is crucial. Pay specific attention to the developmental age.[22]

Block and replace (BR) strategy: for the majority of patients, a dose of 0.3-0.5 mg/kg MMI or 0.5-0.75 mg/kg CBZ will stop endogenous thyroid hormone synthesis. As soon as the FT3 is within the reference range, levothyroxine can be started in an amount that is acceptable for the patient's age and weight. If thyroid hormone concentrations, particularly FT3, do not decrease as anticipated, higher dosages of ATD may be employed (for instance, 1.0 mg/kg MMI or 1.3 mg/kg CBZ).[22]

In the majority of cases, DT is the preferred method of ATD administration.

The use of beta-adrenergic blockade is advised in patients who exhibit obvious symptoms of high thyroid hormone. Once the patient is biochemically euthyroid, this can be stopped. [22]

Patients with untreated GD may experience severe illness and obvious indications of excess thyroid hormone. Such patients ought to be treated in an intensive care or high-dependency unit. According to the clinical course, patients managed with DT or BR should first receive examinations every 3 weeks, then every 2 months, and finally every 3 months.[22]

Because both the underlying illness process and ATD medication can alter them, a baseline white cell count, including neutrophil count, and liver function tests should be performed.[22]

In most patients, thyroid hormone levels (FT4 and FT3) should return to normal in the first 6 weeks, with a discernible improvement in the first 4 weeks. TSH suppression can last for several months. [22]

Families should be informed about the risk of uncontrollable weight gain while receiving ATD therapy. [22]

10 to 20% of individuals experience mild ATD side effects, which are typically momentary. Rarely (2–3 per 100,000) do serious side effects necessitate discontinuing ATD. [22]

It is important to inform patients and their families about the potential negative effects of ATD as well as the conditions under which they should stop taking it and seek medical advice.

Patients who are thyrotoxic despite receiving high doses of CBZ (1.3 mg/kg/day) or MMI (1.0 mg/kg/day) should be considered for alternative treatments such as surgery or RAI.[22]

Patients who experience severe neutropenia, major liver dysfunction, or bothersome side effects that don't go away should think about receiving definitive treatment (total thyroidectomy or RAI). Definitive treatment may also be necessary if a patient cannot adequately disclose probable ATD adverse effects, is having persistent compliance

problems, or has been receiving ATD medication for an extended period of time without experiencing remission. [22]

Antibodies to the TSH receptor (TRAb) can be used to gauge the chance of remission. Remission is unlikely if TRAb levels are high, hence ATD should not be discontinued.[22]

Normally, ATD is given for at least three years before being discontinued once TRAb levels have been low for several months. If the possibility of remission is low based on the characteristics of the disease, longer courses of ATD (5 years) should be taken into consideration. [22]

After 2 years of ATD treatment, the overall remission rate in children with GD is between 20 to 30%, and it may rise with continued ATD use.[22]

When ATD is withdrawn and a protocol for thyroid function testing is agreed upon, the symptoms of excess thyroid hormone should be discussed.[22]

Patients who relapse after completing a course of ATD have the option of choosing definitive treatment or going back to ATD. Age and educational level are two variables that may have an impact on the choice.[22]

Immune modulation with novel medications such as biologics has not been proven to be effective in treating young people with GD.[22]

2.2. The management of ATD side-effects

ATD side effects should be discussed with patients and their families. In the event of indications or symptoms of infection like fever or a sore throat, the patient should stop ATD and undergo neutrophil count determination in the case of agranulocytosis/severe neutropenia. Although there are rare examples of individuals developing neutropenia years into treatment, ATD-associated neutropenia commonly appears in the first month of treatment (median 30 days).[23] The fact that a low neutrophil count can signify either a recent infection or a disease process complicates management. The ATD should

be stopped and alternative treatment should be started if the neutrophil count is less than 0.5 (109/L). Once or twice weekly assessments can be used to closely monitor a neutrophil count between 0.5 and 1.5.[22]

Although some ATD side effects, such as rash, can be treated symptomatically because they typically go away on their own, ATD should be stopped right once if mucosal blistering is present because it could indicate Stevens-Johnson syndrome.[24,25]

ATD should be stopped if the transaminase level rises above three times the upper limit of normal during treatment, and liver function tests should be done if there are any relevant symptoms of liver dysfunction.[26]

A person who has suffered a major problem connected to the earlier administration of MMI/CBZ shouldn't start taking it again. [22]

2.3. Definitive treatment - Radioiodine (RAI)

Complete thyroid ablation is the aim of RAI (I-131) treatment. This will stop thyroid cancer from relapsing or spreading further.

RAI should only be used in patients aged 5 to 10 years when surgery is not a viable option, and it should be avoided in patients under the age of 5. The use of RAI in patients older than 10 years old or post-pubertal youngsters is not contraindicated. [22]

When dosimetry is difficult to organize, RAI activity should preferably be tailored using the activity of 15 MBq (0.4 mCi) per gram thyroid tissue or should aim to deliver at least 300 Gy to the thyroid gland when dosimetry is used. The most accurate method of estimating thyroid weight for I-131 dose calculation is ultrasonography. [22]

ATD should be discontinued for 3 to 7 days before RAI.[22]

RAI therapy should be avoided if Graves' orbitopathy is active. In order to avoid relapse or worsening in the case of inactive GO, a course of steroids should be administered concurrently. [22]

2.4. Definitive treatment - thyroidectomy

A high-volume thyroid surgeon should perform thyroidectomies on pediatric patients. The preferred procedure is a total thyroidectomy.[27,28] Before surgery, the pediatric GD patient needs to be biochemically euthyroid.[29]

ATDs and, if necessary, iodine, a beta-blocker, and glucocorticoids should be used as preoperative treatments. [22]

In individuals who are deficient in vitamin D, pre-operative vitamin D treatment lowers the incidence of post-operative transitory hypocalcemia.[30]

Shortly after thyroid surgery, levothyroxine therapy should be initiated. [22]

2.5. Pediatric Graves' Orbitopathy (GO) management

Children with eye problems should see an orbital expert, ideally at thyroid eye clinics that combine (ophthalmologist/physician) care. [22]

Mild GO symptoms without signs of inflammation can be treated with expectant management or, if necessary, selenium supplementation.[31]

Anti-inflammatory medications, such as intravenous corticosteroids, can be used to treat rare cases with moderate to severe active GO cases.[32]

Surgery can be used to treat chronic inactive stable GO, which may lower quality of life; however, all procedures, with the exception of decompression surgery, should be delayed until the face skull has fully developed.[33]

Children with GO are less likely to experience remission with ATDs and are more likely to experience a severe course of their GD.[34] In cases of active GO, thyroid surgery is preferable to RAI treatment, and if GO treatment is ineffective or has no effect, thyroidectomy may lower the risk of GO exacerbation.[35]

2.6. The risk of thyroid cancer

Like adults, young GD patients may have a somewhat increased chance of developing differentiated thyroid carcinoma.[36,37]

A pediatric endocrinologist should treat GD patients with palpable thyroid nodules in conjunction with the appropriate multidisciplinary team. [22]

Young individuals with thyroid nodules should either have a thyroid ultrasound performed, followed by cytological testing if the results indicate it, or they should have a total thyroidectomy. [22]

2.7. Prognosis

Young people with GD who were identified and treated when they were children may have a lesser quality of life than their peers who are healthy.[38] It is important to keep this in mind and, when necessary, take the proper action to address it.

3. PRACTICAL CHALLANGES OF PEDIATRIC GRAVES' DISEASE – CASE REPORT SERIES

3.1. Case report nr.1

Francisc, a 15-year-old teenage boy is diagnosed at 10 years old (November 2017) with GD after presenting the following symptoms, for about one year: weight loss, false diarrhea, excessive sweating, exophthalmia, palpitations, and fatigue. During that last year, he was seen in different medical specialties: in the Emergency Unit, Cardiology, Gastroenterology, and, finally referred to an endocrinologist, for the suspicion of hyperthyroidism. Laboratory findings confirmed GD (↑FT4 and FT3, ↓TSH, ↑TRAb). ATD treatment (Thiamazole) was started with the gradual lowering of the doses, during the next two years (at age 12) and then, continued with a low daily dose (2,5 mg).

Four months later, being on the minimum ATD dose, the family moves to the opposite side of the country and, this decision causes a lot of psychological stress on our patient. As the parents recall, around the move, the patient went through somewhat of a teenage rebellion, often starting conflicts against his parents for various reasons and overall feeling misunderstood. He also had trouble adapting to the new home and school and found it difficult to make new friends.

Probably, as a result of all this stress, GD relapsed. Discontinuation of treatment by his own decision could not be excluded.

Thiamazole treatment was started again, with maximum recommended doses (30 mg/day), and followed up by a local endocrinologist, with a slowly improved evolution. During the COVID pandemic, he was rarely seen by a doctor, hence, his parents contacted us many times for online/ phone consultations.

Almost one year later, at age 13 (in September 2020), the patient was experiencing biological hypothyroidism but still had a high TRAb titer. At that point, he was on Thiamazole 0.5 mg/kg/day, so our decision was to switch to a „block and replace" regimen, continuing with ATD and a low dose of Levothyroxine (25/50 mcg/day) finally the euthyroid state was attained (FT4, FT3 and TSH levels within normal limits, with normal TRAb titer). Levothyroxine doses were gradually lowered and, finally, discontinued. Three months later, he was euthyroid and the ATD dose was titrated from 5 to 2,5 mg/day.

He remained on 2.5 mg of Thiamazole/day until 14 years of age (December 2021), when he decided by himself, to stop the treatment without consulting any specialist.

Two months later (February 2022), he relapsed displaying symptoms of hyperthyroidism: excessive sweat, restlessness, insomnia, accelerated bowel movements, and weight loss.

He went back on the 2.5 mg dose of Thiamazole, again without consulting a specialist, but the symptoms did not disappear.

He returned to our Clinic three months later (March 2022) with all the above-mentioned symptoms and displaying severe biological hyperthyroidism with a suppressed TSH = 0.002 mU/L (0.48-4.17), with very high FT4 =133 pmol/L (10.7-18.4), FT3 > 30.8 pmol/L (3.54-6.47) and positive high titer of TRAb, TPO and TG antibodies. ATD therapy was started again with Thiamazole 1 mg/kg/day, and, two months later, we switched again to the BR regimen which helped us to

normalize hormonal levels (May to July 2022). However, the TRAb titer remained positive.

At that point, keeping in mind, also the enlarged goiter, and the evolution, we recommended definitive treatment, meaning surgery. Discussions about this option had been attempted before, but the family had always refused any. This time, the parents came with the proposition to have surgery, hence total thyroidectomy was scheduled.

He underwent surgery, this summer, at the age of 15. The procedure went well, with no intro and post-operative complications.

The patient is currently doing well, with a Levothyroxine substitution of 75 mg/day.

3.2. Case report nr. 2

Alessia, 14 years old, was diagnosed with Graves disease at age 13 (March 2021), after having displayed weight loss, restlessness, tachycardia, secondary amenorrhea, and visible enlargement of the thyroid region for approximately one year. She also presented a very significant family history of autoimmune thyroid pathology, including GD. At the time of the diagnosis, she presented suppressed TSH (<0,005), with high FT4= 46.6 pmol/L (10-28.2) and FT3. 15.8 pmol/L (3.54-6.47) and positive, high titer TRAb and TPO antibodies. A thyroid ultrasound exam showed a heterogeneous, hypoechoic thyroid, with increased vascularization ("thyroid inferno"). She was started on ATD therapy, with Thiamazole 0.5 mg/kg/day. After two weeks of treatment, the patient presented a generalized intense rash, associated with arthralgia of the small joints, which the attending physician interpreted as an allergic reaction to Thiamazole, seizing the therapy immediately. She was referred to, and, therefore, admitted to our service for further therapeutic decision, suggesting that PTU should be used instead of TMZ.

Further investigations showed a normal CBC and no changes in the liver function, and, also, confirmed the association of a Celiac disease, with high titer (>10 times the superior limit) of tissue transglutaminase IgA antibodies (TTG-

IgA=135.5 U) and normal serum IgA. Later, an endoscopy was performed in the Gastroendocrinology department, confirming the Celiac disease. A gluten-free diet was started promptly.

All investigations recommended by the specialist in allergology (C3, C4 fragments, the rheumatoid factor, the antinuclear antibodies) were normal and the detailed anamnesis was suggestive of some coincident dyspeptic episode, after the ingestion of some fish, at the time when the ATDs were initiated.

Taking into consideration the possible effects of PTU in children, we preferred to reinitiate ATD therapy with Thiamazole 0.5 mg/kg/day (under close surveillance) associated with a very low dose of Prednisone and antihistamine drug (Levocetirizine). We did encounter any allergic events. CBC count, liver enzyme, and also other usual lab investigations were within normal range.

The patient was gradually weaned off the Prednisone (after the first week) and continued with the Levocetirizine for another 4 weeks. She was released from the hospital, with ATD therapy and a gluten-free diet.

She was instructed to see the allergy specialist immediately, in case of an allergic reaction, in order to perform a basophil activation test for Thiamazole, which evaluates the degree of degranulation following stimulation with an allergen, and also to evaluate the anti-Fc epsilon R1 antibodies, which play a central role in the IgE-mediated allergic response.

Presently, the patient is euthyroid, no allergic reactions have appeared so far, she regained weight, and her menstrual cycles normalized, within the first 2 months of therapy.

She is presently treated with a low dose of Thiamazole, 2,5 mg/kg/day, in the 3rd year of treatment (she completed 2 years of treatment with no relapses).

3.3 Case report 3

Andreea, 14 years old, was diagnosed with Graves Disease at age 11, after displaying weight loss, restlessness,

hand tremors, insomnia, accelerated intestinal transit, tachycardia, and progressive exophthalmia. She also presented a voluminous goiter. At diagnosis, TSH was deeply suppressed, FT3 and FT4 increased↑ and TRAb and both TPO and Tg antibodies were positive, in high titers. Thyroid echography confirmed the increased thyroid volume, a significantly heterogeneous and hypoechoic thyroid tissue, with a pseudo-nodular aspect and an intense vascularization, the specific aspect known in GD as "thyroid inferno". She was started on ATD therapy, with Thiamazole 0.5 mg/kg/day, and, gradually decreased the doses to 0.2 mg/kg/day. During this time, her follow-ups showed a decreasing trend of TRAb titers (from 13.8 U/L to 2.5 U/L), but an increase in thyroid volume, despite becoming euthyroid.

Although initially, the TSH, FT4, and Ft3 normalized, soon after titrating the doses to 0.2 mg/kg/day, the hand tremors, tachycardia, and accelerated bowel movements reappeared. The specialist in her hometown decided, correctly, to increase the dose, once again to 0.5 mg/kg/day, but failed to monitor her properly in the following months because of the lack of compliance to regular visits and therapy adjustments of both, mother and daughter. Actually, the mother was divorced and there were quite important problems in communication between the two of them.

Hence, 4 months later, she becomes clinically hypothyroid and displays a ↑TSH and ↓FT4, FT3, but still high TRAb titer. She contacted us, for medical advice, to avoid the local endocrinologist, so, we switched to the BR regimen, associating a low Levothyroxine dose of 25 mcg to Thiamazole, and then, titrating the ATD doses to 0.2 mg/kg/day and lower. In the following months, the GD was apparently controlled, and, this allowed us to discontinue the Levothyroxine and titrate the Thiamazole dose to 2.5 mg/day.

However, the patient was quite undisciplined with regard to her lifestyle: unorganized meals, no physical activities, and uncontrollable use of electronic devices during the night instead of sleeping.

Meanwhile, although clinically and biologically euthyroid, the patient's goiter continues to progressively grow, to approximately 25 ml in thyroid volume. Apart from the unaesthetic appearance that upsets our patient quite a lot, it starts to induce compressive symptoms.

At this point, the patient is adamant about her wish to undergo a total thyroidectomy. After deliberating with the family, and explaining the pros and cons, we decide to recommend the definitive therapy. Taking into consideration the compressive effect of the voluminous goiter, we recommended surgery, namely total thyroidectomy. She was supplemented with vitamin D (1000 U/day) and Calcium (1000 mg/day) before surgery.

At 13 years and 7 months, she undergoes total thyroidectomy surgery. The procedure went well, with no intro and post-operative complications. Levothyroxine substitution was started after surgery but at a low dose (37,5 mcg/day, 0,9 mcg/kg/day).

At her post-operative endocrinology follow-up, after 20 days of the above-mentioned Levothyroxine substitution dose, her TSH was very high and FT4 slightly low. She was also displaying numbness in her extremities, bone and muscle pain, and overall fatigue. We checked her calcium-phosphorus metabolism, but the results were normal. The Levothyroxine doses were increased to 75 mcg/day (1.8 mcg/kg/day) and the symptoms slowly disappeared.

The patient is currently doing well, with a Levothyroxine substitution of 75 mcg/kg/day, and all hormonal levels normalized.

4. Discussions and conclusions

Treating adolescents with Graves Disease can be challenging in many forms. As each patient with GD can manifest slightly differently, adolescents tend to be somewhat unique patients, having unique types of GD. This statement is based not necessarily on the manifestation of the disease, but on its evolution and on its management.

Most teenagers are the same in the sense that they are so very different from one another. Each teenager has their own struggles and their own experiences and during this time, both the family and the attending physician need to engage in an individually designed approach toward achieving a successful treatment plan.

One needs to keep in mind that GD has a more chaotic development in teenagers. With periods of easily obtainable euthyroid status alternating with very resistant hyperthyroidism or with relapses during unexpected times, any physician needs to approach these patients in the most holistic manner possible.

Attention should be given to the patient's lifestyle. The whole family should be educated on the importance of healthy eating habits, moderate physical activity, and physiological sleeping patterns. The physician should engage the family in making changes together, in order to reduce the pressure on the patient and create a safe and healthy family environment for them. At follow-up examinations, discussions on the subject should always take place in order to monitor their progress and to make sure they stay on the course. If needed, recommendations of nutritionists or sports and leisure facilities in the area can be made.

As highlighted in the three case presentations, adolescents are very prone to discontinue treatment, miss doses, or miss follow-up appointments, due to teenage-specific type of behaviors which can vary from simply being bored with the treatment, to rebellion against their parents or even "the system".

The fight against these situations is through education. No matter how difficult the patient is, the physician needs to explain what GD means in the clearest way possible.

The emphasis should be on the importance of good compliance with the treatment and what are the probable consequences of disregarding medical recommendations.

In many cases, the family needs to be educated as well, because many adults take matters lightly and accept the

adolescent's decisions to disregard treatment without understanding the consequences.

The help of a psychology therapist can be employed when the physician feels that the mental well-being of the adolescent is not well enough to ensure proper compliance with treatment.

In our adolescent patients, BR therapy was useful in all 3 cases when relapses occurred. Although this method might not be very much recommended in this group age, we succeeded in obtaining euthyroid state with this regimen.

Communication with the family and adolescents is an important tool in obtaining the best results. And, as mentioned in the ETA guideline, to maximize compliance, education on GD, particularly its treatment, is crucial.

When discussing with them later, both patients who underwent surgery say they would have preferred to have had the surgery right from the start, instead of spending time trying to obtain euthyroidism with medical treatment. They both considered that their quality of life during medical treatment was not good at all.

In conclusion, adolescence is a difficult time even if healthy, but it becomes even harder with the burden of a chronic disease that seems to be so difficult to control.

