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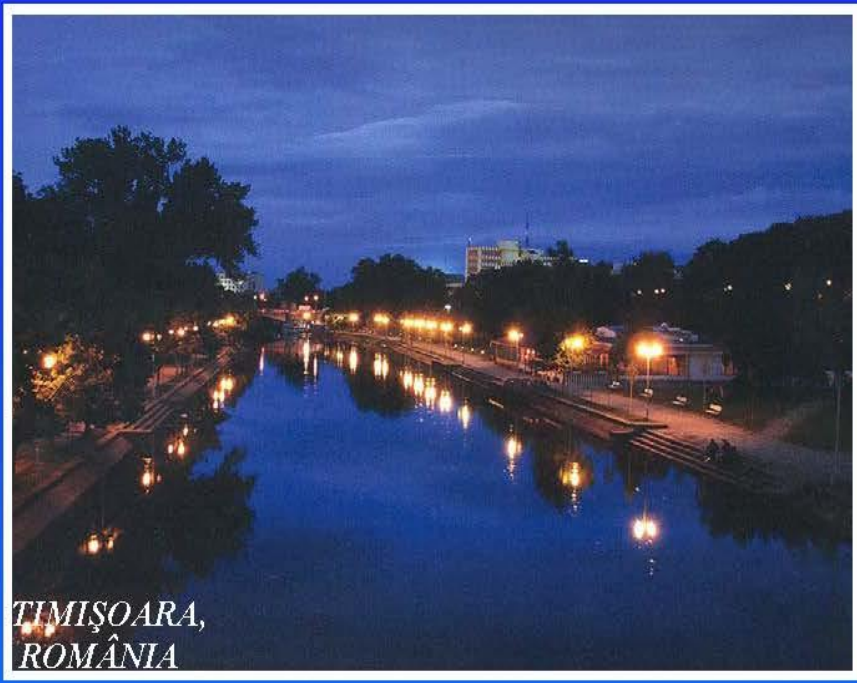

SOCIETATEA ROMANA DE ENDOCRINOLOGIE • SRE •

23 - 26 Mai 2013

CONFERINTA Nationala

cu participare INTERNATIONALA

Grupul de Endocrinologie Pediatrică din cadrul Societăţii Române de Endocrinologie şi Comitetul de Organizare al Congresului, are deosebita plăcere să vă invite la Conferința: Controverse în Endocrinologia Pediatrică: Tulburări de creștere ale adolescentului — Timișoara, România 23-26 mai 2013.

Programul conferinței va oferi o varietate de subiecte în tulburările de creștere ale adolescentului. Sesiunile vor consta din prelegeri susţinute de personalităţi ştiinţifice naţionale şi internaţionale de profil, ateliere de lucru interactive, seminarii și o gamă largă de lucrări prezentate.

Conferința va crea oportunități pentru participanți de a prezenta și împărtăși experiențele lor, de a explora noi direcţii şi teme de dezbatere. Va da o nouă perspectivă în privinţa tulburărilor de creștere ale adolescentului pentru viitorul Endocrinologiei Pediatrice.

Vă aşteptăm cu drag la Timișoara!

Prof.Simona Fica
Preşedinte al SRE

Conf.Dr.Otilia Mărginean
Şef Clinica I Pediatrie
Şef Secţie Endocrinologie

GROWTH FAILURE IN CHILDREN WITH END STAGE RENAL FAILURE ASSOCIATED ADRENOGENITAL SYNDROME

Camelia Daescu [1,2]*, Otilia Marginean [1,2], A Craciun [1,2], Ioana Maris [1,2], Tamara Marcovici [1,2], Andreea Militaru [1,2], Oana Belei [1,2], Daniela Chiru [1,2], Laura Olariu[1,2], Ramona Stroescu [1,2], Giorgiana Brad [1,2], C Popoiu [1,2], Laura Portaru [2], Adina Pavel[2], Pantea Ioana[2], Emilia Barzuca [3]

Abstract

Objectives: To emphasize the negative role of chronic kidney disease in impaired growth and development of a female 7 year old patient, with chronic renal failure associating sexual developmental disorder - adrenogenital syndrome.

Methods: The patient came to monthly follow-ups for the evaluation of her the anthropometric, nutritional and biological status. She was treated with a replacement therapy comprising of growth hormones and cortisone.

Results: The girl was diagnosed at birth with polycystic kidney disease and sexual development disorder, karyotype 46XX - adrenogenital syndrome, salt-losing form. Cortisone replacement therapy was initiated in the neonatal period, under hormonal monitoring. At the age of 4 she had a creatinine clearance (Schwartz formula) of 17 ml/min/m2, height: H2009 = 83 cm, weight: W2009 = 8 kg and the therapy with growth hormones was initiated. In the following years, the increase in height was 12 cm and in weight 3 kg (H2010 = 95 cm, W2010 = 11 kg), while requiring the initiation of peritoneal dialysis. Currently, H2013 is 104 cm and W2013 is 13 kg.

Conclusions: Progression of chronic kidney disease causes retardation of growth and development by: inadequate production of erythropoietin with secondary anemia, bone and mineral disease secondary to renal dysfunction, chronic metabolic acidosis and disruption of the hypothalamic-pituitary growth hormone axis. Adrenogenital syndrome association is an additional factor for impaired growth and development.

Keywords: chronic renal insufficiency, adrenogenital syndrome, growth hormone.

Background

A multitude of modifications in the body's homeostasis are characteristic to chronic kidney disease.