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MINERAL STATUS IN CHILDREN WITH OBESITY

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Introduction

In the last years, a significantly increasing trend in obesity was observed all over the world. In many children and adolescents, obesity is complicated by insulin resistance, arterial hypertension (HTA) and hyperlipidemia.[1]

Micronutrients and macronutrients play an important role in the ethiology of obesity, being involved in the regulation of different metabolic processes.[2] Obese children, in particular, suffer from micronutrient deficiencies (calcium, magnesium, iron, zinc, selenium, cobalt, potassium, copper).[3]

Obesity and macronutrients play an important role in the etiology of type 2 diabetes, but so do micronutrients, the impalance of bioelements such as magnesium, zinc, calcium, copper and selenium beeing significantly associated with obesity.[4,5] Obesity is an important public health issue. Overweight and obesity are risk factors for micronutrient deficiencies. Compared with their normal-weight peers, children with obesity are at higher risk for developing zinc, iron, vitamins A, C, and E deficiencies. In obesity, micronutrient deficits are due to inadequate intake, changes in metabolism and excretion, and may influence:

- physiological functions of the body
- immune response
- risk of comorbidities
- leptin and insulin metabolism
- fat deposits and chronic inflammation.[6,7,8]

The increased prevalence of micronutrient deficits may contribute to the development of obesity, especially in rural areas where the prevalence of these deficits is higher. [7]

Bone mineral status in children with obesity

Calcium status in obesity

Calcium is the most plentiful mineral found in the human body:

- at birth, an infant has 20-30 g of calcium
- the adult human body contains 1.2 kg, the equivalent of 300 μmol or 1-2% of the human body weight.[9,10]

Over 90% of calcium is stored in the extracellular space, especially in bones and teeth.[11] Shortage of Calcium and vitamin D is common in many populations, especially in children with excess weight. Inadequate calcium levels along with low levels of 25-hydroxy-vitamin D are associated with increased cardio-vascular risk, obesity, metabolic syndrome, and type 2 diabetes mellitus.[12]

In 1984, McCarron et al. first reported the relationship between body mass index (BMI) and calcium intake (negative association). Analyses performed on adolescent girls by Abreu et al. showed an inverse correlation between milk intake, BMI and percent of body fat.[13] Epidemiological data claim that a higher calcium intake is linked with a lower prevalence of obesity and insulin resistance. Skinner et et al., quoted by Schrager et al., mention that an intake of 227 ml/day of skimmed milk or low-fat yogurt reduces body fat by 0.40%.[11]

Compared to adults, in whom the role of calcium in obesity has been studied more, there are few studies performed in children, which usually rely on different methods of evaluating the diet (24-hour diatery recall, food frequency questionnaire). They also evaluated the food source from which calcium originated, noting that the effects of calcium from dairy products appear to be stronger on obesity compared to the effects of that coming from fortified or enriched foods.[11,12] In contrast, low milk intake and low

calcium levels can lead to insulin resistance and increase the risk of hypertension (AHT).[11]

The mechanisms involved in the association between calcium and obesity have not been fully elucidated. One of the explanations would be that the low calcium intake increases the serum level of calcitriol that can stimulate the flow of calcium from adipocytes through the membrane receptors of vitamin D. Increased Ca^{2+} intracellular levels of calcium leads to increase in fatty acid synthase activity and inhibits the expression of hormone-sensitive lipase. Thus, lipogenesis is promoted and lipolysis is inhibited, with the accumulation of fatty acids. [12] Increased calcium intake decreases the level of parathormone (PTH) and decreases 1,25-hydroxy vitamin D. Decreased PTH level causes the decrease of intracellular calcium level with the inhibition of lipogenesis and the stimulation of lipolysis.[11] Decreased lipogenesis and increased lipolysis contribute to a smaller number of adipocytes and to the appearance of adipocytes of smaller size, which leads to a decrease in fat accumulation.[14]

Studies on mice have shown that an increased calcium intake is associated with a 51% decrease in the expression of fatty acid synthase and a 3-5-fold increase in lipolysis. [11] Other research on mice have shown that the addition of calcium to drinking water has led to significant weight loss, decreased body fat content, epididymal and inguinal white adipose tissue.[14]

The mechanism by which calcium intake triggers a reduction in abdominal obesity is unclear, but the autocrine production of cortisol in adipose tissue may be an explanation. Calcium-rich diet suppresses the level of calcitriol, leading to the accumulation of fatty acids by decreasing cortisol production in adipose tissue. Other studies claim that calcium supplementation and calcium in the diet can increase the fecal excretion of fats, with the formation of insoluble complexes in the intestine. Few studies have evaluated the role of calcium intake in regulating appetite.[12]

The anti-obesity mechanisms by which calcium acts include:

- regulation of adipogenesis
- modulation of fat metabolism (increased lipolysis, decreased lipogenesis)
- enhanced thermogenesis
- supression of fat absorption
- promotion of fecal fat excretion
- modification of gut microbiota.[14]

According to calcium-body weight hypothesis, dietary calcium acts at gastrointestinal level to increase energy loss through increased fecal-fat excretion.[14]

The inverse correlation between calcium intake and the adiposity observed in children of a higher age can be explained by the growth patterns: in the first years of life, body fat decreases, reaching a minimum at the age of 4-6 years, then the adiposity rebound occurs.[12] The negative correlation between calcium intake and obesity can also be explained by the interference of calcium with the intestinal lipid absorption and by the increased lipolysis determined by increased intracellular calcium concentration.[15]

An increase in calcium intake by 300 mg leads to a 1 kg decrease in body fat in children, and by 2.5-3 kg in adults. Vitamin D with a role in calcium absorption can also influence its anti-obesity effects.[14] Gomes et al., cited by Zhang (2019), mention that a 3-month diet rich in calcium from dairy products helps reduce abdominal fat in patients with overweight diabetes. Different studies showed that supplementation with calcium decreases fat absorption and increases the fecal excretion of insoluble calcium soaps with fatty acids. Augmenting calcium intake up to 1600 mg/day for 7 days with calcium from dairy products leads to a two-fold increase in fat excretion, or an intake of 1241 mg calcium/day increases fecal fat to 5.2 g/day.[14]

Magnesium status with obesity

Magnesium is the fourth most abundant mineral in the body after calcium, sodium and potassium, and the second most important intracellular cation after potassium.[8,17] During pregnancy, the fetus accumulates 8 mg of magnesium,

and annexes - 5 mg.[18] The human body contains 760 mg magnesium at birth, 5 g around 4-5 months and 25 g in the adult age, of which 90% is found in the bones as a constituent of hydroxyapatite (63%) and muscles (27%), 10% being free and less than 1% found in the blood.[17,19,20,21]

Natural sources of magnesium are represented by whole grains, nuts, seeds, vegetables, leafy greens.[17,22] Low intake of magnesium can also be explained by the consumption of large amounts of processed foods.[23]

Magnesium and calcium work together in regulating the metabolic response in overweight and obese patients. Magnesium is an antagonist of calcium, and its metabolic effect should be discussed depending on the concentration of calcium. A calcium/magnesium ratio induced by a diet rich in calcium and low in magnesium increases the risk of developing AHT, insulin resistance and metabolic syndrome.[22] The opening of calcium channels and the activation of N-methyl-aspartate receptors permit entry of calcium ions into cells, the release of neurotransmitters (such as substance P), oxidation of membranes and the activation of nuclear transcription of factor kappa B (NF-kB), which favors inflammation. The decrease in extracellular magnesium induces an increase in the concentration of intracellular calcium with cytokine production. Excess calcium causes the activation of calcium-dependent processes such as the release of proinflammatory cytokines. Magnesium deficiency triggers the production of free radicals and cell sensitivity to the attack of reactive oxygen species (ROS).[23,24] Hypomagnesemia plays a role in reducing the expression and activity of antioxidant enzymes (glutathione peroxidase, superoxide-dismutase, catalase), with the increase of hydrogen peroxide production by inflammatory cells. In the presence of hypomagnesemia, intracellular calcium contributes to the excessive production of uric acid and hydroxyl radicals that react with nitric oxide, with the formation of peroxynitrite. Therefore, the production of reactive species in patients with magnesium deficiency contributes to the inflammatory status present in obese patients.[23]

Around 15-20% of the population has magnesium deficiency, but serum magnesium does not reflect intracellular magnesium which accounts for 99% of total body magnesium and, therefore, many cases with deficiency remain undiagnosed. Magnesium deficiency is associated with inflammation and inflammatory stress which is a risk factor. 24 Magnesium deficiency leads to irritability, convulsions, tetany, hypo-/hyperreflexia, and muscle tremors.[2]

Serum magnesium has a negative correlation with the abdominal perimeter, weight, BMI, blood sugar, VLDL, systolic and diastolic blood pressure, triglyceride levels, insulinemia, interleukin-6 (IL-6) value, TNF-alpha and C-reactive protein (CRP) and a positive correlation with hdl-cholesterol level.[5,15,17,23,25] There is also a positive correlation between urinary magnesium and CRP concentration in obese individuals, hypomagnesemia influencing this inflammatory marker.[23] Different studies have concluded that there is a positive correlation between low dietary intake of magnesium and the risk of developing metabolic syndrome. Low chronic dietary intake of magnesium leads to deficiency of serum and intracellular magnesium which is more evident in obese patients with metabolic syndrome.[22]

In 1990, it was observed that magnesium deficiency is associated with various conditions characterized by the presence of chronic inflammatory stress. In 2007, following animal studies, it was concluded that a magnesium intake of less than 10% of the required intake causes the development of an inflammatory response characterized by the activation of macrophages and leukocytes, the release of cytokines and acute phase proteins, and excessive production of free radicals, in long-term deficits.[24] Magnesium deficiency leads to changes in cellular function, biological changes in molecules, activation of proinflammatory pathways, development of pro-inflammatory status through overproduction and release of cytokines (IL-1β, TNF-α), and at the onset of metabolic diseases related to inflammation.[23]

Some enzymes involved in the oxidation of glucose are dependent on magnesium. Magnesium is necessary for the

activity of lecithin cholesterol acyl-transferase and lipoprotein-lipase, as well as for activation of vitamin B1 in thiamin diphosphate (TDP). In order to become active, TDP-dependent enzymes require magnesium.[22] It also plays a role in glucose and insulin metabolism and may affect glucose transporter 4.[26] Low intracellular concentrations of magnesium and/or TDP may alter oxidative glucose metabolism. In the liver, decreased magnesium activity and TDP-dependent pyruvate-dehydrogenase may influence glucose metabolism, generating an excess of nicotinamide adenine dinucleotide phosphate (NADPH).[22] In obese people, many daily calories come from refined cereals and simple carbohydrates and, consequently, hepatic catabolism of glucose is very active.[22]

Serum magnesium is involved in the pathogenesis of obesity and its related diseases. Magnesium intake is a factor that significantly influences the incidence of obesity, low levels being associated with obesity.[27] Different studies observed abnormalities of serum magnesium levels in obesity and associated diseases.[3,26] According to Bipin et al., cited by Zaakouk (2016), by comparison with normal weight children, obese children have lower serum magnesium levels, despite the increased dietary intake.[26] In the study carried out by Jose et al., cited by Hassan (2017), obese children had lower serum magnesium levels (2.12±0.35 mg/dl), in comparison to normal weight children (2.56±0.24 mg/dl).[3]

Serum magnesium levels are inversely correlated with the degree of obesity and serum lipid profile (total cholesterol, LDL-cholesterol) in obese children and adolescents.[26] Magnesium has a role in determining a person's weight.[3] Children with magnesium deficiency have a higher BMI. Magnesium deficiency may trigger an accumulation of visceral fat, associated with increased proinflammatory citokine production.[1,23] Visceral fat is a modulator of the action of insulin on the hepatic production of glucose.[28]

It was observed that obese children have low serum magnesium levels, despite a high dietary intake of food rich in magnesium, which could be accounted for by a decreased gut absorption of magnesium or its increased excretion.[3,17] In the

gut, a higher intake of calcium or fats could interfere with absorption of magnesium. The high consumption of carbonated beverages could affect the absorption of different nutrients, like magnesium.[3]

Consumption of carbonated drinks with a high phosphorus content can interfere with the absorption of magnesium, while caffeine can increase renal clearance of magnesium.[29] Increased consumption of fast foods and reduced consumption of fiber, whole grains and leafy greens are associated with hypomagnesemia and obesity.[17]

Insulin is one of the important factors that control magnesium levels. In its turn, magnesium influences the level and action of insulin.[28] Low serum magnesium levels may contribute to the development of insulin resistance in obese children, like the poorer status of calcium.[2,3,30] It also causes impaired glucose tolerance, as well as decreased insulin secretion. The mechanism by which magnesium deficiency leads to insulin resistance has not yet been elucidated. Magnesium deficiency can be associated with increased levels of intracellular calcium that lead to insulin resistance. Dietary intake of magnesium is inversely correlated with insulin resistance.[4]

Vitamin D deficiency is common in people with obesity and magnesium is also essential for the synthesis of vitamin D and its activation. Chronic or latent deficiency of magnesium and/or vitamin D deficiency predispose non-diabetic obese to an increased risk of developing cardio-metabolic disease.[22] Magnesium deficiency increases the reactivity of the arteries to vasoconstrictor substances, promotes vasoconstriction and increases peripheral resistance, as well as blood pressure. [31] Intake of omega-3 fatty acids, antioxidant vitamins and flavonoids that alleviate chronic inflammation can also reduce magnesium deficiency.[32]

Iron status in obesity

Iron metabolism and chronic diseases influence each other in various ways, including by oxidative stress in which

iron plays a key role as a prooxidant, when in excess. [33] In 1962, Wenzel et al. were the first to mention the association between obesity and iron deficiency, which was later signaled by Seltzer and Mayer, who proposed different hypotheses: unbalanced diet, greater need for iron due to increased blood volume, decreased myoglobin due to decreased physical activity.[34] Children with central and generalized obesity are more susceptible to iron deficiency, with or without anemia, as they stimulate inflammatory cytokines that are associated with suppression of serum iron levels. Obese patients have a two-fold increased risk of being diagnosed with iron deficiency anemia.[35]

Iron deficiency is common in overweight and obese patients, especially in children aged between 12-16 years and in obese girls who grow faster, requiring routine screening for iron deficiency.[35,36,37] The prevalence of iron deficiency in obese patients is 30.70%, and of iron deficiency anemia - 11.70%.[35]

Obesity is associated with iron deficiency and iron profile abnormalities caused by various factors (low intake, insufficient bioavailability, poor intestinal absorption). [38] The association obesity - iron deficiency may rely on a combination of nutritional factors and functional parameters, as well as genetic factors, lack of physical activity, increase in hepcidin, decrease in iron intake, increased iron needs, absorption disorders, low-iron diet.[35] Inadequate food intake, along with chronic inflammation, may contribute to iron depletion.[39]

Iron deficiency in obese children is common, but the undelying mechanism is unclear.[40] Changes in cytokine production lead to impaired production of erythropoietin and the response of erythropoioid precursors, a mechanism recognized in anemia associated with chronic diseases. Into the duodenal enterocytes, the density of divalent metal transporter 1 (DMT1) increases in the apical membrane, while the 1 and 8 ZIP transporters decrease.[41] The interaction between iron, obesity and inflammation makes it difficult to recognize the specific role each of them play in the risk of

obesity-induced metabolic disease.[42] Inflammation in obesity may determine the storage of iron in tissues, leading to a decrease in iron available for erythropoiesis. Seizure-mediated iron accumulation is associated with the appearance of metabolic syndrome and non-alcoholic fatty liver disease – hepatic manifestation of metabolic syndrome.[42]

The connection between iron and excess adiposity was of interest, and chronic inflammation could be caused by excessive adiposity.[43] Also, inflammation and adiposity exert a concomitant effect on erythropoietic activity.[44] Low cellular levels of iron have a positive effect on the health of adipose tissue and can restrict the absorption of lipids from the intestines.[14]

Inflammation, both acute - caused by infections, and chronic - caused by metabolic disturbances, can affect iron homeostasis by interfering with the regulation and synthesis of acute phase proteins (ferritin, transferrin, hepcidine, haptoglobin), affecting the distribution of iron in cells. Inflammation can adversely influence iron balance by decreasing both food intake and intestinal absorption.[34] Assessment of iron status involves the measurement of several indices. Ferritin and hepcidine are key mediators for the regulation of iron homeostasis and are acute phase reactants with an important role in inflammatory processes. [33]

Ferritin, a major iron storage protein, is considered the best indicator for the detection of iron deficiency in the absence of inflammation, whereas inflammation is associated with a decrease in serum iron and transferrin levels. [42] Between ferritin and BMI there is a positive correlation, while between ferritin and serum iron there is a negative correlation.[33]

Hepcidine (a proinflammatory cytokine) regulates the absorption of iron from the intestine and its release from macrophages is an important regulator of erythropoiesis. Hepcidine is secreted into the plasma, excreted in the urine, and controls ferroportin (iron transporter).[39] Interleukin-6 (IL-6) and leptin secreted by adipose tissue stimulate the secretion of hepcidin.[34] Hepcidine increases with the increase

in IL-6, which acts as a stimulator of hepcidin.[46,47] In obese children and adolescents, serum hepcidin levels are significantly increased.[38] Hepcidine is the main inhibitor of intestinal absorption of iron.

Its expression is increased in the adipose tissue of obese patients.[48,49] In vitro, leptin is able to increase the expression of hepcidine. The increased production of hepcidin, partly mediated by leptin, is the link between obesity and impaired iron metabolism.[48] Increased hepcidin in response to inflammation caused by obesity may be responsible for increased ferritin levels and the reduction of serum iron.[35] Hepcidine has negative correlations with the level of hemoglobin, serum iron and transferrin saturation in obese patients with iron deficiency anemia,[49] and positively correlates with BMI.[33]

Hepcidine cannot be used as a diagnostic method, but it can be useful as a method of screening iron deficiency anemia in obese children.[38] The concentration of hepcidin is related to that of ferritin, and the increase in their concentration is associated with a decrease in the absorption of iron.[33]

The increased accumulation of iron in the liver in non-alcoholic fatty liver disease may be due to a decrease in ferroportin levels induced by a decrease in hepcidin. The growth of hepcidin degrades ferroportin which allows the releasing of iron. The increased expression of hepcidin and the low expression of ferroportin, in these patients, cause iron retention, and this overload with iron may generate more inflammation and oxidative stress.[42]

When iron is not adequately absorbed, an important fraction reaches the liver and serves as a nutrient for bacteria. Therefore, supplementation releases pro-inflammatory markers and exacerbates inflammation, aggravating obesity.[33] Abdominal perimeter correlates negatively with the level of serum iron and transferrin saturation.[35]

Overweight and obese children have a limited response to iron administration.[43,49] Increased adiposity is accompanied by a poor improvement in the status of the iron even after supplementation or fortification.[33] The connection between

systemic inflammation related to adipose tissue, hepcidin and cellular transport of iron provides a plausible explanation for the reduction in iron status and the response to oral iron treatment in these children.[43] Iron treatment can create lipolysis and affect glucose absorption in response to the action of insulin.[42] Weight loss reduces chronic inflammation and the concentration of hepcidin, and improves iron status in obese children by increasing its absorption.[33,50] Reduction in BMI and fat mass, CRP, IL-6, ferritin, hepcidin, and in soluble receptor of transferrin leads to increased serum iron concentration.[50]

Zinc status in obesity

Zinc plays a critical role in cell growth and in the fight against infections. It also has a role in stimulating food absorption, protein synthesis, appetite and taste acuity. It is involved in the development of metabolic syndrome, regulating the expression of cytokines in carbohydrate and lipid metabolism (regulateing insulin expression).[2,51,52]

The signs of zinc deficiency are represented by:

- growth retardation
- anorexia
- severe steatorrhea
- increased sensitivity to infections
- delayed gondal development.