Chronic acidosis causes an increase in protein degradation, a decrease in albumin synthesis, the demineralization of the bones, as well as inhibition to growth hormone secretion. (1-4)

Renal anemia, together with mineral and bone disease secondary to renal dysfunction lead to the alteration of the patients' nutritional status.

In populations with chronic renal disease, the term *malnutrition* should be replaced with *protein-caloric loss*, since the imbalance is caused by metabolic and inflammatory modifications. (5)

A child with chronic kidney disease, uremic stage, may benefit from extrarenal purging techniques or transplantation. Peritoneal dialysis is to be preferred when attempting an extrarenal purge in children, as the circumstances allow it. It can achieve a constant control of uremia, less restrictions of the child's diet, as well as an extra source for calories due to glucose absorption from the dialysis fluid. (6-8)

The clinical assessment of the peritoneal dialysis's efficiency should be made considering the following parameters:

- Hydration status
- Nutrition status
- Intake of calories, proteins, salt, mineral
- Acid-base balance
- Control of anemia
- Control of blood pressure
- Mental growth and development
- Psycho-social rehabilitation
- The patient's well-being

Objective

To emphasize the negative role of chronic kidney disease in impaired growth and development in children.

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Case report

History

This is the presentation of a 7 year old female patient held under medical surveillance in the Nephrology Department of the „Louis Țurcanu" Children's Emergency Hospital Timişoara. The child's parents are young and not consanguine. There is no relevant family history.

The girl is initially diagnosed during her first month after birth with abnormal sexual development, 46XX karyotype (fig. 1), adrenal-genital syndrome, salt losing type. Biologically, with the exception of her hydric, electrolytic and acid-base imbalance, she has shown high serum levels of urea and creatinine.

The ultrasonography showed bilateral polycystic kidney disease (fig. 2), confirmed by uroMRI (fig. 3). Chronic renal failure is well documented by renal scintigraphy. (fig. 4)

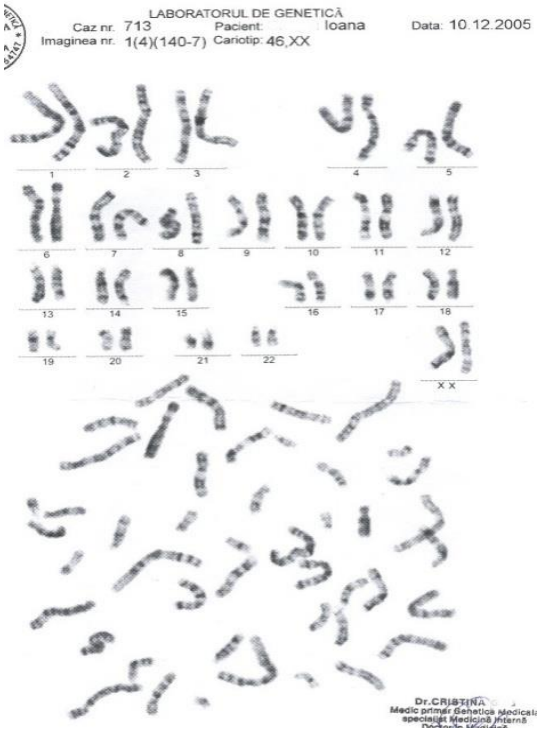

Figure 1. 46XX karyotype.

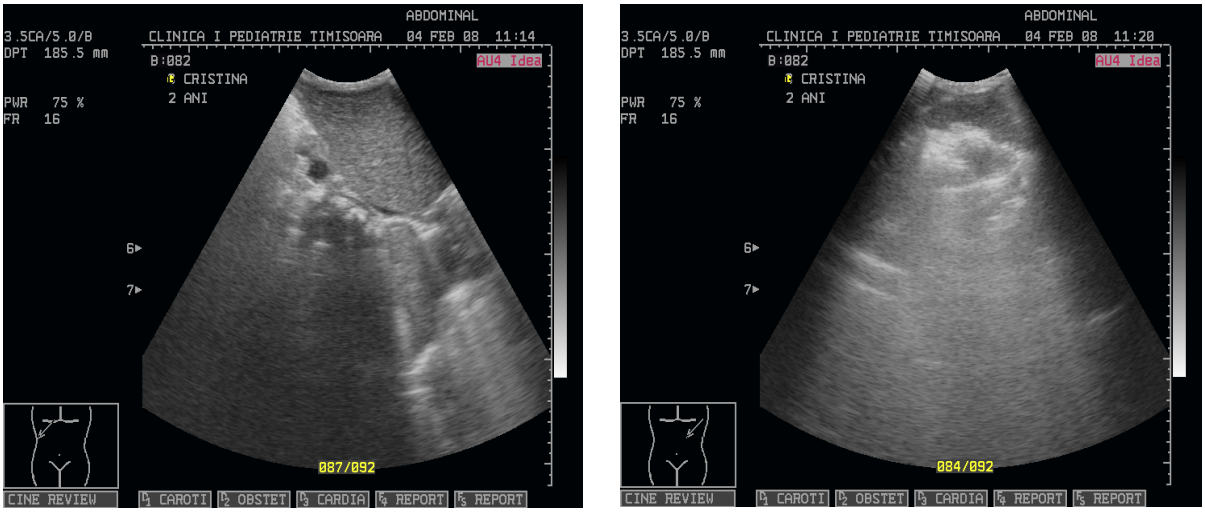

Figure 2 Abdominal echography.