This deficiency may be associated with insulin-resistance, hyperglycemia, impaired glucose tolerance (high HOMA-IR), increased levels of inflammation.[7,53]

Low concentrations of zinc, vitamins A and E, in overweight and obese children are associated with inflammation and insulin resistance. The study of Ortega et al., cited by Garcia et al (2013), claims the presence of an increased risk of developing insulin resistance in patients with high BMI and low zinc concentrations. Zinc deficiency is also a potential risk factor for insulin resistance associated with type 2 diabetes mellitus. The expression of adipocitokine zinc-alpha-2-glycoprotein (ZAG), involved in the stimulation of

lipolysis in adipocytes, is reduced in obesity and is correlated with insulin resistance.[7]

Disturbances in zinc homeostasis have been observed in various diseases (diabetes mellitus, autoimmune diseases, cardio-vascular diseases, cancer). Various studies have shown that obese people have low concentrations of zinc in plasma, serum and erythrocytes. Plasma zinc is influenced by several pathophysiological factors in response to various situations (infections, stress, hormonal factors, food intake, catabolism). Patients who receive a diet low in zinc show a higher level of systemic inflammation in parallel with alteration of the lipid profile.[54]

Nivelul zincului în eritrocite la obezi este scăzut ca urmare a influenţei procesului inflamator asupra metabolismului zincului. Inflamaţia promovează acumularea zincului în ficat și adipocite care poate contribui la corelaţii negative ale zincului seric cu BMI, perimetrul abdominal și grosimea pliului cutanat. Corelatii negative au fost găsite și între zincul seric și trigliceride și LDL-colesterol. Între perimetrul abdominal, BMI, LDL-colesterol și concentraţia plasmatică a zincului există o relaţie inversă, acest fapt fiind asociat cu acumularea de ţesut adipos, cu creșterea producţiei de cortizol și adipocytokine.[53] Zincul scăzut se asociază cu valori crescute ale lipidelor, inflamaţie și insulino-rezistenţă.[2,8]

The level of zinc in erythrocytes in obese is decreased as a result of the influence of the inflammatory process on the metabolism of zinc. Inflammation promotes the accumulation of zinc in the liver and adipocytes that can contribute to negative correlations of serum zinc with BMI, the abdominal perimeter and the thickness of the skin fold. Negative correlations have also been found between serum zinc and triglycerides and LDL-cholesterol. Between the abdominal perimeter, BMI, LDL-cholesterol and the plasma concentration of zinc there is an inverse relationship, this fact being associated with the accumulation of adipose tissue, with the increase of cortisol and adipocytokine production.[53] Low zinc is associated with high lipid levels, inflammation and insulin resistance.[2,8]

Cortisol induces the expression of the metallothionein genes and of the Zip 14 transporter, which favors the redistribution of plasma zinc in different tissues (adipose tissue, liver), leading to the development of hyposincemia in obesity. Cortisol affects the distribution of zinc in obese patients, helping to compromise the action of insulin. Changes in cortisol-induced zinc homeostasis may contribute to the development of insulin resistance in obese people. Also, the presence of hormonal changes in obesity can have repercussions on zinc metabolism.[55]

The decrease in the concentration of serum zinc is accompanied by an increase in its urinary concentration, being an indicator of the increased excretion of zinc in obesity. The low status of zinc in obesity is associated with the aggravation of metabolic disorders related to obesity (insulin-resistance, inflammation, alteration in the lipid profile).[51] It is unclear how deficiencies of zinc and magnesium affect each other, causing pathophysiological alterations in obesity.[8]

Zinc supplementation is beneficial on the lipid profile of patients with metabolic syndrome and diabetes mellitus. Zinc supplementation is associated with improved lipid profile (decrease in apolipoprotein B and A1, total cholesterol, LDL-cholesterol). Supplementation with 30 mg zinc/day for 8 weeks increases serum zinc by 15%.[53] Administration of 30 mg zinc/day for one month leads to weight loss, decrease in BMI and triglycerides. 50 mg zinc/day administered for 12 weeks twice increases the level of adiponectin.[51] Weight loss increases the circulating levels of zinc.[54]

Conclusions

A diet plan for weight loss, but also the consumption of a diet high in calories and low in nutrients, may be followed by nutritional deficiency, in particular iron.

Alteration of iron metabolism is not only a consequence of obesity, but can play an important role in the development of metabolic disorders in obesity. Low status of iron and anemia in obesity may be attributed to inflammation rather than to a reduced iron intake.

Ferritin is influenced by inflammation and, therefore, the parameters of inflammation should be measured along with those for iron metabolism. Patients with obesity, especially those at high risk (including children and adolescents), must undergo a regular screening for iron status.

Iron supplementation should be carefully recommended and monitored, so as to first treat the inflammation and then the anemia. Increasing daily calcium intake can contribute to weight loss and fat loss.

The presence of magnesium deficiency favors chronic inflammation in obese people. Since magnesium deficiency occurs in people who do not receive the recommended dose, magnesium should be considered an element of good nutrition, important to health. The problem of magnesium deficiency is difficult to be compensated only by consuming foods reach in magnesium. Serum magnesium can be used as a biomarker for obesity – related comorbidities.

Adequate intake of magnesium, in amounts to counteract chronic inflammation, can reduce the risk of developing obesity. Due to the fact that magnesium has beneficial effects on cardio-vascular system, its supplementation is important in obese patients, which have an increased risk of cardio-vascular morbidity and mortality.

The low status of zinc in obesity is associated with the aggravation of metabolic disorders related to obesity.

Clinicians should consider addressing possible deficiencies of these micronutrients when advising obese patients.

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UNCONTROLLED DIABETES COMPLICATED BY GLYCOGENIC HEPATOPATHY IN MAURIAC SYNDROME

Cristina Maria Mihai, Tatiana Chisnoiu

Introduction

Glycogenic hepatopathy or hepatic glycogenosis is a rare complication in patients with type 1 diabetes mellitus (T1DM) in cases with inadequate glicemic control.

In 1930, Mauriac first described hepatic glycogen reload as a component of Mauriac syndrome (MS) in children, a rare condition characterized by hepatomegaly with elevated transaminases, puberty and growth failure, dwarfism, dyslipidemia, insulin-like growth factor inhibition 1 and cushingoid manifestations.

Most cases occur during adolescence and two different forms of Mauriac syndrome have been described depending on the presence or absence of obesity. Insufficient glucose in tissues, low insulin levels such as growth factor 1 and growth hormone levels, and excess levels of cortisol can lead to delayed growth and puberty. Hepatomegaly is thought to be due to glycogen deposition in the liver. Growth failure, delayed puberty, and hepatomegaly in Mauriac syndrome improve with glycemic control.

Definition

Mauriac syndrome represents a rare complication of type 1 diabetes (T1D) with inadequate glycemic control that occurs more frequently in adolescents, characterized by[1]:

- Hepatomegaly/hepatic glycogenosis
- Growth failure
- Abdominal distension
- Delay puberty
- Cushingoid features
- Hyperlipidaemia

Mauriac syndrome was first described in 1930 by Mauriac in children with type 1 diabetes. Most cases occur during adolescence, with an equal sex ratio. Depending on the presence or absence of obesity, two different forms of Mauriac syndrome have been described. Growth failure, delayed puberty, and hepatomegaly in Mauriac syndrome improve with glycaemic control and are often associated with retinopathy and nephropathy[1].

Mauriac syndrome - pathophysiology

The pathogenesis of growth failure is unclear but is thought to be multifactorial. Mauriac syndrome may be caused by a variety of factors, including tissue glucose insufficiency and reduced levels of insulin-like growth factor I (IGF-1) and growth hormone or resistant/deficiency hormone receptors.

However, the exact etiology has not been elucidated. It is unclear why it is not common in children with poorly controlled DM1 but occurs occasionally.

The large fluctuations in blood glucose levels that accompany periods of hyperglycaemia and hyperinsulinemia appear to be the central element to the pathophysiology of Mauriac syndrome. High glucose levels promote the influx of glucose into liver cells, while hyperinsulinemia stimulates glycogen synthase, resulting in the conversion of glucose-6-

phosphate to glycogen. In addition, serum levels of cortisol, a counter-regulatory hormone in response to hypoglycaemia, are also elevated, which is common in patients with poorly controlled T1D2.

In recent years, several paediatric cases of Mauriac Syndrome have been reported in the specialized literature. Most reports have demonstrated that adequate management to achieve optimal glycaemic control can lead to clinical, laboratory and histological remission of abnormalities[3].

Ref.	Age/Sex	Duration of diabetes	Clinical features	Follow-up
Franzese (2001)	14 ys/F	11 years	Hepatomegaly, cushingoid appearance, puberty delay, elevation of aminotransferases and triglycerides	Resolution
Carcione (2003)	3 ys/F	1 month	Hepatomegaly, elevation of aminotransferases	Resolution
Mahesh (2007)	3 ys/M	2 years	Hepatomegaly, short stature, elevation of aminotransferases	Resolution
Aljabri (2011)	13 ys/M	3 years	Hepatomegaly, elevation of aminotransferases	Unknown
Dantuluri (2012)	14 ys/F	5 years	Mild hepatomegaly	Unknown
Lin (2012)	10 ys/F	7 years	Hepatomegaly, elevation of aminotransferases	Resolution
Saisuka (2013)	13 ys/F	4 years	Hepatomegaly, elevation of aminotransferases	Unknown
Gutch (2013)	15 ys/M	8 years	Hepatomegaly, short stature, puberty delay, elevation of aminotransferases	Resolution
Oeschgef (2014)	11 ys/F 10 ys/M 14 ys/F 14 ys/F 13 ys/F	2 years 3 years 11 years 8 years 10 years	Hepatomegaly, cushingoid appearance, elevation of aminotransferases and triglycerides Hepatomegaly, short stature, elevation of aminotrasferases Hepatomegaly, short stature, cushingoid appearance, puberty delay, elevation of aminotransferases Hepatomegaly, short stature, cushingoid appearance, puberty delay, elevation of aminotransferases Hepatomegaly, short stature, cushingoid appearance, puberty delay, elevation of aminotransferases	Unknown Resolution Resolution Poor improvement Resolution
Butts (2014)	13 ys/F	2 years	Hepatomegaly, elevation of aminotransferases	Unknown
Chandel (2017)	12 ys/F	5 years	Hepatomegaly, elevation of aminotransferases	Resolution
Al Sarkhy (2017)	6 ys/F	4 years	Hepatomegaly, elevation of aminotransferases	Resolution
Kocova (2018)	13 ys/M	8 years	Hepatomegaly, short stature, cushingoid appearance, puberty delay, elevation of aminotransferases	Resolution

Fig 1: Major pediatric case reports with hepatic glycogenosis in type 1 diabetes

Mauriac syndrome and hepatomegaly

Hepatomegaly is an important feature of Mauriac syndrome present in most cases, which occurs due to hepatic glycogen deposition due to the facilitated diffusion of glucose into hepatocytes. The diagnosis of glycogenic hepatopathy includes the exclusion of other causes of liver damage, namely infectious, metabolic, obstructive or autoimmune diseases[4].

Glycogenic hepatopathy was described for the first time by Mauriac in 1930 as "hepatic glycogenosis", in children presenting "brittle diabetes", cushingoid features, poor growth and hyperlipidemia. Later reports showed the presence of hepatic glycogenosis without other features of the syndrome. The pathophysiological process of glycogen hepatopathy involves two components: hyperglycemia and hyperinsulinization[5].

Increased enzyme activity promotes hepatic glycogen storage by converting glucose-1-phosphate to glycogen. Since the entry of glucose into the liver via the GLUT-2 mechanism is independent of insulin, hyperglycemia itself also initiates glycogen synthesis. In some cases, glycogen can also be stored in the kidneys, causing nephromegaly.

Although the most common cause of aquired glycogenic hepatopathy is uncontrolled T1D, uncontroleed type 2 diabetes and corticosteroid use can also cause this type of glycogenic hepatopathy. In glycogenic hepatopathy, hypercortisolism also contributes to glycogen storage in the liver. Hypercortisolism also causes delayed sexual maturation in patients with Mauriac syndrome[5].

Mauriac syndrome vs Non alcooholic fatty liver disease

Mauriac syndrome is considered a rare entity in the era of intensive insulin treatment for T1D patients. However, it still exists and may be underdiagnosed due to difficulties in differential diagnosis with non-alcoholic fatty liver disease (NAFLD). Current evidence suggests that NAFLD is rare in T1DM, with a prevalence of less than 10%, which is lower than the general population, while the prevalence of NAFLD in type 2 diabetes is approximately 70%[6].

Although non-invasive methods are explored for the diagnosis of hepatic glycogenosis, such as CT, MRI, liver biopsy is essential for the differential diagnosis, namely with

NAFLD. The distinction between these two entities is very clinically relevant. In NAFLD, progressive fibrosis and cirrhosis may occur in a significant number of patients, with an increased risk of developing hepatocarcinoma. On the contrary, hepatic glycogenosis shows a favorable evolution, without evidence of significant fibrosis[7].

It is important to distinguish nonalcooholic steatohepatitis from glycogenic hepatopathy. The main means of distinguishing them is a liver biopsy. However, if glycogenic liver disease is suspected, empiric therapy to regulate glycaemic control could be initiated and biopsy may not be necessary. In some cases, glycogenosis and steatosis can exist simultaneously in the same patient[7].

Mauriac syndrome and Evolution

In patients with Mauriac syndrome, all clinical features regress with optimal insulin therapy and strict glycaemic control. During follow-up, in patients with glycogenic hepatopathy, hepatomegaly and elevated liver enzyme levels usually normalize with strict metabolic control for at least four weeks[8].

In a patient with type 1 DM, if hepatomegaly persists for more than four weeks, other causes should be investigated.

In a large review of 18 patients (1971-2008), Kim et al. suggest that hepatomegaly and elevated liver enzymes were the first to improve when metabolic control was achieved. Growth acceleration is variable with improved metabolic control and final height depends on age and initial lack of growth.[9]

Hypoglycaemia can occur in patients with type 1 DM as a result of aggressive insulin treatment or impaired counterregulatory hormone response[10].

Possible mechanisms of short stature in Mauriac syndrome include insufficient glucose utilization, reduced circulating IGF-I, and a state of relative growth hormone

resistance. Mauras et al. investigated the mechanisms involved in growth failure in two patients with Mauriac syndrome. No hypothalamic-pituitary dysfunction was observed in these. Growth resumes with adequate insulin treatment in patients with Mauriac syndrome[11].

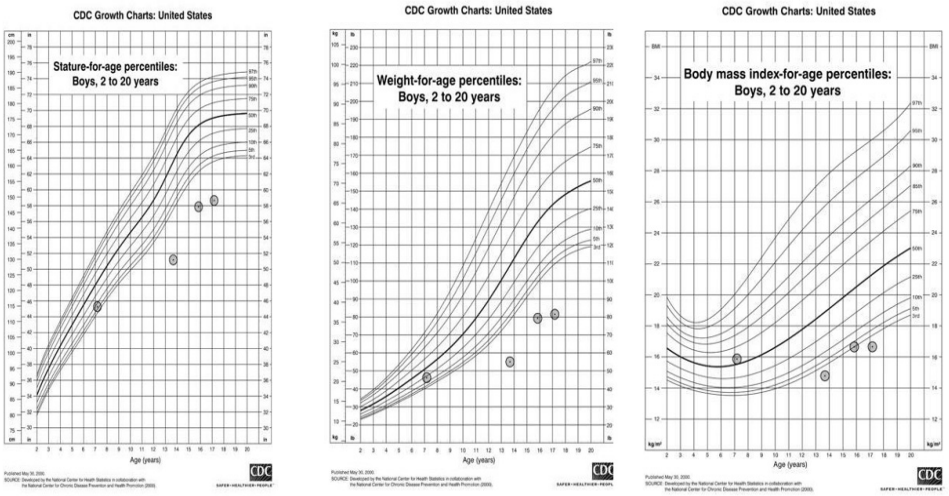

Fig 2: Growth chart with growth failure in a 17 year old boy with T1D

Adolescent growth and maturation in patients with type 1 DM should be closely monitored with optimal therapy. Delayed puberty in Mauriac syndrome can also be reversed with optimal insulin therapy. Trassman et al. followed a patient diagnosed with Mauriac Syndrome for 22 years and it was observed that she carried out two successful pregnancies despite delayed sexual development[12].

Cushing-like features may be due to secondary hyperadrenocorticism.

Improvement of metabolic control in children with Mauriac syndrome is mandatory, including treatment with insulin analogs. However, if good glycaemic control is achieved quickly, retinopathy may be induced or existing retinopathy and/or kidney disease may worsen over several months.

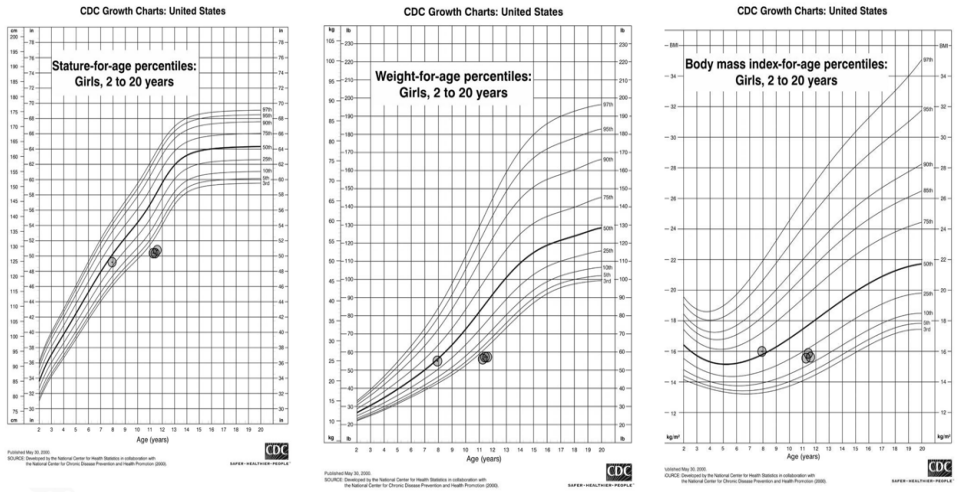

Fig 3: Growth chart with growth failure in a 12 year old girl with T1D

Because of the potential to gradually improve metabolic control and avoid large glycaemic fluctuations, continuous insulin administration may be an adequate therapeutic option for patients with Mauriac syndrome.

International studies regarding insulin pump therapy show that the improvement in metabolic control is gradual, in the range of 0.5-1.0 for HbA1c[14].

Conclusions

In conclusion, despite improvements in metabolic control in children with diabetes worldwide, patients with Mauriac syndrome are still being identified, although it is a rare entity in developed countries.

Mauriac syndrome should be considered in a T1D patient with poor metabolic control and hepatomegaly associated with transaminase abnormalities.

The development of non-invasive perspective imaging methods may be useful in the differential diagnosis of NAFLD, but currently, liver biopsy is still necessary.

Although patients with type 1 diabetes have indiscriminate access to the best types of insulin, self-monitoring tests, continuous glucose monitoring systems, insulin pumps, we (still) diagnose Mauriac syndrome.

Poor glycemic control is only one of the causes, as long as there are patients with unsatisfactory glycemic control who do not develop this complication.

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LIMITED JOINT MOBILITY (LJM) AS A NO-COST RISK FACTOR ALERT FOR COMPLICATIONS WITH PEDIATRIC, ADOLESCENT AND YOUNG ADULT TYPE 1 DIABETES MELLITUS

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Introduction

Limited joint mobility (LJM)[1,2,3] seems to be another example of tissue glycosylation in patients with type 1 diabetes mellitus (T1DM) with a unique characteristic that it seems associated with other known complications of T1DM hyperglycemia[4] such as retinopathy, neuropathy, nephropathy as well problems like hypertension and other associated microvascular and macrovascular problems.[5] If this is the case and LJM precedes (or co-exists) the development of subclinical as well as clinical diabetes complications,[6] then actually checking for LJM at least annually[7,8,9] should be routinely recommended for every patient around the world with T1DM (and documented in their medical records) with the hopes that this "free" examination[10] will precede the onset of subclinical and clinical complications associated with chronic hyperglycemia with sufficient time to intervene with more and better education, more and better nutrition and psychosocial counseling and more intensive home glucose monitoring as well as insulin administration possibilities.[11] In so doing, this may also identify those people with diabetes (PWD) who may be able to benefit from improved glucose levels with sufficient time to not only identify those

PWD and get specific complications monitoring done (if not already done), arrange for appropriate specialty consultation (ophthalmology, nephrology, neurology), empower improved glucose control and either slow down and/or hopefully reverse such early difficulties by identifying those most in need.[12]

LJM has been called flexion contractures and joint contractures in the medical literature.[13] It was first described in 1957 by Lundbeck[14] but "medically forgotten" until Jung redescribed the "diabetic hand syndrome" 14 years later in 1971.[15] Rosenbloom and Frias[16] presented a small report in 1974 of three such younger patients as a "new syndrome" and then followup evaluation of a cohort of 228 campers in Florida.[17] This was followed up by larger prospective as well as family history studies of joint abnormalities by Rosenbloom and colleagues[18,19,20,21] including a follow up study at the same specialty practice twenty years following their first observations in Florida.[22]

Confirmatory studies from our own patients in Boston[6,7,8] have been reported as have been many others from California[23], France[24], Germany[25] and the United Kingdom,[26] for example, with most studies[27] involving the direct observation and evaluation of the fingers, hands and wrists either in the "prayer or clapping position" (*Table 1*) as well as asking the patients to place their fingers and hands palm down on a flat surface. Slama and colleagues[24] have used a mechanical goniometer as a means of such assessment.

Much to the chagrin of our own group as well as several others (and as acknowledged by Professor Rosenbloom in several oral presentations as well as his research reports and reviews of LJM) because LJM was not causing pain or interfering with day-to-day functioning, it was almost always somewhat of a surprise for investigators and clinicians to be able to document these findings. This has also been important for the PWD and his or her family to be able to see what looks like the first "obvious" sign that diabetes is causing some physical problems - and not just the potential for the scary and worrisome long-term issues. If pain or other neuromuscular finding are also present, other disorders such

as tenosynovitis or carpal tunnel syndrome, osteoarthritis, osteoporosis, Dupuytren disease and gout should be considered.[9]

Table 1.
Assessment of LJM using "Flat surface, palm down" and "Clapping" or "Prayer" positions [28]

1. Observe and gently shake both hands of the subject to assess any pain or discomfort as well as any waxy, skin thickening
2. Ask subject to place hands palm downward on a flat surface. The entire palmar surface should make contact with the surface with the fingers fanned and observe to see if there are any finger contractures. Also observe if there is any contracture of the wrist joints which normally should make a 90° angle between the palm and the forearm.
3. In the "clapping" or "prayer" position with upper arm and forearm parallel to the floor, ask the subject to hold their hands outward with both palmar and finger surfaces touching each other and with the fingers slightly fanned (see *Figure 1*). If there is inability to juxtapose the fingers, usually because of recognized or unrecognized stiffness, or actual discomfort and pain, then the observer should gently attempt to do so to document this per se.
4. The wrist area as well as the elbows, lateral bending of the neck and any limited mobility of the spine should also be assessed with the usually normally able to extend at least 70° and the elbows a full 180°.

The method for evaluating LJM as shown in *Table 1*, *Table 2* and *Figure 1* was proposed by Professor Rosenbloom and colleagues. Our own study suggested some minor staging criteria (*Table 2*). Typically, changes usually begin in the metacarpophalangeal and proximal interphalangeal joints of the fifth finger and spread medially to other fingers. Wrist, elbow and other large joints may also be affected including the cervical and thoracolumbar spine but this is much less commonly seen.

Table 2
Brink-Starkman Limited Joint Mobility (LJM) Staging Criteria [29]

Stage 0	No stiffness and no joint abnormalities
Stage I	Stiffness of skin only but no actual contractures
Stage II bilaterally	Flexion contractures only of opposing fifth fingers
Stage III bilaterally	Bilateral contractures of more than the fifth fingers
Stage IV	Wrist contractures bilaterally
Stage V	Other joint involvement

Evaluation for LJM begins with having the patient attempt to approximate the palm surfaces of the interphalangeal joints on a flat surface and then both palms juxtaposed. Then the hands outstretched in front of the patient in the prayer or clapping position. Either the patient and/or the examiner would then extend the phalangeal joints (and expect 180 degrees extension if not compromised) and metacarpophalangeal joints and also attempt to maximally extend the wrists (approximately 70-90 degrees) and elbow (about 180 degrees) if there is no limitation by stiffness or discomfort. Borderline results are "scored" as negative if there is any inconsistency of interpretation between right and left side of the body (or if there are more than two LJM different scorers).

In our study, slightly modified to stratify into different stages, we started with no stiffening or contractures and going through five different stages depending on degree of involvement (*Table 2*). Different analyses have been presented by different researchers with different methods of grouping the findings depending on the research questions being posed and the analysis data.

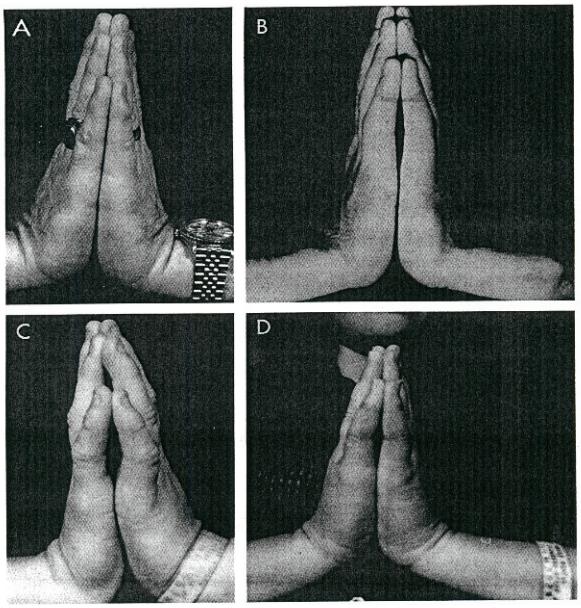

Figure 1. Stages of LJM using Brink-Starkman classification [32]

A. normal joint mobility with all fingers touching the opposite hand's fingers and the wrist near 90° extension in the "clapping" or "prayer" position.
B. stage II LJM: bilateral contractures of only the fifth fingers.
C. stage III LJM: bilateral contracture of more than the fifth fingers without wrist involvement.
D. stage IV LJM: wrist contractures bilaterally as well as joint contractures. (Not shown: Stage O is completely normal finger, hand and wrist examination and Stage V would be other bodily joint involvement as well as fingers and wrist.)

Some of the studies were convenience samples of patients available for evaluation and others were more refined and prospective as well as larger sample size. In some studies, statistical analysis grouped together what we have called stage 0 and I into one group comparing this observation with stage II and the also grouping what we have called stage III and IV into a proposed higher risk grouping for analysis.[6] Depending on known or unknown ascertainment biases of the studies as well as patients age, duration and glycemic control,

prevalence figures run from 3% to almost 60% in these studies with varying degrees of significance.[30]

As an example of such results (*Table 3, Table 4, Figure 2, Figure 3*), our own patient data analyzing 819 toddlers, children and adolescents through age 18 followed over a five year time period in a large, diabetes-specialty program produced significant increased male vs female LJM (*Table 3*) and somewhat less prevalence (12%, *Table 4*) compared to other comparable reports; we presumed this was related to a more intensified treatment regimen with lower achieved target goals utilizing a multidisciplinary team approach at the time but nevertheless confirmed LJM that had been "missed" because it was just not being clinically checked by health care providers (HCPs) previously.

Table 3.

Brink Cohort: Stage II or greater LJM in 97 of 819 patients <18 years old [32]

	Number	%
Females	29	7
Males	68	17
Total	97	12

$\chi^2 = 25.89$, $p < 0.001$

Table 4.

Brink Cohort: LJM by Stage and Sex in 97 of 819 patients <18 years old [32]

Stage	Description	Females	Males	Total	
O	No stiffness or contractures	386	322	708	
I	Stiffness only	6	8	14	
II	Bilateral 5th finger contractures	19	49	68	
III	Bilateral contractures of more than 5th finger	8	7	15	97
IV	Wrist involvement bilaterally	2	12	14	
V	Other joint involvement	0	0	0	
Totals		421	398	819	

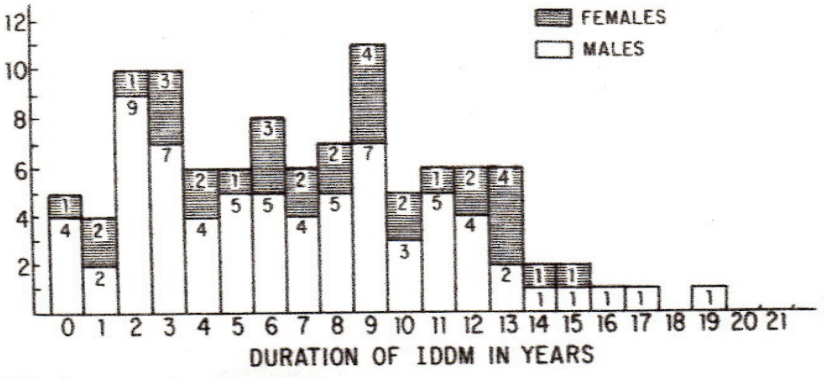

Figure 2. - Brink Cohort: Number of patients with stage II or higher LJM vs duration in 97 of 819 patients < 18 years old [32]

More recent longer duration studies[20,21] associated with documented improvements in intensity of education and support, more physiologic insulin preparations (analogs, insulin pens, insulin pumps) associated with more self-blood glucose monitoring and "tighter" target goals have also supported such assumptions with decreased prevalence seen. Short term diabetes duration data (*Figure 2*) generally do not show as significant findings except for virtually complete absence of LJM prior to puberty, again for reasons not well understood (*Figure 3*).

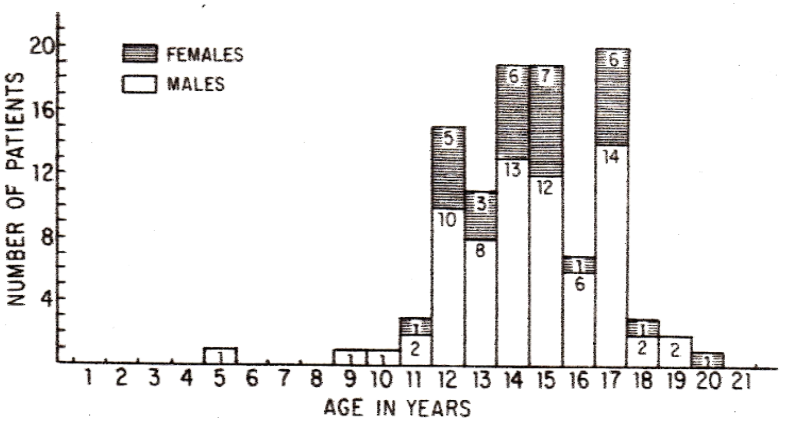

Figure 3. - Brink Cohort: Age of detection of LJM in 97 of 819 patients <18 years old [32]

Longer term life-table analysis of probability of microvascular complications (*Figure 4*) by Rosenbloom and colleagues[21] according to presence or absence of LJM is associated with diabetes duration. By the sixteenth year of diabetes duration, overall risk projection if LJM was present showed 83% risk for microvascular complications compared to 25% risk without LJM. Studies from Germany[25] extending the age of patients followed from 14 through 40 years. In this study cohort of 335 unselected patients, albumin excretion rate, hypertension, retinopathy where related to LJM and these complications showed LJM as an independent predictor in men but not women. Analysis of studies in Belfast[26] confirmed the observations that the prevalence of LJM is lower over the past twenty years falling from 43 to 23% in their study populations.

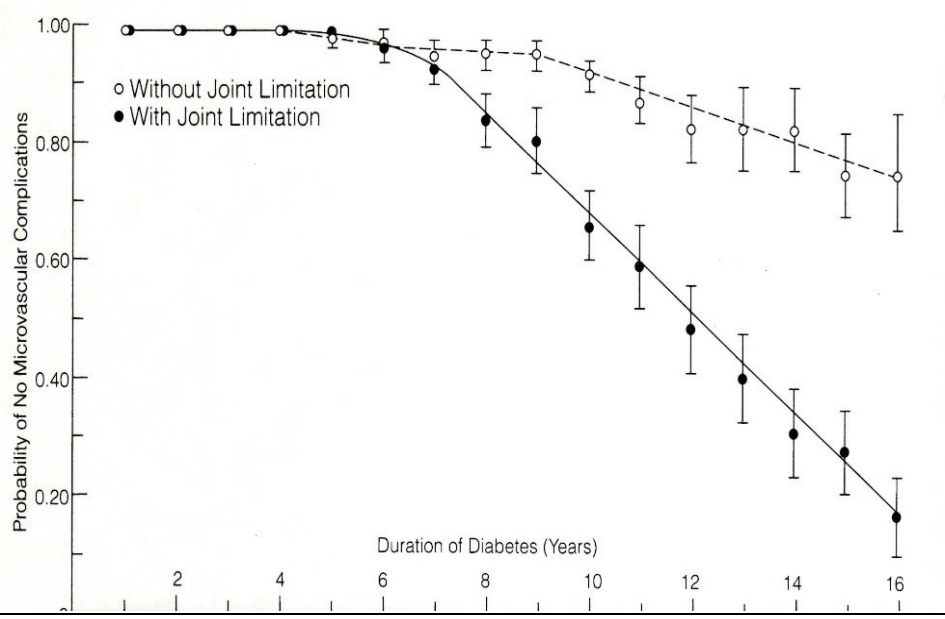

Figure 4. Rosenbloom Cohort: Life-table Duration Analysis of risks for development of microvascular complications with and without LJM [9]

Follow-up studies by Rosenbloom and colleagues[13,19] have documented a > 4-fold reduction (31% vs 7%, p <0.001) in frequency of LJM between 1976 and 1998 analysis and also

a decrease in the proportion of more moderate or severe LJM from 35% down to 9% (p = 0.025). Analysis of complications has shown some worrisome results but consistent with the hypothesis previously proposed that recognition of LJM by health care workers as well as the PWD and their family may allow earlier identification of those at highest risk for abnormal growth/puberty, hepatomegaly, retinopathy, nephropathy, neuropathy as well as overt hypertension and other macrovascular complications. Our own younger cohort complications vs LJM analysis for a shorter overall age period shown in *Table 5* shows the results as relative risk in our cohort of 400-600%.[7]

Table 5.
Brink Cohort: Complications risk with LJM in 97 of 819 patients <18 years old [32]

Relative Risk	***Complication***
4:1	Growth velocity deceleration
4:1	Hypertension
4:1	Retinopathy
4:1	Neuropathy
5:1	Hepatomegaly
6:1	Nephropathy

Attained age seems to be more important than duration of diabetes[42] in the expression of LJM and the lack of LJM in the prepubertal years suggests some associated process that may be related to the awakening of the neural-hypophyseal-adrenal-gonadal axis as another cofactor that comes along with the pubertal process.[42]

In some but not all studies, growth deceleration or overt growth failure has also been demonstrated and Rosenbloom and colleagues[16,20] have shown without apparent LJM, 38% of their study cohort had stature below the 25th percentile while about 80% of those with mild, moderate or severe LJM (grouped together for their analysis) were below the 25th percentile in height. (*Figure 5*)

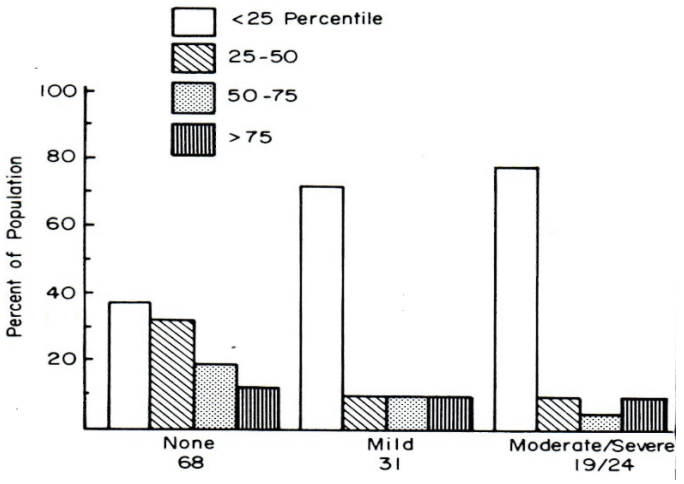

Figure 5. Rosenbloom height percentile distribution vs LJM.

Data from Rosenbloom and colleagues is shown in *Figure 6* [1] with more and/or more severe LJM associated with more complications.

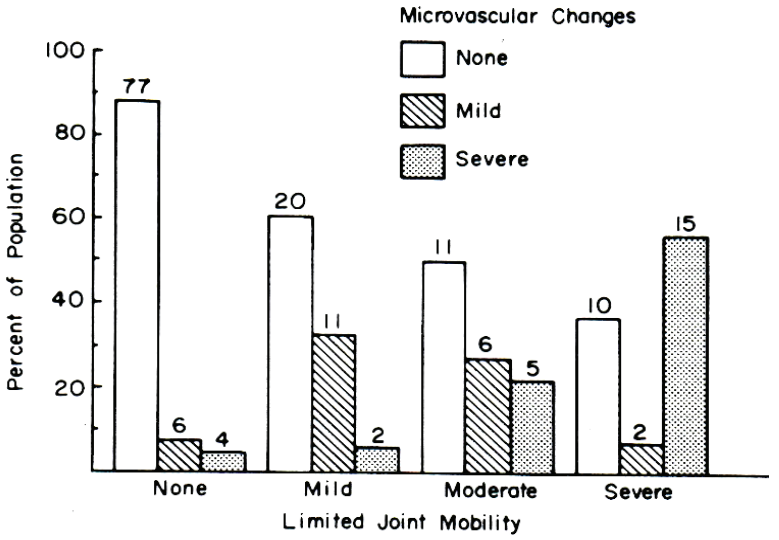

Figure 6. Rosenbloom microvascular changes vs LJM [1]

Longer duration studies[22,25] with larger study cohorts most often show significant associations of LJM with duration of T1DM. (*Figure 7 & 8*).