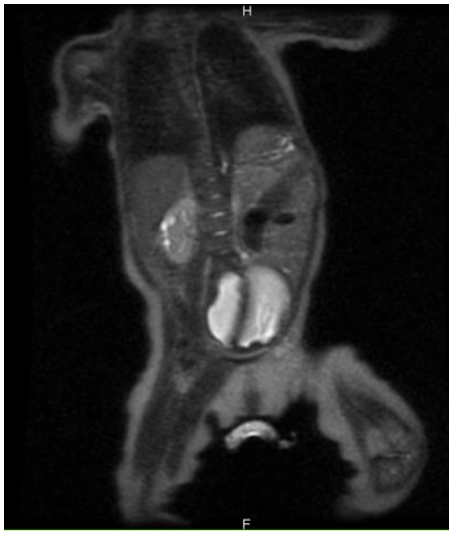

Figure 3 UroMRI aspect.

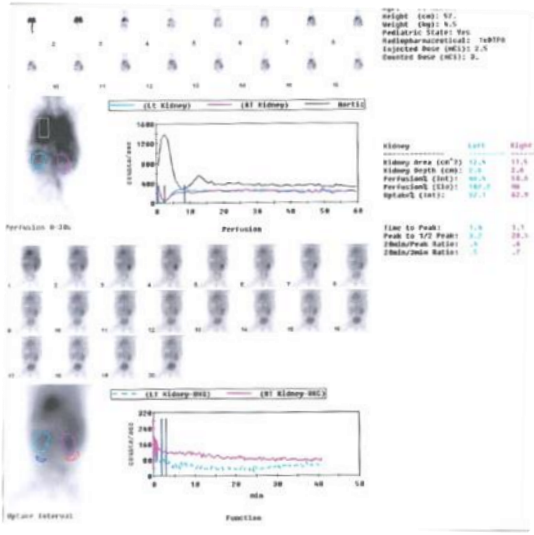

Figure 4 Renal scintigraphy.

At the age of 4, when the chronic kidney disease had reached level 4, the patient had suffered afebrile generalized tonic-clonic convulsions, with no hydric, electrolytic or acid-base imbalance. Also, there was a modification in her EEG but a normal cerebral MRI.

Clinical examination

Currently, she is severely underweight (Weight =13 kg, height = 104 cm, below the 3rd percentile for age WHO, BMI=12, 01 kg/m^2). She is pale with an abdominal scar due to the peritoneal dialysis catheter insertion. Her blood pressure is normal for her gender, age and height. Ambiguous genitalia with clitoromegaly. Diuresis is 3.5 ml/kg/h. The patient presented multiplanar *deformities* of the upper and lower *limbs*, *bilateral coxo-femoral subluxation*, while walking was only possible with braces. The clinical examination showed otherwise normal results.

Blood work:

- KT/V (fractional clearance of urea) = 2.84
- Creatinine clearance 16.72 ml/min/1.73 m^2
- Normal serum levels of protein and albumin
- Constant level of Hb at 12.2 g/dl.
- ↑ Serum cholesterol
- Normal serum levels of calcium, phosphorus, normal levels of Ca x P
- FAL ↑↑↑, PTH ↑↑↑
- Normal acid-base balance

Consults

The endocrinologist concluded she has sexual developmental disorder – adrenal-genital syndrome, salt-losing type. The patient required substitution with cortisone. For her growth deficit, within the context of chronic kidney disease, growth hormone therapy is initiated.

The neurologist introduces carbamazepine in her therapy in order to manage the afebrile convulsive episodes.

The nephrologist underlines the complications of end-stage chronic kidney disease: renal anemia, mineral and bone disease secondary to renal dysfunction, chronic metabolic acidosis. Continuous manual peritoneal dialysis improves her nutritional status and her growth. The velocity of the growth process in these patients is strongly related to creatinine clearance, residual GFR, fractional clearance of urea - Kt/V urea. (9) The increase in Kt/V urea is associated with a low serum level of albumin, suggesting that the increase of the dialysis dose can reach a level where benefits are annulled, with a loss of albumins in the dialysis fluid. (10)

Treatment and follow-up

The patient undergoes a substitution treatment with cortisone during the first month after birth. Periodic hormone evaluation shows a satisfactory control of the adrenal-genital syndrome: no clinical evolution; biologically: normal electrolytes, glycaemia, gas analysis (BGA).

An optimal level of hemoglobin is reached by substitution treatment with erythropoietin, vitamin and iron supplements.

Mineral and bone disease secondary to renal dysfunction is progressive, despite an appropriate diet, treatment with vitamin D and analogues, calcimimetics.

Growth hormone therapy has led to a somatic growth of 12 cm in height throughout the first year (at the age of 4). The initiation of peritoneal dialysis at the age of 5 caused an improvement in the patient's growth. (fig. 5)

Currently, H_{2013} is 104 cm and W_{2013} is 13 kg.