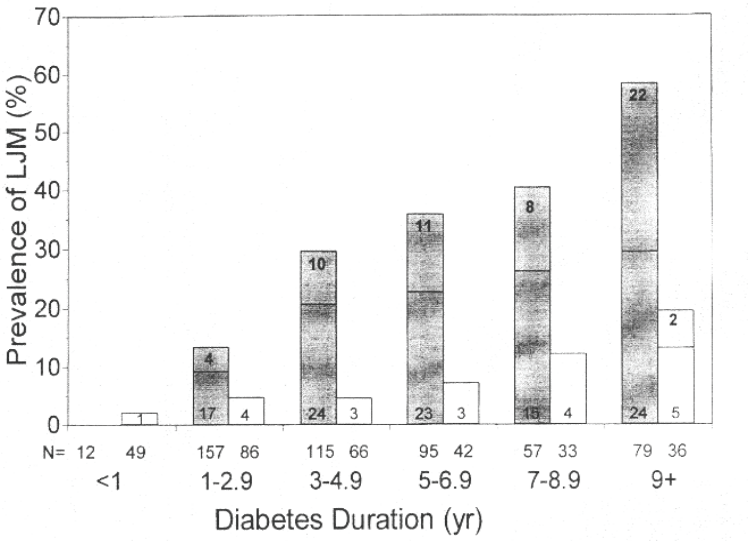

Figure 7. Rosenbloom Duration of T1DM re: LJM [22]

Duration of T1DM	LJM Prevalence
10 years	13%
10-20 years	19%
20-30 years	30%
>30 years	65%
N=204	P<0.001

Figure 8. Belfast Duration of T1DM re: LJM and complications assessment [25]

Some but not all reports[31] have demonstrated associations of LJM with HbA1c levels suggesting, again, the need for more and larger ascertainment of study populations with longer duration of diabetes.[1,6,7,9,22,32] Few studies to date have evaluated cumulative A1c results over longer periods of time, however, so that random blood glucose or A1c not taken over a longer period of time may not be so relevant in such

data analyses. More specific analysis and consistency of definitions for degrees of nephropathy,[33] retinopathy and neuropathy have also been available in recent years[34,35] with the results of the DCCT serving as a basis for such definitions in addition to more specific research on each of these areas of complications. A more recent EDIC evaluation of LJM utilized cumulative A1c results over a 24 year time period for 955 of the original 1400 plus DCCT participants and as shown in *Figure 9* showed rising LJM prevalence from 18% to 20% and then to 30% with rising A1c grouped results ($p<0.001$).[36]

To date no specific genetic associations have been proven to see if there was any distinct metabolic explanation for these associations. Alternative methods for analysis such as ultrasonography, xray or nuclear imaging with CT or MRI have not shown any more definitive results for LJM staging to date but obviously add significant scheduling and cost factors – but without proven benefit.

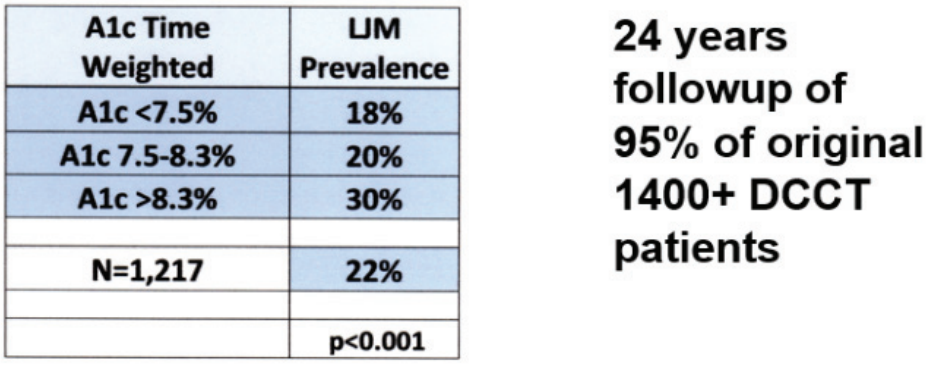

Figure 9: DCCT/EDIC LJM 24 year. Prevalence assessment [34]

Biopsies of patients with LJM have shown increased cross-linking and glucosylation of collagen[6,19,37] suggesting that there may be some patients who are more or less genetically prone to produce LJM in this fashion. This could, if confirmed with future research, explain some of the differences in LJM associations with specific patients' duration of diabetes, long term A1c results etc. and current

genetic metabolomic association research may prove valuable in the coming years.[38, 37, 41]

Histochemical and histomorphological studies have shown that such PWD with LJM exhibit an impairment of mucopolysaccharide in the skin, collagen and elastic fiber in preliminary studies from Havana.[39]

A hypothesis that would unite all these findings leads to the following speculation: if LJM is an index of connective tissue glycosylation[40] or sensitivity to glycosylation in children, adolescents and adults with diabetes mellitus, and if these PWD are therefore more likely to develop complications, either earlier or of more severe character because they are genetically and/or metabolically more prone to glycosylate not only tissue collagen but also microvasculature and microvasculature. Thus, more retinopathy, nephropathy, neuropathy, cardiac and brain vascular problems associated with short and long-term glycemic exposure in this presumed "genetic" risk subset.

The DCCT and its followup EDIC Study as well as many other studies have documented the glycemic exposure connection quite dramatically and there is mounting evidence that variable glycosylation and its effects[37,41,41] may also be important constructs to consider as explanation and perhaps intervention strategies.

As stated earlier, the ability to identify the PWD as having LJM at virtually no cost, have them actually see and feel something that is happening to them, instead of just hearing (worrying) about blindness or heart attacks, strokes or amputations may be extremely important when understanding the psychosocial explanations for why the PWD decides to place more or less efforts into their own care. Such approaches using LJM as a prime motivational factor may allow more direct more therapeutic efforts to identify the subset of patients at an earlier time to change their efforts, psychologically understand the importance of such behavioral changes and couple this with stricter target goals vis-à-vis self-monitoring, self-adjustments, more vigorous insulin responsivity, more frequent visits and support - or some

combination of any or all of these efforts. In the DCCT and EDIC [42] studies have shown this is possible with more frequent visits utilizing a consistent multidisciplinary health care team and is helpful to reduce short and long term morbidity and mortality.

The differential diagnosis for LJM in the PWD, especially in children, adolescents and young adults is straightforward.[11] There is no other condition that results in painless, noninflammatory limitation of motion of the finger, hand and wrist region.

- Rheumatoid arthritis presents differently and with laboratory inflammatory markers usually present.
- Dupuytren disease is the only other condition that can present without pain but it is virtually never seen in such young patients.
- Similarly, flexor tenosynovitis, stiff-hand syndrome, shoulder-hand syndrome and osteoarthritis mostly are conditions seen in middle to elderly patients and not those of such young ages as described. The presence of pain or paresthesia, specific neuromuscular findings, disability to point of the PWD (or family members) complaining and noticing the problem, finger locking, localized swelling, nodules, muscle atrophy, palmer or facia thickening as well as radiologic evidence of vessel calcification of the hand should all be considered as a need for further diagnostic evaluation.

There is not much specific regarding actual management of LJM in diabetes[43] since is does not cause specific pain or distress and is not very limiting on a day-to-day basis except for its importance as a marker of serious long term diabetes-associated complications as previously indicated.

Clinical application of LJM[43 44] in children, adolescents and young adults over the past almost 50 years suggests that a unified HCP approach should be considered while we await efforts to potentially intervene with the presumed genetically defined glucosylation process and/or prolonged improvement in glycemic control:[44]

- IF LJM is an index of connective tissue glucosylation or sensitivity to glucosylation with some genetic basis for explaining why not all PWD seem to show LJM at the same levels of glycemia/A1c.
- And IF PWD increase the importance of directly evaluating LJM, routinely doing so every 6 months as documented in the medical records (by hand or computer) to see if LJM is present, changing or absent
- And IF the PWD with LJM is more likely to develop any complications associated with diabetes (growth, hepatomegaly, retinopathy, neuropathy, nephropathy, hypertension, cardiac or cerebral atherosclerotic abnormalities) because they glucosylate their basement membranes and other tissues proteins in similar fashion
- THEN more intensive educational, psychomotivational[45] and therapeutic efforts including more frequent followup visits, for every PWD around the world, directed at this identifiable subset of patients at higher risk for diabetes-associated complications can help motivate more intensive achievement of target goals by a multidisciplinary diabetes specialty team while minimizing excessive hypoglycemia with newer technologies, better/more automatic self-glucose monitoring coupled with more frequent and more targeted direct efforts by the HCP team safely to achieve such goals.

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PHYSICAL EXERCISE AS A THERAPEUTIC ELEMENT IN CHILDREN WITH TYPE 1 DIABETES MELLITUS

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INTRODUCTION

Once the diagnosis of type 1 diabetes (DM type 1) has been established, the therapeutic recommendations are based on 4 components whose importance in the treatment of type 1 diabetes is equal, namely: insulin substitution, specific fractional nutrition and the mandatory calculation of carbohydrates at each meal (including snacks), specific and continuous medical education of the family and the child with DM type 1 and the practice of physical exercises.

If with regard to the first 3 components things seem simple, with regard to physical exercises in patients with DM type 1, the recommendations may be easier to apply to adults than to children.

For the child with DM type 1, these recommendations encounter difficulties. In most cases, the younger they are, children with DM type 1, just like non-diabetic children of the same age, have an unpredictable physical activity (both in terms of duration and intensity), difficult to quantify from one day to the next, the child being often difficult to control.

Exercising regularly from an early age can establish a healthy lifestyle that supports health later in life. Although these concepts apply to the general population, they may be even more relevant to specific categories of subjects such as patients with type 1 DM.

Regular participation in physical activity, including structured and competitive sports, should be encouraged in these children.

According to the ISAPD guide, children between the ages of 6 and 18 should practice physical activity daily for 60 minutes/day in the form of at least moderate aerobic activity. Despite these recommendations, both the duration and the intensity of physical activity are difficult to achieve in children with DM type 1 due to the parents' anxiety generated by the fear of hypoglycemia.

In favor of the recommendations to practice physical exercises by patients with DM type 1, the names of athletes who have performed in various sports can be cited as arguments, such as:

- *Jay Christopher Cutler*, American football quarterback in the National Football League (NFL);
- *Gary Wayne Hall Jr.* represented the United States in swimming at the 1996, 2000 and 2004 Olympic Games. After being diagnosed with Type 1 DM, by regularly testing his blood sugar every 45 minutes, he was able to train up to eight hours a day. During his career, he won ten Olympic medals, five of which were gold.
- *Pär Johan Zetterberg* played football as a professional. He knew his glory period at the R.S.C. Anderlecht Brussels. He was selected 30 times in the Swedish national team, between 1993 and 1999, for which he scored six goals. In 1997 he received the award for the best footballer of the year in Sweden.
- *Alexander Zverev*, professional tennis player, once ranked number 2 in the world, has DZ type 1 since the age of 4. As a performance athlete, he won 19 tennis tournaments and was also an Olympic champion. The foundation that bears his name started its activity in August 2022.

PHYSIOLOGY OF MUSCLE CONTRACTION

The main use of glucose is as an energy substrate, but its metabolism depends on the type of cell and the physiological state of the body, so for neurons and erythrocytes, glucose represents the immediate source of energy without the intervention of insulin.[1]

The vast majority of cells in the human body carry out their metabolism in aerobic conditions.[2] The exception to this mechanism are erythrocytes, which do not have mitochondria and temporarily muscle fibers during intense effort, a situation in which energy metabolism takes place in partial anaerobiosis. ATP, which provides the energy, is formed in large quantities in the aerobic stage and in small quantities in the anaerobic stage.[2,3]

The coupling of ADP with the energy-generating processes is carried out in two different ways: either through the phosphorylation reaction (oxidative substrate phosphorylation), a metabolic pathway that takes place in the mitochondria through the synthesis of ATP, or through the oxidative phosphorylation of the respiratory chain.

In the absence of oxygen, glucose is degraded through anaerobic glycolysis, resulting in lactic acid. Compared to the aerobic pathway, the process is weakly energetic, synthesizing only 2 ATP molecules. This is a temporary mechanism that takes place under the conditions of a temporary lack of oxygen, such as the case of skeletal muscle during an intense and prolonged physical effort. In these situations, there is a waste of glucose to cover the energy needs due to the imbalance between the energy requirement and the oxygen supply.

Insulin is the anabolic hormone that exercises control over the processes of storage and mobilization of energy reserves. In conditions of caloric intake, it favors the "hoarding" mechanisms in the form of glycogen, triglycerides, proteins, and during fasting periods it disinhibits the mechanisms for mobilizing energy reserves.

So, the biochemical mechanisms involved in the regulation of blood glucose depend on the physiological state, and on the time of food intake (early postprandial or late postprandial).[3,4]

Early postprandial, excess dietary glucose requires its utilization with storage of the excess as glycogen or lipids.

Glycogenogenesis (glycogen synthesis) takes place under the conditions of an excess of glucose (endogenous or exogenous) compared to the body's energy needs. At the skeletal muscle level, glycogen is synthesized from free glucose as well as from the glucose-6-phosphate product (of gluconeogenetic origin), using lactate as a precursor. In these conditions, the action of insulin is important, which on the one hand increases the cellular permeability for glucose, and at the cellular level activates glucose metabolism. Simultaneously, insulin inhibits the metabolic pathways (gluconeogenesis, glycogenolysis, lipolysis) that produce or remove glucose from reserves.

The action of insulin is achieved through a phosphorylation-dephosphorylation regulation mechanism, interconversion or synthesis of the key enzymes of the controlled metabolic pathways.[1]

Late postprandial, in the state of hunger, a glucose deficit occurs, as a result of the lack of food intake, which requires the production of glucose and the use of alternative energy sources. At this stage, the actions of hyperglycemic hormones intervene simultaneously with the decrease to the stop of insulin secretion, thus contributing to the maintenance of blood glucose within normal limits.

Glycogenolysis, allows the use of the carbohydrate store, depending on the needs of glucose compared to the intake.

In conclusion, insulin has the main role in maintaining euglycemia. On the one hand, it stimulates all the metabolic ways of storing energy substances (glycogenogenesis, lipogenesis, protein synthesis), and on the other hand, it inhibits the ways that consume these reserves (glycogenolysis, lipolysis, proteolysis).

Glucose metabolism in the muscle cell

It should be mentioned that insulin influences the glucose permeability of the muscle cell membrane, being able to increase the rate of glucose transport in resting muscle cells by more than 10-20 times.

During the fasting period, blood sugar drops, insulinemia drops, the muscle cell membrane becomes less permeable to glucose.

During most of the day, muscle tissue uses fatty acids to cover energy needs.

In the early postprandial healthy person, blood sugar rises, insulinemia rises and there is an increased uptake of glucose in muscle cells. The release of fatty acids from adipose tissue is inhibited and muscle cells preferentially use carbohydrates as an energy substrate over fatty acids.

During periods of moderate or heavy physical exertion, the exercising muscle fibers become very permeable to glucose even in the absence of insulin. In these conditions, due to muscle contractility, the muscles use large amounts of glucose, without the need for large amounts of insulin.[4,5]

Physical exercise as a therapeutic element in DM type 1

Practicing physical exercises in children with type 1 DM is recommended to be performed as much as possible in the euglycemic range, exercises being contraindicated or postponed if the blood glucose determined before exercise is below 80 mg/dl or above 250 mg/dl.

Depending on the nature of the muscle contraction, the presence or absence of external force, the exercise can be: active exercise, assistance exercise and passive exercise.[6]

Aerobic exercises (those that increase inhalation, delivery and use of oxygen in the body) can improve insulin sensitivity and implicitly improve glycemic control and carbohydrate metabolism.[7,8]

Aerobic exercise (eg, walking, cycling, jogging, and swimming) involves repeated and continuous movement of

large muscle groups that rely primarily on aerobic energy-producing systems for energy.[9]

Strength exercises using weights, machines, body weight, or elastic resistance bands rely primarily on anaerobic energy-producing systems.

It is currently unclear which forms of exercise are most effective for improving cardiometabolic control in type 1 diabetes.[10]

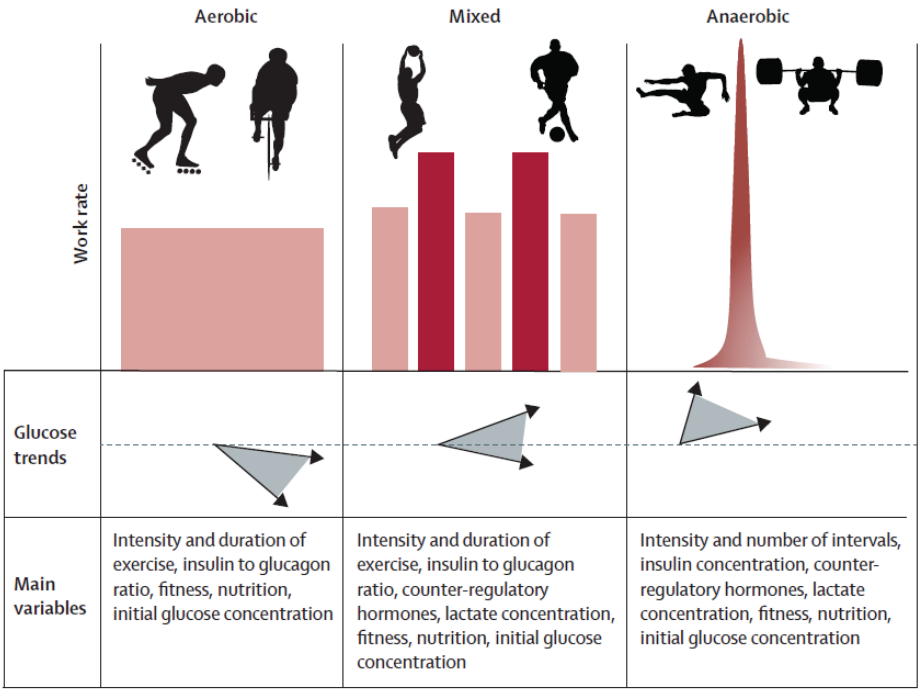

Figure 1: Variability in blood glucose responses to different forms of exercise in people with type 1 diabetes. High individual variability exists in the blood glucose responses to different form of exercise, as denoted by the arrows and grey shading. In general, aerobic exercise decreases glycaemia, anaerobic exercise increases glycaemia, and mixed activities are associated with glucose stability. Individual responses are dependent on various additional factors, including the duration and intensity of the activity, initial blood glucose concentrations, individual fitness, concentrations of insulin, glucagon, and other counter-regulatory hormones in the circulation, and the nutritional status of the individual.[9]

INITIATING PHYSICAL EXERCISE IN THE CHILD WITH DM TYPE 1 (INITIAL RECOMMENDATIONS)

It should be stated from the beginning that physical exercises depending on the type, intensity and duration have an effect on the mobilization and use of carbohydrates and at the same time influence the kinetics of insulin with fluctuations in blood sugar, both during and after exercise with hypoglycemia sometimes immediately but sometimes also at away from physical exercise.[11] It should be noted that hypoglycemia develops in most patients with type 1 DM within approximately 45 minutes of starting aerobic exercise.[12,13]

In DM type 1, the glycemic response to exercise is dependent on: the type of insulin, the site of insulin administration, the amount of active insulin in the circulation, the blood glucose value before exercise, the composition of the last meal and/or snack, the intensity and duration of the exercise. [14]

Choosing the injection site.