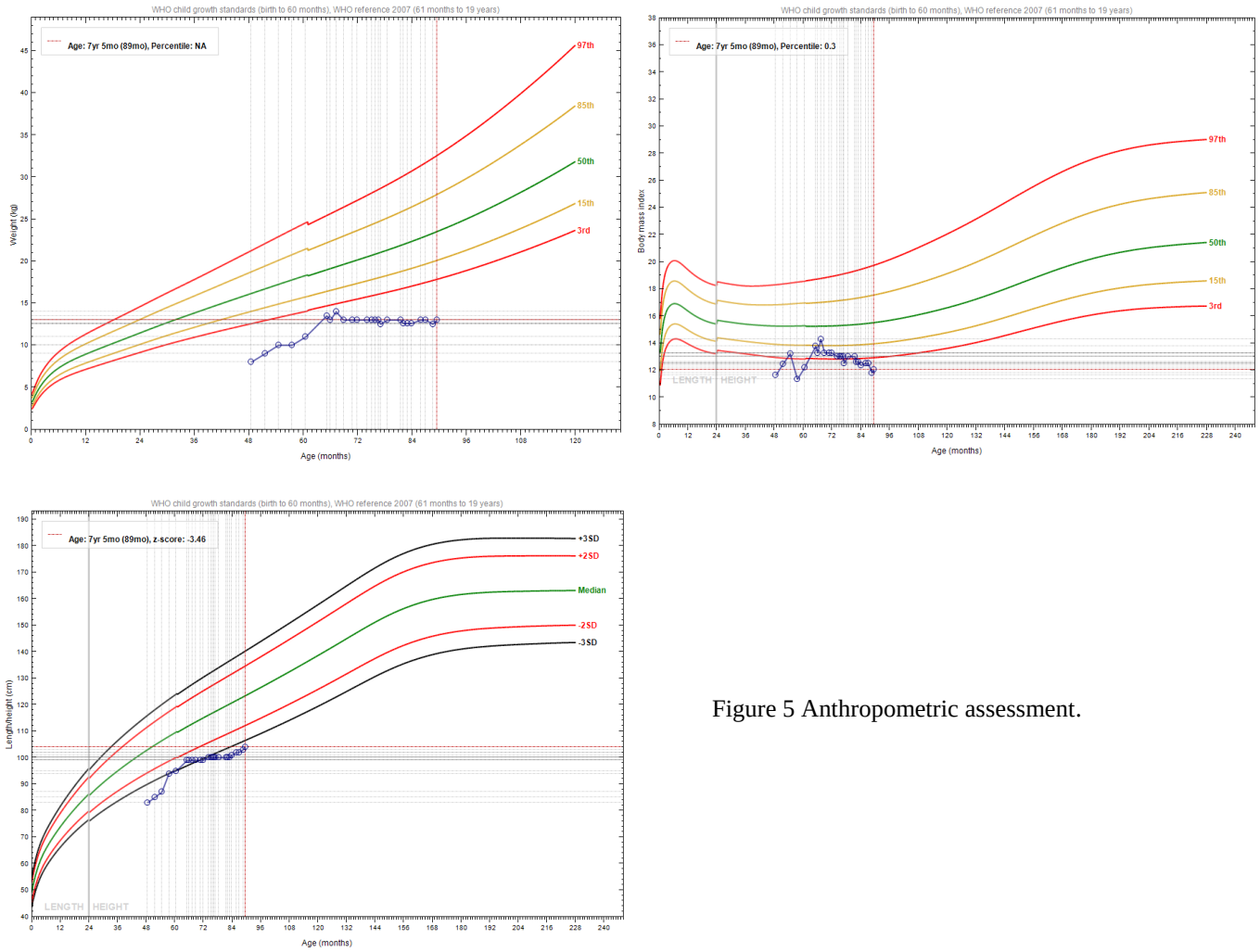

Figure 5 Anthropometric assessment.

Conclusions

Secondary anemia, metabolic acidosis caused by chronic kidney dysfunction, as well as mineral and bone disease secondary to renal dysfunction lead to impaired somatic growth. The disruption of the hypothalamic-pituitary growth hormone axis is associated. This child has achieved somatic growth based on the growth hormone treatment and on the initiation of peritoneal dialysis as a means of extra-renal purging. The patient needed periodic hormone monitoring due to her adrenal-genital syndrome.

Ethical considerations

Written informed consent was obtained from the patient for publication of this case report and accompanying images.

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PUBERTY DISORDERS IN GIRLS

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Abstract:

Introduction: During puberty, menarche represents the most important event in females. Amenorrhea is defined as the absence of menstruation during puberty. ***Aim:*** To evaluate the adolescents with amenorrhea and to analyzed the management of these patients. ***Material and method:*** We analyzed 216 patients admitted to the Endocrinology Department over a period of five years, from 2007 to 2012. The study protocol was complex and it consisted in the patients' history, physical examination and anthropometric measurements. Laboratory evaluation included the measurements of LH, FSH, estradiol, testosterone, DHEA, 17 OH progesterone, TSH, prolactin. Karyotypes, imagistic studies, gynecological and psycological consult were performed in selected cases. Results: Out of 216 adolescents studied with a mean age of 13.8 ± 0.8 years old, 74% of girls were diagnosed with secondary amenorrhea, while the rest had primary amenorrhea. Regarding the etiology of the secondary amenorrhea, 156 patients had secondary amenorrhea caused by stress and 4 cases had mental anorexia. The majority cases of primary amenorrhea were secondary to polycystic ovaries syndrome (60.71%), late form of 21 hydroxylase deficit (7.41%) or Turner syndrome (25%). Therapeutic strategy for patients with secondary amenorrhea consisted in psychotherapy and sedative medication while the treatment of the patients with primary amenorrhea depended of form and etiology. ***Conclusions and discussions:*** Amenorrhea can hide behind a symptom complex pathology. A complex evaluation of the patients with irregular menstruation is required. Treatment should be as early as possible.

Key words: puberty, adolescents, amenorrhea

Introduction:

Puberty is a stage of life characterized by hormonal changes and physical and psychological modifications leading children from childhood to adolescence. During this period, menarche represents the most important event in females. Age of menarche is different among populations and it is useful marker of socio-economic status, as well as dietary and environmental patterns . Generally, the first menstrual cycle takes place between 12 and 13 years of age, with 98% of girls having menarche by 15 years of age . The normal range for menstrual cycles is between 21 and 45 days, with flow length varying from 2 to 7 days. During the first 2 years after menarche, menses length is often abnormal due to immaturity of the hypothalamic-pituitary-ovarian axis2.

Amenorrhea is defined as the absence of menstruation during puberty. It can be presented in girls with their age over 14 years without the development of the sexual characters or in teenagers over 16 years with normal development of secondary sexual characters presented. Amenorrhea may be primary or secondary. The primary amenorrhea is characterized by the absence of installation cycle.

For the diagnosis of the amenorrhea is important two etiological coordinates: the presence of secondary sexual characteristics and the serum follicle stimulating hormone (FSH). Based on these criteria we have the following cases:

A. Primary amenorrhea with normal pubic development and normal or low FSH level

It implies the presence of anatomical abnormalities such as labial agglutination, hymen aplasia, and agenesis of the uterus (Rokitansky syndrome). Also it was described adolescents with female phenotype but with 46XY genotype presents without menses secundary to Mülerian agenesis .

B. Primary amenorrhea with delayed development of secondary sexual characteristics and increased FSH

This form can be congenital or acquired. Short stature associated with a particular phenotype with widely spaced nipples, the presence of ptesigium coli and the 4th metacarpal shorter Turner syndrome may be suspected and the karyotype is required to be performed. Hypogonadism hypergonadotopic can be associated with Albright syndrome or a deficiency of 17 α hidroxilase. Autoimmune oophoritis, tumors, radiation to the pelvis are other causes of acquired ovarian failure.

C. Primary amenorrhea, delayed secondary sexual characters and decreased levels of FSH

These characteristics are described in Kallman syndrome (congenital absence of GnRH and anosmia) or Prader - Willi syndrome (obesity, hypogonadism, delayed puberty, small hands, round eyes, mental retardation), Laurence - Moon - Bardet - Bield (mental retardation, retinitis pigmentosa).

D. Primary amenorrhea virilizing

It is caused by the deficit of the 21 - hydroxylase due to excess of adrenal androgen overstimulation induced by ACTH, cortisol deficiency.

Secondary amenorrhea is defined as no menstrual cycles for a period of four-six months that occurs after the first year of the onset of menarche. It may be due to polycystic ovaries, gonadal dysgenesis, anorexia - nervosa, stress, brain or adrenal tumors, late form of 21 hydroxylase deficit, hyperprolactinemia (functional or tumor) or due to pregnancy. Incidentally, it is also present in patients with X/ autosomal translocations.

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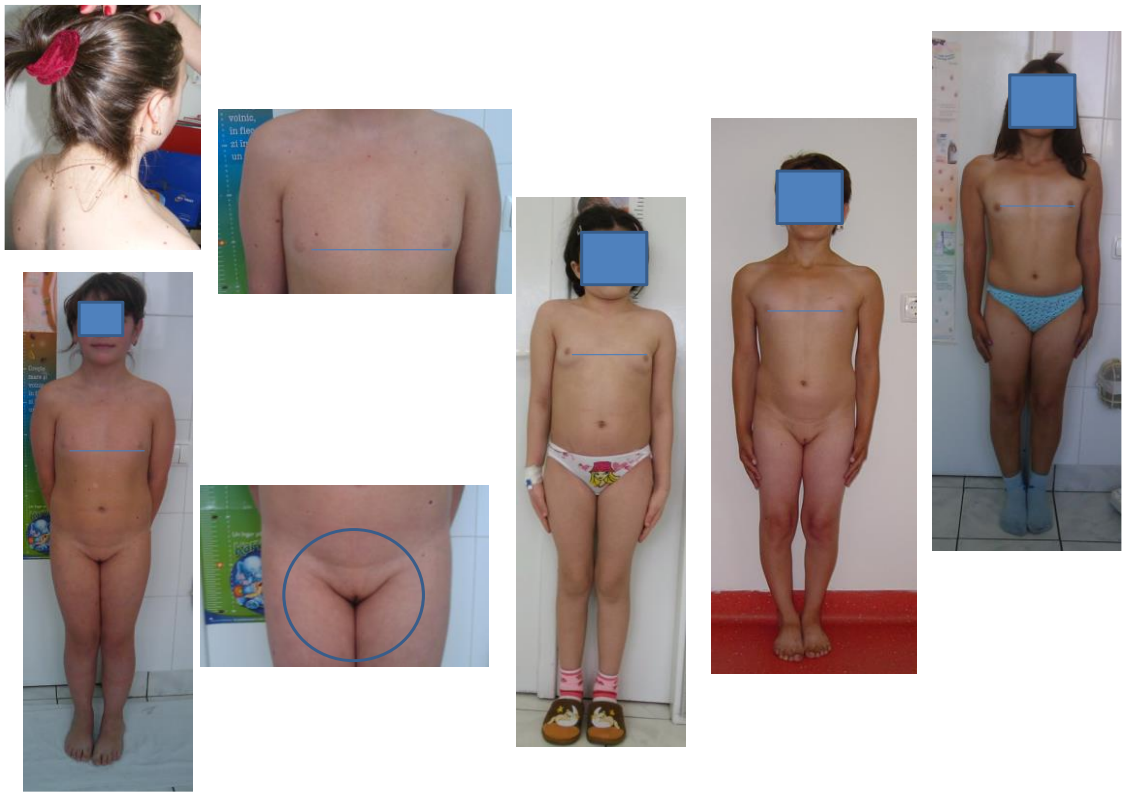