To avoid hypoglycemia, special attention will be paid to the insulin injection site. Exposure to physical exertion of the area where the insulin injection was performed may lead to an excessive mobilization of insulin into the bloodstream with transient hyperinsulinemia and hypoglycemia.

The ambient temperature and humidity in which the exercise takes place can also cause unexpected and unwanted glycemic fluctuations.

Unanticipated changes during exercise can lead to unexpected glycemic responses.

It is known that periods of intense exertion can have a strong hyperglycemic effect during exercise. Based on these records, the patient can make the decision of prior adjustment (prior to the exercise) either to increase the dose of insulin or to decrease the intake of carbohydrates.

Unexpectedly changing the exercise program by switching to low or moderate intensity exercise predisposes to

hypoglycemia due to the pre-exercise decision that was based on the probability of performing an intense physical effort.[15]

Insulin therapy scheme

Patients using the multiple injection regimen are unable to reduce the long-acting component of their therapy but can compensate by ingesting an additional amount of carbohydrates. Adjustments for food and insulin should be based on individual records in the treatment book, based on previous results obtained under similar conditions of physical exertion. Thus, good results can be anticipated for similar types and durations of exercise, being reserved when subjected to new exercise formats.

For example, patients using insulin pumps may choose to lower, or sometimes completely stop, their basal insulin rate in anticipation of familiar (familiar) exercise patterns.

In patients on continuous subcutaneous insulin infusion, it should be noted that although basal insulin rates are halved 60 minutes before the start of exercise, circulating free insulin concentrations do not fall sufficiently at the start of exercise and concentrations tend to rise transiently during the activity.[16] Increased circulating insulin concentrations cause increased glucose release during exercise relative to hepatic glucose production, delaying lipolysis and increasing muscle reliance on glucose as an energy source.[9]

Observational studies show that both trained and untrained individuals with type 1 DM usually require increased carbohydrate intake or reduced insulin dose, or both, before beginning aerobic exercise.

Immediate hypoglycemia and at a distance from physical exercise.

In the patient with type 1 DM, hypoglycemia occurs when there is an imbalance between tissue energy needs and circulating glucose, or when circulating insulin levels are higher than blood glucose levels. The blood glucose value < 70 mg/dL is the reference value that biochemically defines hypoglycemia. At values below the defined one, the release of

counter-regulatory hormones (glucagon, epinephrine, GH and cortisol) is triggered to prevent or limit the duration and even the severity of the hypoglycemic episode even if clinical symptoms have not yet set in.[17]

If in non-diabetic individuals the risk of hypoglycemia is significantly reduced by decreasing pancreatic insulin secretion, in the case of patients with DM type 1 due to the "inappropriate" administration of insulin (and insulin deposits resulting from the use of intermediate and slow-acting insulins) the response to hypoglycemia can be significantly modified, and the patient may be prone to hypoglycemia. Among the causes responsible for the appearance of hypoglycemia in the first place is the lack of adaptation of insulin doses to the scheduled physical exercise. In the case of an unscheduled physical activity, the risk of hypoglycemia increases exponentially with the duration and intensity of the physical exercise, but also with the young age of the patient.

In the healthy individual, who practices regular, prolonged and moderate physical exercises, there is a decrease in pancreatic insulin secretion by up to 40-50%. The extrapolation of this physiological "pattern" in patients with type 1 DM requires the acquisition of a personal experience of the patient depending on the type of exercise practiced, the time of exercise, the time of insulin administration, the type of insulin that acts both during exercise and and after exercise.

The second mechanism involved in the hypoglycemic response to physical exertion is the prior stimulation of the hypothalamic-pituitary-adrenal (HPA) axis. Repeated hypoglycemia appears to dampen the response of counterregulatory hormones involved in preventing hypoglycemia during exercise.[18]

Some studies suggest, in adults with type 1 DM, different responses by sex, with men developing significantly greater neuroendocrine responses (eg. epinephrine, glucagon) to exercise comparable to women. In case of a history of hypoglycemia, men with T1DM showed substantially lower exercise responses, while exercise responses in women with T1DM were only slightly affected.[19]

Although these responses have not been proven in children with type 1 DM, before puberty the responses appear to be similar between boys and girls, while during puberty boys may become more susceptible to the diminished response of counterregulatory hormones to exposure to hypoglycemia. previous and repeated.[20]
Immediately after a workout, insulin sensitivity is increased, muscle glycogen reserves are depleted, which is why most of the body's glucose uptake is directed to skeletal muscle,[21] which increases the risk of a hypoglycemic episode.

Given that the responses of counterregulatory hormones are physiologically diminished during sleep we can expect a new hypoglycemic episode "at a distance" during sleep.

Hyperglycemia and physical exercises

Current guidelines recommend refraining from physical exercise if blood sugar before exercise is ≥ 250 mg/dl.

If moderate-intensity exercise produces a decrease in blood sugar to varying degrees, intense exercise produces the opposite effect and can lead to hyperglycemia.[22] On the other hand, hyperglycemia after exercise occurs following an excess of carbohydrates or a too large reduction in the insulin dose in relation to the duration and intensity of the physical effort or in competition conditions due to the release of stress catecholamines. In this situation, you can resort to a correction with a maximum 50% insulin dose. [23]

The moment of physical exercise

Most school children are more active in the morning (at school) or in the afternoon after school hours. With them, caution is necessary in achieving a hyperinsulinemic state during these periods of the day, especially since there may be days when the child is less mobile (he does not have sports class, the weather does not allow him to exercise during the breaks between classes, etc).

Exceptions to the rule are preschool children who have an uncontrolled, explosive and especially difficult to control

physical activity and for whom the recommendations cannot be generalized from one child to another.

Nutritional recommendations in case of physical exercises

The main condition for a child with DM type 1 to regularly practice physical exercises is to strictly observe the meal times for both main meals and snacks, as well as the calculation of carbohydrates at each meal and compliance with the amounts of carbohydrates prescribed at each table.

Meals should be eaten at least 1 hour or even 2 hours before exercise to avoid hypoglycemia. This time interval is sufficient to achieve digestion and a sufficient concentration of glucose in the blood, a concentration necessary to ensure the energy substrate for the muscle fiber under conditions of light to moderate effort. In the situation where, from one day to the next, the tendency to hypoglycemia persists after the same type of exercise, performed in the same time interval, it is mandatory to reduce the dose of insulin responsible for hypoglycemia by up to 50%.

Carbohydrate supplementation before exercise depends on: the length of time between the insulin injection and the time of exercise, the type and purpose of the exercise [24] but especially when the exercise is unscheduled. In these situations, it is recommended to supplement with foods that contain carbohydrates with a high glycemic index and low lipid content. It is unproductive to give chocolate to children because the lipids in the composition decrease the absorption rate of carbohydrates and thus increase the risk of hypoglycemia.

If liquid losses with a potential risk of dehydration are estimated, isotonic drinks containing ≈ 6% sugar (sucrose, fructose, dextrose) [24] will be used because they are absorbed much better than fruit juices containing 15-16 g carbohydrates / 100 ml.

During exercises/activities lasting 60 minutes or longer, one can resort to carbohydrate supplementation, but only after checking the blood sugar level and the type of exercise

(moderate or severe).[24] Up to 1.5 g of carbohydrates/kilogram of body weight / hour of exercise can be administered. [25]

Table 1: Carbohydrate requirements for preventing hypoglycaemia (modified after 26)

The type of table	Recommendations for the patient with DM type 1
Meal (low fat, low glycemic index) eaten before exercise	Minimum 1g of carbohydrates per kg of body weight, depending on the intensity and type of exercise
Meal or snack consumed immediately before exercise (high glycemic index)	No need for carbs for performance
Meal consumed after exercise	1.0–1.2 g of carbohydrates per kg of body weight
Exercise (up to 30 minutes)	No need for carbs for performance
Exercise (duration 30-60 min)	Small amounts of carbohydrates (10-15 g/h) may improve performance
Exercise (duration 60-150 min)	30-60 g of carbohydrates per hour
Exercise (duration >150 min); mixture of carbohydrate sources	60–90 g of carbohydrates per hour spread throughout the activity (eg 20–30 g of carbohydrates every 20 minutes). Use carbohydrate sources that use different intestinal transporters (eg glucose and fructose)

Post-exercise intake of carbohydrates as well as protein can be beneficial for both hypoglycemia prevention and muscle recovery. The composition of the meals after physical effort will be decided according to the child's previous experiences, taking into account the immediate and remote glycemic response obtained after the respective meal consumed after the effort. This is essential because insulin sensitivity remains elevated even up to a few hours after physical exertion, and the timely restoration of glycogen

reserves contributes to reducing the risk of hypoglycemia "at a distance" from physical exertion.[25]

To increase the rate of carbohydrate absorption during exercise and maintain hydration, sports drinks containing glucose and fructose may be preferable.

Contraindications of physical exercises.

Although they are putrid, they must be known and recognized by the patient.

Ketosis

The detection of ketone bodies (in blood ≥ 1·5 mmol/L or urine ≥ 2+ or 4.0 mmol/L) before the scheduled physical effort is a contraindication for physical exercise.

Exercising is suspended until ketosis is resolved, and on the other hand, the cause will be identified (illness, excessive carbohydrate intake, a recent episode of prolonged exercise or insulin omission, insulin pump failure).

Prolonged physical exercise (e.g. marathons and hiking) and very low-carbohydrate diets can increase blood ketone body concentrations in patients without a significant increase in blood glucose, leading to so-called "starvation ketosis".

A value of ketone bodies in the blood of 3.0 mmol/L or more requires presentation to a hospital emergency service and contacting the attending physician).

Recent hypoglycemia

Severe hypoglycemia (blood glucose ≤ 50 mg/dL) or a hypoglycemic event with loss of consciousness within the last 24 hours is a firm contraindication to exercise because of the very high risk of a new, even more severe hypoglycemic episode. [27]

In situations where mild hypoglycemia has occurred (level 1 blood glucose: 50–70 mg/dL), there is a risk of recurrence that must be taken into account. [28]

CGMS

Blood glucose monitoring is key to maintaining glycemic balance in the active child with type 1 DM so that trends in glycemic responses can be identified.

The records in the treatment notebook must include: blood sugar (before, during and after the end of the exercise), the duration and intensity of the physical exercises, as well as the measures taken to keep the blood sugar within normal limits.

Regarding the determination of blood sugar, special attention must be paid to the trend (direction) of blood sugar evolution. In this sense, patients using continuous glycemic monitoring systems (CGMS) currently have a special advantage, which have the advantage of being able to detect in a timely manner both the blood glucose trend and the value of this trend (1, 2, or 3 arrows down or in above) being able to take effective measures in a timely manner but can analyze the results with the attending physician by reading the reports that can be analyzed at 7, 14 or 30 days.

Thus, CGMS proved to be a valuable adjunct for blood glucose monitoring both in the prevention and early detection of exercise-induced hypoglycemia[29,30], both immediate and especially late, during the night.

Case report.

C.V., 14 years old, male, plays football, follows treatment with insulin through multiple injections. He has CGMS for 10 months.

CGMS shows a good metabolic balance in the last 30 days with Time in range of 84%, level 1 hypoglycemia (between 70 - 54 mg/dl) of only 1%, coefficient of variability of 29.1% and a GMI (Glucose Management Indicator) that is, an estimated HbA1c of 6.6% under the conditions of using the sensor 93% of the time. (*Figure 2*)

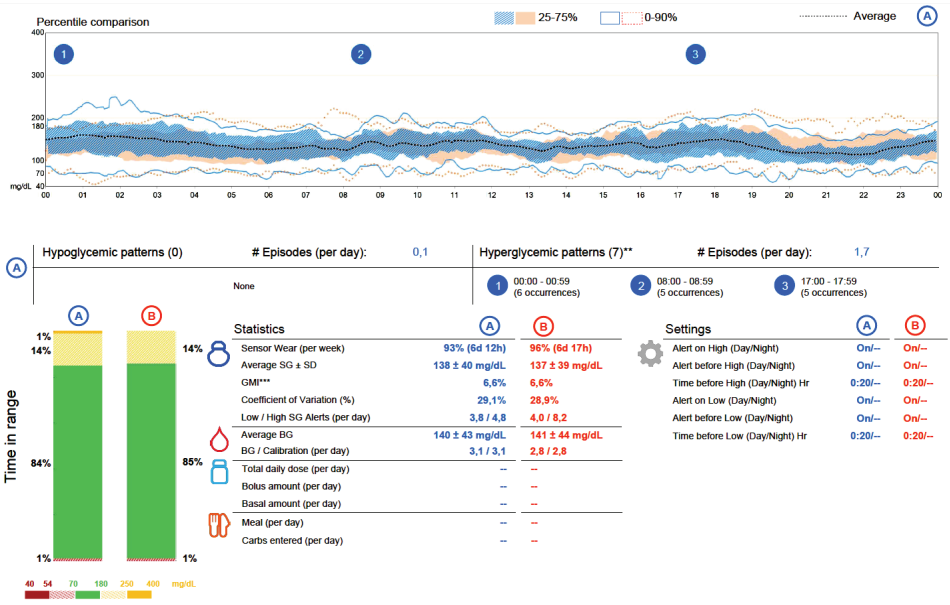

Figure 2 – C.V., male, 14 years old, monthly glycemic sensor report (He has CGMS for 10 months.)

The daily developer of the glycemic curves shows, on the day he has an official match (compared to normal training days), an increase in blood sugar immediately after the match (also confirmed in the capillary blood of 212 mg/dl), secondary to intense physical exercise, followed by of the tendency to hypoglycemia with a capillary blood value of 56 mg/dl. (*Figure 3*)

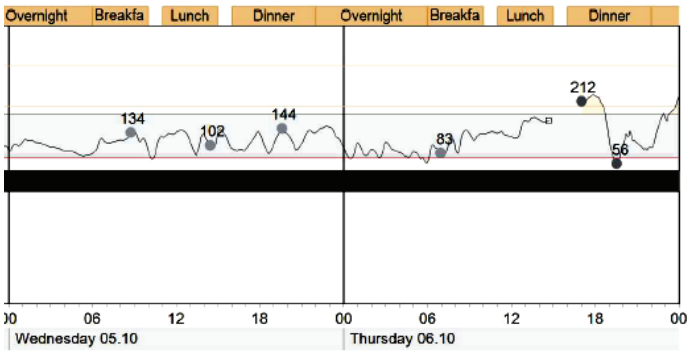

Figure 3 - The daily developer of the glycemic curves

Insulin pumps

Insulin pump users have the advantage of not having insulin stores in the subcutaneous tissue, which allows better management of insulin delivery under conditions of physical exertion. Thus, in order to obtain a decrease in the effect of basal insulin, the insulin pump must be disconnected before physical effort, and the patient can be disconnected for a maximum of 120 minutes. Exceeding this time interval can lead to hyperglycemia and even ketosis

Even after re-pumping, there is a risk of hyperglycemia that can last for about 2 hours after exercise if the patient has exercised intensely even for a short period of time. This hyperglycemia is the result of catecholamine discharge.

In case of hyperglycemia detected when the pump is reconnected, a correction bolus of 50% can be used (50% of the basal insulin not delivered during the suspension of the pump).

Case report.

T. P. 9 years old, female, is on insulin replacement treatment through an augmented insulin pump with a glycemic sensor and practices karate.

The monthly reports downloaded from the application show a good metabolic balance in the last 30 days with: Time in range of 87%, 11% hyperglycemia and 2% level 1 hypoglycemia (between 70 - 54 mg/dl) of 2%, a coefficient of variability <30%, and a GMI of 6.4%, with a weekly Smart Guard operation of 99% and a CGMS usage of 97% of the time/week. (*Figure 4*).

On the day of the exam - contest for the "belt" the child presents throughout the contest a significant increase in blood glucose values secondary, most likely, to the discharge of catecholamines due to stress, emotions, followed by a return to normal after the exam is over. (*Figure 5*)

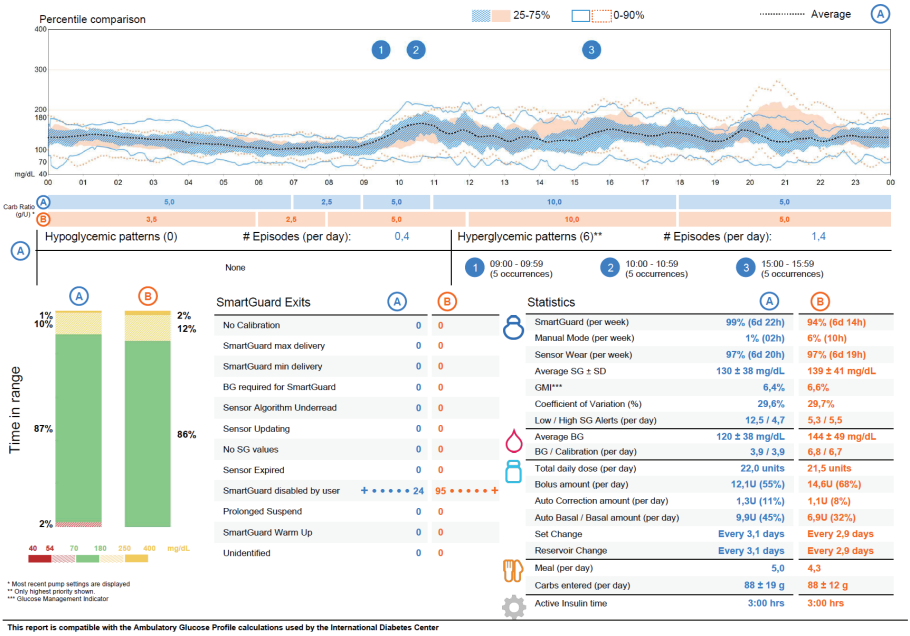

Figure 4 – T.P., female, 9 years old, monthly report of the use of the augmented pump with glucose sensor.

Figure 5 - The daily developer of the glycemic curves

The new types of pumps equipped with the smart guard algorithm have the possibility of stopping the delivery of the basal rate to the tendency of hypoglycemia (suspend before low) signaled by the glucose sensor. This function is beneficial and reduces the risk of hypoglycemia, especially in small

children who make unpredictable, uncontrolled and unscheduled physical exertion.

Table 2 – Prandial (bolus) insulin adjustment for postprandial exercise when exercise is conducted in hyperinsulinemic state (after 24)

	Meal before exercise		Meal after exercise
	Activities lasting 30-45 minutes	Activities lasting > 45 minutes	
Continuous, moderate to vigorous intensity aerobic activities (eg. Jogging/running, moderate intensity swimming, bicycling, cross country, aerobic play)	25% - 50% bolus reduction	50% - 75% bolus reduction	Up to 50% bolus reduction
Mixed aerobic and anaerobic burst activities (eg. Hopping, skipping, dance, gymnastics, tag, dodgeball, field and team sports, individual racquet sports etc)	≈ 25% bolus reduction	≈ 50% bolus reduction	Up to 50% bolus reduction

Conclusions:

Due to these impediments, the medical team must identify whether the child in question has sports aspirations or not, whether he practices physical exercise as a therapeutic element regularly or not, in order to provide the most appropriate recommendations.