Figure 1: Five cases with Turner Syndrome from our study

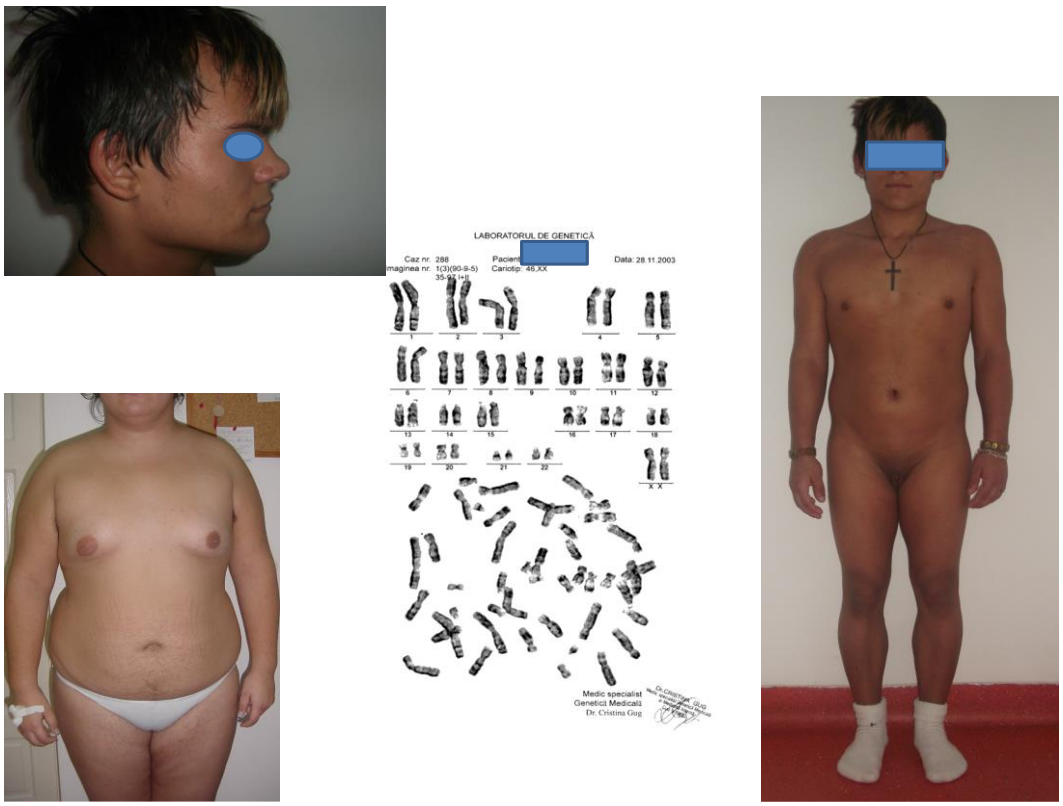

Figure 2: B.R. and B.B - Late onset Form of 21 Hydroxilase deficiency

Objectives:

The authors aimed to evaluate the adolescents with amenorrhea and to analyze the diagnosis and management of these patients.

Materials and methods:

We analyzed 216 patients admitted to the Endocrinology Department of "Louis Turcanu" Children Emergency Department with abnormalities of the menstrual cycle. This study took place over a period of five years, from 2007 to 2012.

The study protocol was complex.

It consisted in the patients' and their family history, their physical examination and anthropometric measurements (height, height standard deviation score, weight, body mass index, growth velocity). Also it was noted the stage of pubertal development according to the Tanner criteria, signs of androgen excess (acne, hirsutism, deepening of the voice), signs or symptoms of systemic diseases or endocrine disorders (goiter, central obesity, purplish skin striae, muscle weakness), and stigmata of genetic anomalies (short stature, misshapen ears, broad chest, widely spaced nipples, cubitus valgus). Hirsutism was quantificated using Ferrimann - Galaway scale. Blood pressure should be measured in order to quantify hypertension.

Laboratory evaluation of amenorrheic adolescents included the measurements of LH, FSH, estradiol, testosterone, DHEA, 17 OH progesterone, TSH, prolactin. Also fasting insulin and glucose, insulin and HOMA index, adrenocorticotropic hormone, cortisol were performed. Because pregnancy represents the most frequent cause of secondary amenorrhea, pregnancy test was done in all cases.

Karyotypes were generated from the peripheral blood lymphocyte cultures and the cytogenetic analysis was performed. Metaphase chromosome preparations from peripheral blood were made according to the standard cytogenetic protocols. Chromosomal analyses were performed by G-banding using trypsin and Giemsa at approximately 400 – 450 band level. Further nucleolar organizing regions staining and C-banding and heterochromatic region.

Gynecological consult performed a careful examination of the external genitalia to assess clitoris, hymen permeability and vaginal and uterine development

Psychological consult were performed in selected cases.

Pelvic transabdominal ultrasonography scanning measured the length of uterus and ovaries and endometrial thickness while magnetic resonance imaging of the hypothalamus and pituitary gland, and magnetic resonance imaging of the pelvis played an important role in the evaluation of an adolescent with irregular menses. Osteodensitometry was performed for obtaining information about the structure of the bone.

Written consents were taken from all the patients of their parents or legal tutor.

Results and Discussion

The mean age of patients analyzed was 13.8 ± 0.8 years old. 77% of them were from rural areas.

Out of 216 adolescents studied, 74.04% (160 cases) of girls were diagnosed with secondary amenorrhea, while the rest had primary amenorrhea.

56 adolescences had primary amenorrhea. The cases secondary to polycystic ovaries syndrome, Turner syndrome (Figure 1) or late onset form of 21 hydroxylase deficit (Figure 2) are shown in Figure 3.

The distribution of ethnologic of primary amenorrhea show a high incidence of PCOS and Turner syndrome and the low incidence of other cases like Rokytansky syndrome, 46XY DSD and Prader Willi syndrome.

Other causes of primary amenorrhea were 46XY DSD (Figure 4). In these casesc we have severe emotional problem in the girls and their family

Regarding the etiology of the secondary amenorrhea, 156 patients had secondary amenorrhea caused by stress and psychological problems and 4 cases had mental anorexia.

In all cases, patients showed osteoporosis or osteopenia.

Therapeutic strategy for patients with secondary amenorrhea consisted in psychotherapy and sedative medication.

The treatment of the patients with primary amenorrhea depended of form and etiology.

Patients with Turner syndrome received Etimil Estradiol orally, 10μg/day, continuously for 1 year. After this period, estrogen administration was discontinuous from day 1 to 21, then Medroxyprogesterone 5 mg/day from day 15 to 21 was prescribed, while no hormone was given from day 21 until day 28.The patients with polycystic ovaries syndrome received first treatment with progesterone and after that with an estrogen and progesterone mixed (Yos, Yasmine, Diane). Late form of 21 hydroxylase deficiency received hydrocortisone replacement therapy. In depress girls specific was administrated.

Under etiological treatment, the menstrual cycle occurred in almost all patients, except those with anatomical defects and 8 patients with Turner syndrome.

Patients diagnosed with Rokitanski syndrome and 46XY patients received psychotherapy.

According to WHO, amenorrhea stands as sixth largest major cause of female infertility. Genetic factors like single gene disorders, chromosomal or multifactorial disorders are contribute to the constitutional etiology of amenorrhea. Cytogenetic investigations have underlined the importance of chromosomal abnormalities as a major cause of amenorrhea . In the medical literature it is described that the percentage of chromosomal abnormalities varies from 15.9% to 63.3 % in the primary amenorrhea and 3.8% to 44.4 % in secondary amenorrhea .

In many studies reviewed, the most frequent chromosomal anomaly in amenorrhea patients is Turner syndrome (45, XO) followed by a male karyotype . In this study the prevalence of Turner syndrome (25%) was higher, followed by male karyotype 46 XY DSD (3.57%).