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INFUNDIBULONEUROHYPHOPHYSITIS- AN UNDERDIAGNOSED CLINICAL ENTITY IN THE CENTRAL DIABETES INSIPIDUS DIAGNOSTIC CHALLENGE

Rodica Elena Cornean, Bianca Simionescu

Abstract

Hypophysitis is the generic term for an extremely heterogenous condition resulting from acute or chronic inflammation of the adeno and/or neuropituitary gland.

The clinical hallmark of neuropituitary involvement is the onset of central diabetes insipidus (CDI).

Although inflammatory/autoimmune hypophysitis is reported with low incidence in the pediatric medical care, in the last decades, the number of such cases seems to have increased among children with CDI.

To date, about one-third of the children with the clinical symptoms of central diabetes insipidus (CDI), display pituitary stalk thickening (PST) with infundibuloneurohypophysitis at their first magnetic resonance imaging (MRI) assessment.

The definitive diagnosis of autoimmune hypophysitis requires a transsphenoidal pituitary biopsy. The invasiveness of the pituitary biopsy is not only an issue of concern for patients and their doctors but also the main reason why this medical condition is still underdiagnosed.

Without a pituitary biopsy, the autoimmune etiology of the hypophysitis remains to be confirmed by the circulating anti-pituitary antibodies (APAs).

However, even if the APAs are a reliable surrogate marker of pituitary autoimmune involvement, they have relatively limited diagnostic accuracy as they could not distinguish between primary or secondary autoimmune hypophysitis, adeno or neurohypophysitis not to mention between different histological types of immune hypophysitis (e.g. IgG4-mediated, lymphocytic hypophysitis, etc.)

Despite the fact that without pituitary biopsy autoimmune neurohypophysitis diagnosis remains a diagnosis of exclusion, this medical condition has to be considered in the differential diagnosis of any child with acute onset of CDI.

Key words: infundibuloneurohypophysitis, central diabetes insipidus, pituitary stalk thickening, autoimmune hypophysitis

Introduction

Central diabetes insipidus (CDI) is a rather uncommon disorder in children. CDI is due to a deficit in the neurohypophyseal secretion of vasopressin/antidiuretic hormone (ADH). It results from the destruction or loss of the magnocellular neurons of the hypothalamic supraoptic and paraventricular nuclei.

Diagnostic criteria include polyuria and polydipsia with the intensity of polyuria depending on the degree of ADH deficiency, the osmotic threshold for thirst and the osmotic burden to be excreted.

The characteristic aspects of CDI consist in the excretion of an abnormal volume of diluted urine (more than 2L/m^2/24hours, more than 4ml/kg/h or more than 2ml/kg/h if the patient weighs less than 40kg; urine osmolality <300mOsmol/kg) with compensatory polydipsia.

If the water volume is not restored by the compensation mechanisms, severe hypernatremic dehydration (with subsequent convulsions), decreased arterial pressure, and hypovolemic shock may occur.

This situation is relatively rare and occurs only when some circumstances interfere with either the hypothalamic

centre controlling thirst (hypothalamic tumours or any other underlying pathology responsible for CDI) or the free access to water (reduced level of consciousness, anaesthesia, traumatisms, etc.) of these patients.

Nocturia is also a frequent and very disturbing symptom of the CDI clinical definitory triad. In the majority of cases it has an acute onset, which is clearly different from nocturia due to nephrological polyuria which occurs progressively.

In the last two decades, the efficacy of using magnetic resonance imaging (MRI) in the diagnosis of hypothalamic-pituitary pathologies has become evident, so, cranial MRI is the ”gold standard” in the etiological diagnosis of CDI as well. Regardless of the underlying pathology responsible for CDI (Table 1), the classical common denominator of the MRI of the hypothalamic-pituitary area appearance is the absence of the bright signal of the pituitary posterior lobe in T1sequence.

The CDI aetiology is complex. While the genetic and congenital medical conditions are not only rare but unmasked by particular phenotype, the diagnosis of the acquired causes of CDI remains a real challenge as brain imaging and hormonal findings may be overlapping. With such limited diagnostic tools and without a biopsy, often, the clinical distinction between the listed medical entities in Table 1 is difficult to be done. *Table 1*.

Although head trauma, CNS tumours (germinomas in particular), neoplasms and Langerhans cell histiocytosis (LCH) or infections (Mycobacterium tuberculosis, toxoplasmosis, listeria monocytogenes, cytomegalovirus, etc.) are still the most common reported causes responsible for CDI, over the past decade, a dramatic increase in the prevalence of hypophysitis among children with this kind of medical pathology has been observed.

Table 1. Etiology of Central Diabetes Insipidus

Genetic	Familial Diabetes insipidus • The vasopressin-neurophysin gene (AVP-NF II gene) - Autosomal dominant - Autosomal recessive Wolfram syndrome (4p/WFS 1 gene) X-linked recessive (Xq28)
Congenital malformations	Agenesis of the pituitary Holoprosenchephaly Midline craniofacial defects Septo-optic dysplasia
Acquired	Traumatic injury - CNS surgery - head trauma - hypoxic injury Tumours/neoplasms - pituitary adenoma - germinoma, dysgerminoma - craniopharyngioma - meningioma - leukaemia, lymphoma Infiltration/granulomas - Langerhans cell histiocytosis - neurosarcoidosis Infections (meningitis/encephalitis) - Mycobacterium tuberculosis - toxoplasmosis - listeria monocytogenes - cytomegalovirus (CMV) Inflammatory/autoimmune hypophysitis - lymphocytic hypophysitis • adenohypophysitis (LAH) • infundibuloneurohypophysitis (LINH) • panhypophysitis - IgG4-related hypophysitis - Pituitary disfunction induced by ICIs Drugs (immune checkpoint inhibitors ICIs, corticoids, phenytoin, ethanol, etc.) Idiopathic

HYPOPHYSITIS

Background

Defined as acute or chronic inflammation of the pituitary gland and infundibulum and/or suprasellar region (e.g. stalk thickening, etc.), hypophysitis might be responsible for hypopituitarism and/or central diabetes insipidus.

Classification of Hypophysitis

Hypophysitis is a rare medical condition accounting for only 0,24-0,93 % of all pituitary disorders[1,2,3] but with a continuous increase with the wide use of immune checkpoint inhibitors (ICIs) and of the pituitary surgical cases.

Hypophysitis can be classified according to anatomical, aetiological, and histopathological criteria

Based on **anatomical location**, hypophysitis has been classified according to the involvement of anterior pituitary gland (adenohypophysis), posterior gland and pituitary stalk (infundibuloneurohypophysis) or the entire gland (panhypophysitis).

According to this approach, central diabetes insipidus (related to ADH deficiency) is present only when neurohypophysis is affected in case of infundibuloneurohypophysis or panhypophysitis.

Where the **aetiological** criterion is concerned, hypophysitis might occur either as a primary local inflammation of the hypothalamo-pituitary structures or as a secondary inflammation to multisystemic inflammatory predisposing conditions.

As already mentioned above, both primary and secondary hypophysitis are rare cases in general population not to mention the pediatric patients.

Primary hypophysitis.

Autoimmunity seems to have an important contribution to the pathogenesis of primary hypophysitis.

The different forms of primary hypophysitis have distinctive immunological profiles and histopathological features.

Lymphocytic hypophysitis (LH) is the most common form of autoimmune hypophysitis, followed by granulomatous and xantomatous hypophysitis.

IgG-4 hypophysitis is a new emerging cause of autoimmune hypophysitis also known as plasmocytic hypophysitis[4,5,6,7]. It may occur as part of IgG-4 related disease (autoimmune pancreatitis, Riedel's thyroiditis, Mikulicz's disease, etc.) or it may occur as a distinct and singular involvement of the pituitary gland.

In the absence of a pituitary biopsy-proven IgG-4 disorder, diagnosis is supported by imaging evidence of hypophysitis and elevated serum IgG4 antibody levels (>140 mg/dl)[4] Accurate diagnosis is crucial since this subtype of hypophysitis is responsive to glucocorticoid therapy with subsequent decrease of the circulating IgG4 levels [8,9] in the acute, inflammatory phase of disorder.

Successful transsphenoidal pituitary biopsy is mandatory both for the histological classification and the final diagnosis of primary hypophysitis. But even in this situation, the accurate distinction between different histological subtypes (e.g. lymphocytic, granulomatous and xanthomatous lesions, etc.)[10,11] is not always possible due to their potential overlap.

Table 2. Classification of primary hypophysitis based on histology

Classification of primary hypophysitis based on histology
Lymphocytic hypophysitis
Granulomatous hypophysitis
Xantomatous hypophysitis
Plasmocytic/IgG4-related hypophysitis
Necrotising hypophysitis
Mixed forms (lympho or xanthogranulomatous)

Secondary hypophysitis can arise from systemic (autoimmune, inflammatory, vascular, etc.), sellar and parasellar disorders (e.g tumours, infiltrative or infective diseases, etc.) which are accompanied by inflammation in the

pituitary gland. Same is valid for the secondary hypophysitis after the use of the immune modulatory therapy (interferon alpha, immune checkpoints inhibitors/ICIs-medication targeting cytotoxic T-lymphocyte antigen-4 [CTLA-4], programmed cell death1 [PD-1] (e.g. ipilimumab for malignant melanoma)[10,11]. *Table 3.*

Table 3. Medical conditions predisposing to secondary hypophysitis

Medical conditions predisposing to secondary hypophysitis
Local tumour effect (sellar disorder) - Germinoma - craniopharyngioma - Rupture of Rathke's cleft cyst - lymphoma
Infiltrative lesions - Langerhans cell histiocytosis (LCH)
Systemic inflammatory disorders - Sarcoidosis - Crohn's, Takayasu's or Castlemans disorder - IgG4-disease
Autoimmune disorders - Systemic lupus erythematosus SLE) - Sjogren's syndrome - Bechet's syndrome - Graves's disease, Hashimoto's thyroiditis, Type 1 Diabetes mellitus - Autoimmune polyglandular syndromes (APS) - Coeliac disease - Isolated ACTH deficiency (paraneoplastic syndrome)
Infections - Tuberculosis - Syphilis - Fungal infection
Drug induced Hypophysitis Immune checkpoint inhibitors (ICIs): monoclonal Ab - cytotoxic T-lymphocyte antigen-4 (CTLA4-Ab) - programmed cell death 1 (PD-1 Ab) - Interferon alpha - Interleukin 2

Clinical presentation

The clinical presentation varies from an asymptomatic form to a lethal condition (e.g. central adrenal insufficiency or acute presentation with severe mass effects, etc).

All types of hypophysitis may develop the following clinical tetrad:

- symptoms of the deficiency of the anterior pituitary hormones,
- symptoms of the deficiency of the posterior pituitary ADH/vasopressin (e.g. central diabetes insipidus CDI: polyuria, polydipsia, nocturia, dehydration, hypernatremia, etc.),
- hyperprolactinemia and
- symptoms of mass effects (headaches, visual disturbances, cranial nerves compression, etc.[2,11,12]

1.The usual sequence of hormonal deficiency in panhypopituitarism is loss of GH, followed by LH/FSH, TSH and finally ACTH (mnemonic "Go Look For The Adenoma").[13] In contrast, when panhypopituitarism is due to hypophysitis the most vulnerable one is ACTH followed by LH/FSH, TSH with GH and prolactin secretion being less frequently affected.[11,14]

2. Central diabetes insipidus is related to infundibulo-neurohypophysitis or panhypophysitis.[15] Clinicians should be aware of the following aspects:

a. central diabetes insipidus (CDI) is masked by central adrenal insufficiency and unveiled by glucocorticoid replacement[13,16,17, 20]
b. concomitant hypothalamic involvement with potential adipsic DI may be responsible for severe hypernatremia.[13,19, 20]
c. weight gain and temperature dysregulation are also manifestations of the simultaneous associated hypothalamic involvement.[20]
d. Sellar germinomas can mimic lymphocytic infundibuloneurohypophysitis with CDI and also

hypopituitarism with GH deficiency and symptoms of mass effects.[18,21]

3. Hyperprolactinemia within hypophysitis may be due either to concomitant hypothalamic inflammation with decreased dopamine synthesis and/or disruption of the inhibitory hypothalamic dopaminergic signals because of pituitary stalk inflammation or compression.[20]

4. Symptoms of mass effects are the most common presenting features of hypophysitis and of course, their severity is related to the extension of the disruption within sellar region (e.g. panhypophysitis) and its adjacent anatomical structures.

- headaches are a constant, generalized and severe presence and they occur secondary to upward extension of the inflamed, enlarged pituitary gland upon dura mater and optic chiasm or due to lateral expansion with subsequent compression of the cavernous sinus.
- visual symptoms are clinically validated when enlarged, inflamed pituitary gland encroaches on the optic chiasm (bitemporal quadrantopsia or hemianopsia). Compression of the inflamed pituitary gland on cranial nerves (oculomotor/III, trochlear/IV or abducens VI) results in pupillary defects or diplopia.

Diagnosis of hypophysitis

Modern imaging techniques, histological classification and immune profiling are improving not only the accuracy of the diagnosis of the patient with hypophysitis but also the treatment approach.

Current diagnostic approach involves hormonal and standard biochemical assessment, immune assessment of the potential secondary causes of autoimmune hypophysitis and imaging evaluation.

Biochemical assessment should comprise a full hormonal work up with the dosage of pituitary and their related-target hormones (ACTH, cortisol, GH, IGF1, FSH, LH,

oestradiol, testosterone, TSH, FT4, PRL, ADH/vasopressin and/or copeptin, etc.)

In patients with CDI, plasma/urine osmolality and electrolytes should also be part of the initial evaluation.

A serum sodium >145mEq/L, plasma osmolality ≥295 mosm/kg and a urine osmolality >300 mosm/kg are indicative of DI.[13,20]

Standard baseline investigations such as full blood count, peripheral smear, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), liver, renal and bone biochemical parameters should be done not only as routine biochemical evaluation but as part of the differential diagnosis with the inflammatory causes of secondary hypophysitis.[22]

Based on clinical suspicion or a need for differential diagnosis a wide battery of tests can be supplemented. Table 4

Table 4. More diagnostic tests for suspected hypophysitis (adapted from Mamta N Joshi et al. 2018) [22]

Hypophysitis Medical conditions	**Tests**
Lymphocytic hypophysitis	- pituitary antibodies, - thyroid antibodies (TPO) - anti-nuclear antibodies (ANA) - if concomitant other autoimmune features are present: • Anti-Ro • anti-La • anti-Ssa • anti-ds-DNA antibodies
Granulomatous lesions	Chest X-ray ANCA antibodies CSF analysis for glucose, proteins, ACE Serum ACE levels chest, abdomen and pelvis CT (in case of sarcoidosis)
IgG4-related disease	Immunoglobulins serum levels, particularly IgG4
Langerhans cell histiocytosis (LCH)	Skeletal survey, Whole body scan
Germinoma	Serum and CSF alpha-fetoprotein (AFP) and human chorionic gonadotropin (hCG)

Imagistic evaluation

Currently, gadolinium-enhanced pituitary MRI is considered to be the investigation of choice for diagnosing hypophysitis.[23, 24, 25]

The MRI findings considered to be most prominent for the diagnosis of hypophysitis are:

- pituitary enlargement[25, 26]
- homogeneous pituitary gland contrast enhancement[26]
- pituitary stalk thickening (>4mm antero-posterior diameter on sagittal section) with no obvious stalk deviation[26,27,28]
- loss of the posterior pituitary bright signal on T1-weighted imaging[26]
- symmetrical suprasella extension and enhancement of the adjacent dura referred to as ”dura tail” or ”meningeal tail” (contrast - enhanced inflamed tissue along the dura mater) or
- an empty sella during the late stages of the disease as the atrophic response of the burnt out inflammatory process.[28]

While the above MRI imaging appearances of the different histological types of primary hypophysitis are quite similar, the main challenge of the imagistic diagnosis remains the distinction between hypophysitis and pituitary adenomas, pituitary metastases or other sellar and parasellar tumours.

A radiologic scoring system was proposed by Gutenberg et al. for the distinction between hypophysitis and pituitary adenoma.[29]

The score is based on eight predictors: the relation to pregnancy, pituitary mass volume and symmetry, signal intensity and signal intensity homogeneity after gadolinium administration, posterior pituitary bright spot presence, stalk size and mucosal swelling for the calculation of the score (Table 5). The score ranges from -13 to +8. A score of ≥1 is suggestive of adenoma, whereas a score of ≤ 0 is suggestive of hypophysitis.

Table 5. Gutenberg features score by Gutenberg et al.(29)

Features criteria	**Score**
1. Related to pregnancy Yes	- 4
2. Pituitary mass volume 6 cm^3	2
3. Asymmetry	3
4. Gadolinium enhancement type Medium/High	-1
5. Gadolinium enhancement features Heterogenous	1
6. Lost of the posterior pituitary bright spot	- 2
7. Enlarged stalk size	- 5
8. Mucosal swelling	2

Treatment of hypophysitis

There is no clear consensus regarding the therapeutic management of this rare and extremely heterogenous disorder in terms of clinical presentation and natural history.

The therapeutic approach is distinctive during the acute phase of hypophysitis (which may require primary treatment) compared to the chronic or the so-called ”burnt out” phase when only hypopituitarism and CDI need to be treated.

In the acute phase of the disorder, the main goal is the reduction of the pituitary inflammation and the mass-related effects.

The therapeutic protocol includes anti-inflammatory medication, surgical intervention and radiotherapy.

Glucocorticoid therapy is considered the cornerstone of the anti-inflammatory and immunosuppressive therapy but unfortunately, after the well-known initial good answer to steroid drugs, its effectiveness is limited by the well-known long-term side effects of this treatment. Furthermore, only some histologic types of hypophysitis are sensitive to glucocorticoid therapy.

The surgical interventions (surgical decompression) should be performed only in the presence of serious

complication (deficit of the visual field, acuity or increased intracranial pressure) not responding to pharmacological therapy.

If after glucocorticoids, surgical decompression and hormone replacement therapy (according to conventional recommendations), no resolution of symptoms occurs, immunosuppressive agents, transsphenoidal hypophysectomy or sellar radiation are the last therapeutic option of these patients.

Conclusion

To date, about one-third of the children with the clinical symptoms of central diabetes insipidus (CDI), display pituitary stalk thickening (PST) with adeno and/or infundibuloneuro-hypophysitis at their first MRI assessment.

Primary autoimmune hypophysitis is an underdiagnosed disease due to the difficulty in reaching a definitive diagnosis which requires an invasive transsphenoidal pituitary biopsy.

Despite significant progress in the understanding of this complex disorder and the fact that this medical condition has gained greater clinical recognition over time, diagnosis and treatment management remain an issue of concern.

Although CNS tumours (germinomas in particular) are the most common causes of pituitary stalk thickening while primary autoimmune hypophysitis is reported with low incidence in the pediatric medical care, pan or infundibulo-neurohypophysitis has to be considered in the differential diagnosis of any child with acute onset of CDI.

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FIBRODYSPLASIA OSSIFICANS PROGRESSIVA- A ROMANIAN BOY IMPRISONED IN HIS OWN SKELETON- A CASE BASED REVIEW

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Abstract

Background.

Fibrodysplasia ossificans progressiva (FOP) is a very rare and extremely disabling genetic disease characterized by heterotopic ossification in the soft tissues, as muscles, tendons, and ligaments. FOP has been related to a mutation of the ACVR1/ALK2 gene that induces osteoblast activation.

Method:

We are reporting a case of fibrodysplasia ossificans progressiva in a young boy. His major complaint was a painful inflammation, a so called “flare up” in the sternocleidomastoid muscles, following a prolonged position with the mouth opened during a dental intervention.

He was referred in the Pediatrics Department, because of the presumption of a bilateral lymph node swelling.

Besides the neck inflammation he presented also newly appeared deformities of the skull surface. We noticed a congenital malformation – the bilateral monophalangia of the big toes.

At birth, the mother was told that this abnormality is just a physiological variation, and subsequently, the other physicians did not notice this anomaly.

This was the keystone in our diagnostic algorithm, because the FOP is characterised by these flare-ups in the soft tissues, in individuals with this pathognomonic toe deformity.

All laboratory investigations were normal.

In the following three years, he developed swellings of the shoulder girdles, which severely limited his movements of abduction, and subcutaneous lumps emerged along the spine, which were provoked by minor trauma, evolving as palpable "bars" of ossification.

Results:

The genetic test supported the diagnostic, showing a mutation on Activin Receptor IA (ACVR1) gene. The patient is included in the international FOP registry, hoping to be included in a therapeutical trial.

Knowing there is no curative treatment for FOP; he is treated at least once a year a short course of steroids within the first days of the flare-ups after minor trauma, to diminish the inflammatory process.

Conclusion: The diagnosis of this rare condition is mainly clinical. The treatment is conservative, with avoidance of trauma, and anti-inflammatory drugs, if needed. The surgical interventions are not recommended, because there is a high risk of aggravation the disease, with more bone formation.

Keywords*: fibrodysplasia ossificans progressiva (FOP), Heterotopic ossification (HO)*

CASE REPORT:

A 5 years and 6 months old boy was referred to the Pediatric Clinic nr 2 in Cluj- Napoca, Romania in September 2017 by the paediatrics department of his hometown.

His major complaint was a painful bilateral inflammation in the sternocleidomastoid muscles.

The patient was the first-born child of a non-consanguineous couple with no history of similar illness in his family. The parents and his younger sister were in good health condition.

The clinical onset of his disease started in April 2017, following a prolonged position with the mouth large opened during a dental intervention. It was a routine dental consultation, without injections or extractions, but, immediately after, he reported muscular neck strain, followed by oedema and erythema of the anterior region of the neck, with the contracture of both sternocleidomastoid muscles.

The initial soft swelling evolved with indurations of similar consistency to that of the bone.

The first investigation recommended by the paediatrician from the city of origin was an ultrasound of the thyroid lodge, with normal results. The TSH and FT4 dosages were also normal. Then, the physician suspected a torticollis or laterocervical adenopathy and directed the patient to the Pediatric Onco-Haematology Department of the Children's Hospital in Cluj-Napoca.

The blood count and the blood smear were normal, the C reactive protein negative. The serology ruled out an acute infection with Epstein Barr virus, Cytomegalovirus or Toxoplasma.

A second ultrasound examination revealed that the inflammation was linked to a symmetrical inflammation of both sternocleidomastoid muscles, not to a lymphadenitis.

Despite the clinical and ultrasound findings, the laboratory tests were not concordant with a myositis, because the aspartate aminotransferase (AST/GOT) and alanine aminotransferase (ALT/GPT), Lactate dehydrogenase (LDH) and creatin phosphokinase, (CPK) had values in the normal range.

He was referred to the neurologist in the Infantile Neurology Clinic in Cluj. The electromyogram registered a myositis aspect. Then the MRI of the cervical region showed an inflammatory phenomenon in the lodges of sternocleidomastoids.

The patient received five days of oral Prednisone 1 mg/kg/day with subsequent reduction of the dose, and then 5 days of oral Ibuprofen, with a significant improvement of the clinical inflammation and contracture.

He spent time at home without significant medical problems from April until September 2017.

Then, without a history of preceding trauma or illness, he developed bony -hard bumps on the scalp, with spontaneous regression. Also, the symptoms progressed rapidly with "weird" swelling attacks. These appeared spontaneously or after minor trauma, in the posterior thoracal and lumbar regions. These trunk swellings persisted and acquired a bone consistency. Subsequently, the patient presented a decreasing mobility in the scapulohumeral joints.

During the acute phase of this flare-ups, he never presented fever and he described a bearable pain. Between these episodes of acute inflammation, the swellings were not painful, but evolved with progressive hardening.

The mother asked for a second opinion in the same hospital in Cluj, in the General Pediatrics Department.

In September 2017, the patient was in a very good medical condition, excepting the finding of the swellings of a hard texture localised in the interscapulovertebral and bilateral paravertebral regions (*Figure 1*), more pronounced on the right side, limiting the abduction of the arms to approximative 60 degrees (*Figure 2*). We noticed a congenital malformation-the bilateral monophalangia of the big toes (*Figure 3*).

At birth, the mother was told that this abnormality is just a physiological variation, and subsequently, the other physicians did not notice this anomaly.

Figure 1 - Bony hard swellings in the thoracal and lumbar region

Figure 2. Gross restriction of range of motion of the shoulders

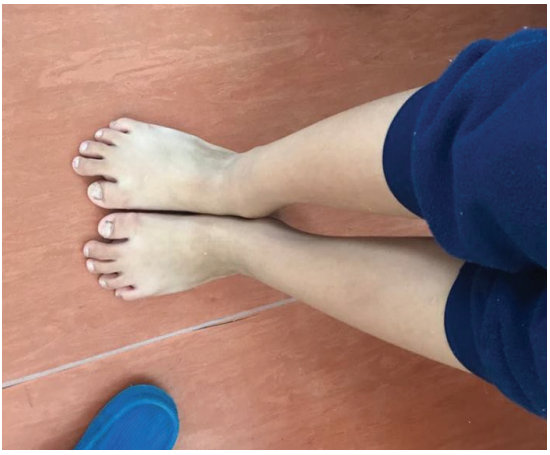

Figure 3 Bilateral monophalangia of the toes

Because none of the doctors in our hospital could recognise a certain medical entity, we presumed that we were facing a rare disease.

What rare disease could it be? An ossificant disease? An ossifying myositis? An entity that evolves with fibrosis? A type of fibromatosis? Maybe a bone dysplasia?

Utilizing these keywords and "malformation of the big toes", after a search of the medical literature on Internet we found out that our patient had the typical features of fibrodysplasia ossificans progressiva (FOP).

We presented to the family our clinical diagnosis, and, knowing that for the moment there is no medical cure, we referred the patient in Necker Hospital Paris, in the Rare Disease Department. The clinical diagnosis was confirmed, and because the specialist considered that the boy must have a spontaneous mutation and the parents didn't want any other descendants, the patient was registered, waiting to be possibly included in an experimental therapeutic trial. Knowing that even the minor traumatism could evolve with flare-up with subsequent heterotopic ossification of the soft tissues, we recommended regular follow up in our hospital, avoidance of trauma and muscular straining and short cures of oral Prednisone in case of flare-ups.

In 2021 we performed a genetic test in the Invitae laboratory in the United States of America, which confirmed a typical mutation in the Activin receptor 1 gene. It was found a pathogenic variant associated with autosomal dominant fibrodysplasia ossificans progressiva, a heterozygous pathogen variant of ACVR1: c.617G>A (pArg206His).

The patient was recorded in the International FOP registry, hoping to be included in a therapeutical trial.

In the five years following the clinical diagnosis, he evolved with spontaneous and posttraumatic flare -ups, treated with short cures of oral Prednisone or Ibuprofen. Otherwise, he presented only minor upper respiratory infections.

The family has now another baby child, the third sibling, which is in good health.

In 2022, our patient has a very limited capacity of mouth opening (Figure 4), which limits severely the possibility of correct stomatology treatment. It's also known that the prolonged strain on the muscles of the face and neck and the local anesthesia could induce a new flare-up in these patients.

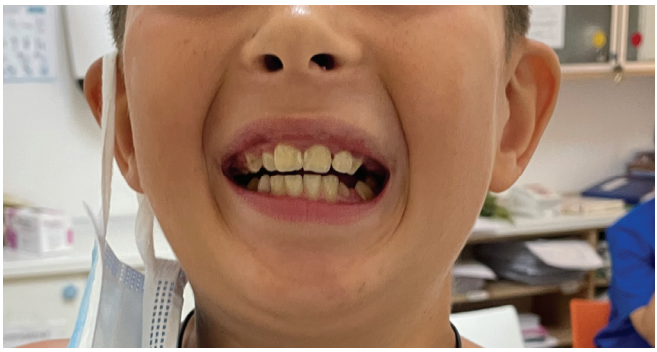

Figure 4 Ankylose of the jaw

He has a progressive limitation of the arms abduction, with a significant impairment of his quality of life (*Figure 5*). In the paravertebral region he evolves with a bony cord swelling (*Figure 6*)

Conclusion

The clinical suspicion of FOP based on the presence of malformed great toes can lead to prompt clinical diagnosis, avoiding the expensive and potential harmful diagnostic procedures. The biochemical tests do not contribute to the diagnosis. The main message for the clinician is: always remove the socks and watch the toes!

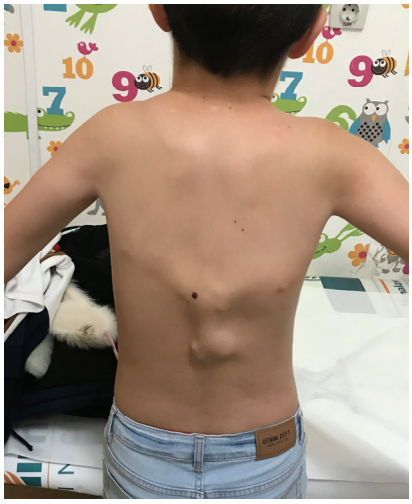

Figure 5 - Gross restriction of range of motion of the shoulders

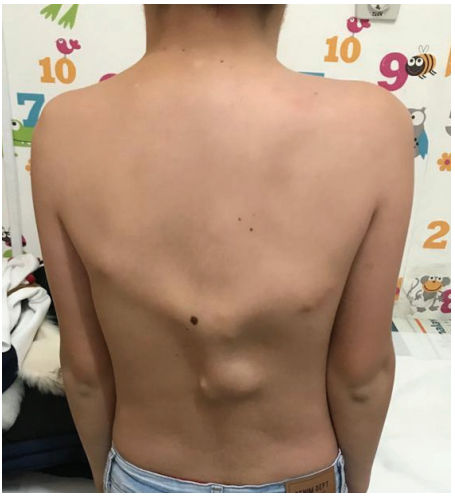

Figure 6 - The bony cord swelling in the paravertebral and interscapulovertebral region

DISCUSSION AND LITERATURE REVIEW:

Fibrodysplasia ossificans progressiva (FOP) is a rare genetic disorder of the connective tissue characterized by congenital malformations of the great toes and progressive heterotopic ossification (HO).

The connective tissue turns into a skeleton in specific extra skeletal anatomical sites. It is considered the most devastating disorder of heterotopic ossification in humans.

The disease is ultra-rare. There are around 800 confirmed cases in the world.[1]

The worldwide prevalence is approximately 1/2,000,000.[1,2] There is no ethnic, racial, gender, or geographic predilection to FOP.

The disease was described in 1692 by the French physician Guy Patin.[1] The most legendary of all patients with FOP is Harry Raymond Eastlack, who made the decision to donate his skeleton to The Mutter Museum in Philadelphia USA, so that physicians could further learn about FOP. [1]

The diagnosis is mainly clinical but must be confirmed by genetic testing.

Individuals with FOP appear normal at birth, except for characteristic malformations of the great toes that are present in all classically affected patients.[3] The malformation can vary from a fibular deviation of the great toes to monophalangia or even the complete absence of the great toe. [1]

During the first decade of life, most children with FOP develop episodic attacks of painful inflammatory soft tissue swellings (called flare-ups).[4] These are often erroneous diagnosed firstly as tumours. Knowing the disease is very rare and the symptoms are cumulative, the initial diagnostic error rate is high, around 60%-80%.

The first phenomenon in chronological order can be the neck stiffening, followed by episodes of tumor-looking swellings of the soft tissues, with subsequent transformation of the lesions into bone-like tissues. The soft tissues affected by ossification are skeletal muscles, tendons, specific joints, aponeurosis, fascias and ligaments. Some exacerbations could spontaneously regress. Finally, the patient is trapped in a

second skeleton, because the flare-ups can transform the soft tissues trough an ossification transformation into ribbons, cords, sheets, or plates of heterotopic bone.

Typically, the heterotopic ossification follows specific anatomic patterns. It starts in the neck, shoulders, and back regions. The progression of the HO is as following: dorsal into ventral, proximal into distal, axial into appendicular, and cranial into distal regions.[1,3]

The attempt to remove the heterotopic bone tissue is followed by an explosive proliferation of additional bone.

There will appear an early ankylose of the cervical spine. Some soft tissues are spared of the HO. It's about the smooth muscles, the myocardium, the diaphragm, the tongue, and the extra-ocular muscles where the heterotopic ossifications never occur.[1,3]

In addition to the progressive incarceration in the second skeleton with severe impairment of the joint movements, other life-threatening complications include: severe weight loss due to the ankylosis of the jaw and respiratory and heart insufficiency, because of the thoracic cage rigidity. Singing and swimming should be encouraged to maintain lung function. After four years of age is recommended to perform the baseline pulmonary function tests, echocardiogram, chest x-ray and pulse oximetry.

Later in life, the patients develop swellings of the lower limbs with lymphatic and vascular compressions, and transmission hearing loss (due to the middle ear ossification), but also sensorineural deafness (due to the the inner ear, cochlea, or the auditory nerve impairement).[4] The patients should generally have audiology evaluations at least every other year. The hearing impairment can lead to developmental problems.

Atypical features reported as associated with FOP include intraarticular synovial osteochondromatosis and degenerative joint disease of the hips, mild cognitive impairment, severe growth retardation, ocular problems (like cataracts, retinal detachment, childhood glaucoma), tumours (craniopharygioma), persistence of primary teeth in adulthood,

anatomic abnormalities of the cerebellum, seizures, primary amenorrhea, aplastic anemia, hypospadias, and cerebral cavernous malformations.[5,6]

Some manifestations of precocious aging may be attributed to both primary and secondary effects of FOP. The existence of the primarily effects of FOP like osteoarthritis, hearing loss, alopecia, subcutaneous lipodystrophy, menstrual abnormalities, and sometimes nephrolithiasis are progeroid features. Other secondary disabilities following the progressive heterotopic ossification may be related to immobilization, risk of fractures because of impaired mobility of the arms, decreased vital capacity, osteoporosis, sarcopenia.[7] For these reasons, FOP is considered one of the segmental progeroid syndromes.[7]

There are more some mysteries related to the clinical features of FOP: The age of the onset is variable. It generally occurs at the age of 1 to5 years, but in other cases the symptoms start in adolescence or in adulthood.

The flare-ups cannot be predicted: some major traumas do not trigger FOP phenomena, but sometimes even long stroll can trigger a flare-up.

The average life span is 40-45 years. The death often results from complications of thoracic insufficiency syndrome.

A special category are the females affected by FOP. During pregnancy there are high risks for the mother and the child. Complications in the mother are the flare-ups during pregnancy, respiratory difficulties, and the labour-related complications.

If the mother is affected by FOP, knowing that the transmission is autosomal dominant, there is a 50% risk of disease in the baby. They are prone also to premature birth.

The main differential diagnosis must be made with the progressive bone heteroplasia, also a genetic disease linked to another mutation. The letter is not evolving into flare -ups. Bone tissue grows in the skin and in the adipose tissue. The bone growth stretches like a network from the surface (skin) into the subcutaneous tissue and the muscles. The typical clinical signs is the presence of rice-like granules under the skin.

The FOP genetics was discovered in 2006.

The phenotype is linked to a mutation in the Activin Receptor type 1 gene (ACVR1).[8]

De novo mutations are the origin of the disease in most cases, but also autosomal dominant transmission is possible. The gene encodes the receptor activin protein type 1 (ACVR 1) The ACVR1protein is a bone morphogenetic protein (BMP), It controls and regulates the bone growth and the ossification of long bones.

Most patients (97%) have an identical single nucleotide mutation in ACRV1 (c.617G>A R206H). It means there is a substitution of histidine for arginine at codon 206 (p.R206H) in the intracellular domain of the receptor. This mutation corresponds to the classical form of FOP. 3% of FOP patients have phenotypic and genotypic ACVR1 variants.[9]

The FOP is viewed and classified as a genetic disorder of the osteochondrogenesis (9,10). Following the mutation, this ACVR1 gene receptor induces osteoblast activation.[11]

The heterotopic ossification process evolves in four phases: during the first phase, there is a fibroblast cell proliferation around the muscle cells, in the second phase, de novo blood vessels are formed in the connective tissue next to the fibromatous lesion, the third phase, when the cells inside the fibromatous area begin to have morphology of chondrocytes, and the fourth phase, when the hypertrophic chondrocytes are surrounded by fibroblast-like cells.

The experimental studies in murine animal models of FOP strongly sustain the role of the innate immunity in inducing heterotopic ossification.

The classical imaging studies such as X-rays and computed tomography (CT) scans identify mature heterotopic ossification. The ultrasound, MRI, and the positron emission tomography (PET) scans can detect early ossification. [11]

There are many cases when the biopsies executed on these swellings were reported as sarcomas, aggressive fibromatosis, or nodular fasciitis.[12] In FOP patients, the swellings tend to evolve rapidly, worsening after invasive surgical interventions. [12]

The treatment of FOP is a challenge. The Fibrodysplasia Ossificans Progressiva (FOP) Connection Registry is an international study that collects demographic and disease information. [13] To build this database could be very useful, because FOP is frequently misdiagnosed and unreported.

The discovery of the pathophysiology of the FOP is very difficult. The disease is extremely rare, and the biopsies are contraindicated because of the increased risk for flare-ups. On the other hand, after the identification of the ACVR1 mutation, the research tries to find an innovative treatment solution, but for the moment the FOP treatment consists in prevention of the accidents and to take special trauma precautions in the event of medical procedures. The iatrogenic harm is high in these patients. The old "primum non nocere" principle is crucial. Injuries are not operated on. It is highly recommended to avoid intramuscular injections. The children can receive subcutaneous vaccines, the intravenous and subcutaneous injections are allowed, also they can tolerate peripheral blood collection performed by a skilled person.

There must be a particular attention regarding the dental treatments because the long-standing strain on the muscles of the face and neck and the local anesthesia can induce a neck and jaw flare-up.

Glucocorticoids such as Prednisone are the standard of care for flare-ups in the appendicular skeleton, anterior neck, and jaw. A short cure of 4 days of Prednisone 2 mg/kg once a day is recommended only in case of damage the large joints or temporomandibular joint. Otherwise, the patients will receive non-steroidal anti-inflammatory drugs (NSAIDs), myorelaxants and gentle physiotherapy.[14]

The therapeutic research offered some hope and futuristic ideas, but despite the efforts, still there is no specific treatment approved for FOP.[15,16]

The first clinical trial with Pavolarotene (a retinoic acid receptor-gamma agonist which inhibits HO) started in adults in 2014, and two years after, a similar trial started in children. There are newer clinical trials with Rapamycin (2017) and monoclonal antibodies against Activin A (2018). [15]

FOP intimate mechanism discovery and treatment still face many challenges. The international information gain and collaboration is essential to achieve a curative treatment for the FOP patients.

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