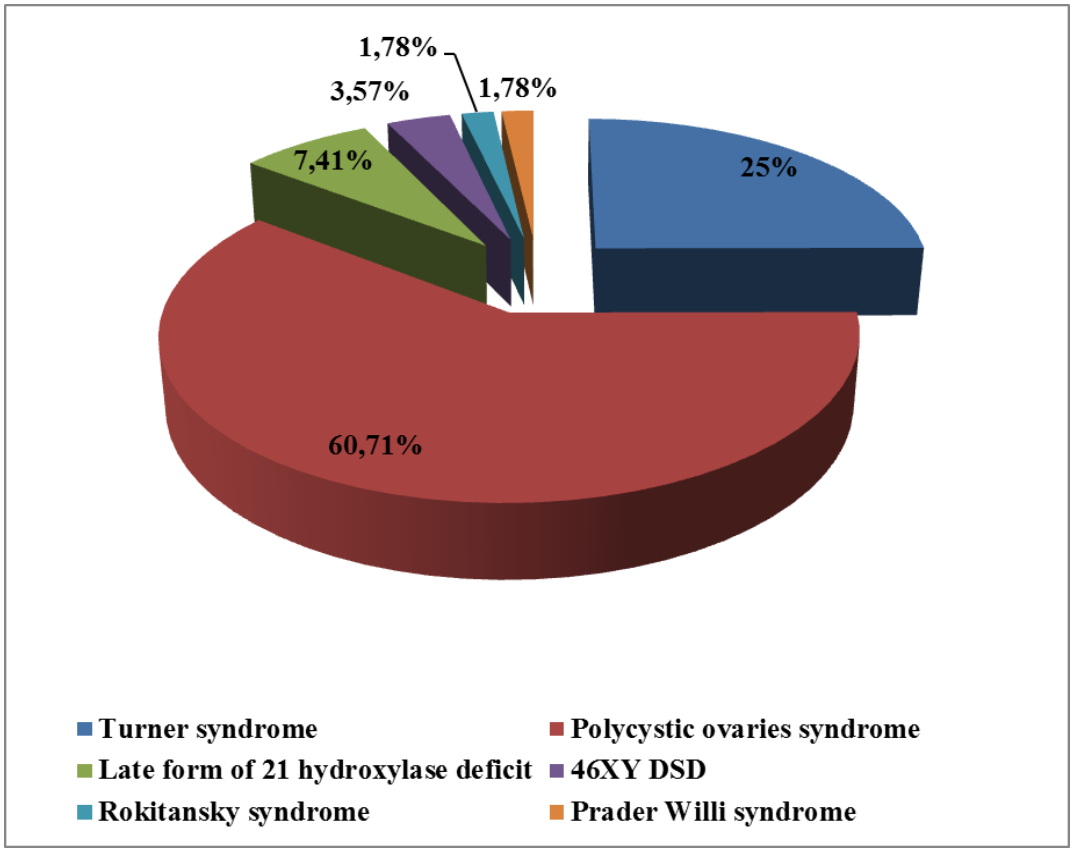

Figure 3 : Distribution of patients with primary amenorrhea

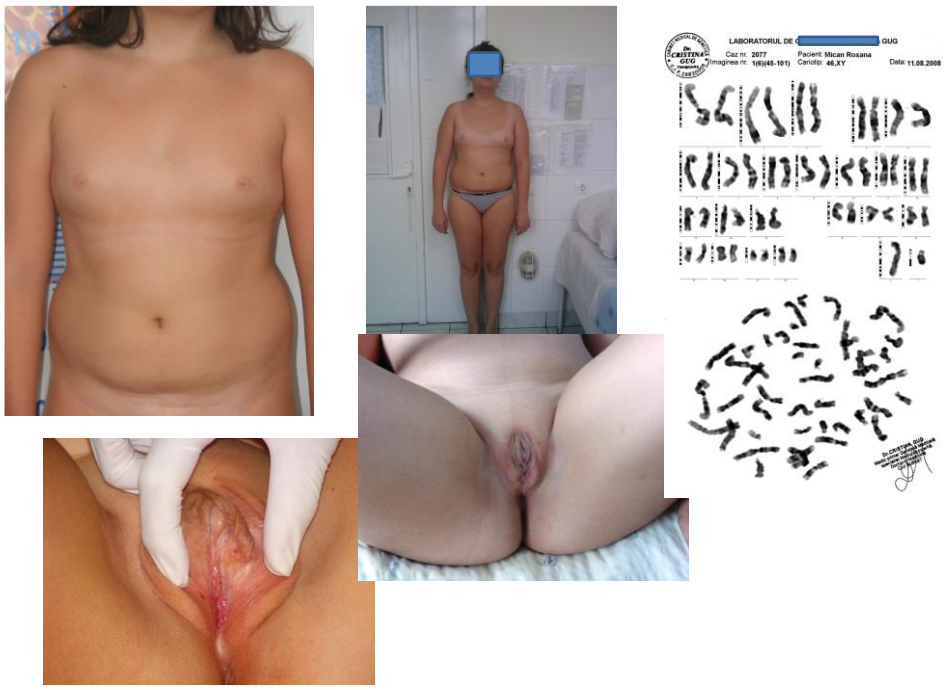

Figure 4: MR 46 DSD

The major cause of the primary amenorrhea in our study was polycystic ovarian syndrome (60.71%). It is an interesting fact that many investigators have suggested that this syndrome may be genetically determined. Some reports

have also shown chromosome alterations in a few patients with POS , secondary to X chromosome deletions or translocations.

Detection of such chromosomal abnormalities at an early stage helps in surgery, counseling, and if mosaic to state the reproductive stages and premenopausal details .

The karyotype aids in the confirmation of the diagnosis, a better phenotype-genotype correlation for a better understand of the clinical form heterogeneity, and in genetic counseling. Genetic counseling should include the risk of gonadal malignancy for patients with 46 XY DSD gonadal dysgenesis, the risk of premature menopause for patients with TS and the use of hormonal replacement therapy.

Conclusions:

1. Amenorrhea can hide behind a symptom complex pathology.
2. A complex evaluation of the patients with irregular menstruation is required.
3. Treatment should be as early as possible.

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WHEN SHOULD ENDOCRINOLOGISTS THINK OF CELIAC DISEASE IN CHILDREN?

Belei Oana[1], Marginean Otilia[1], Brad Giorgiana[1], Daescu Camelia[1]

Abstract

Background: Recent researches proved that classical definition of celiac disease (CD) comprises only 30% of cases with genetic predisposition, the vast majority of patients being pauci-symptomatic. Active-case finding in groups at risk for CD is considered a cost/effective strategy. The association of CD with several autoimmune conditions is well-known. ***Objectives:*** The aim of this study was to determine the prevalence of CD in a pediatric population from the Western part of Romania with associated autoimmune thyroid disorders (AITD) and insulin-depended mellitus diabetes (IDDM) as well as in a control lot and to assess the clinical forms of presentation and the HLA polymorphism in all cases. ***Methods:*** Between Oct 2009 and Dec 2012 there were screened for CD 74 children with AITD (lot 1), 98 children with IDDM (lot 2) and 80 healthy children (control lot). In patients with at least one positive serologic test for CD, intestinal biopsy was performed. All children underwent HLA typing for DQ2/DQ8. ***Results:*** CD prevalence after screening in lot 1 was 7% (5 patients), in lot 2 it was 6% (6 patients). In the control lot there there weren't any CD cases diganosed by screening.There were not significant differences between the frecquency of CD cases among children with AITD and the frecquency of CD cases among children with IDDM (p>0,05). Most of the cases presented as silent CD (82%) - 9 cases out of 11. All children diagnosed with CD presented DQ2 or DQ8 haplotype. 20% of the control subjects associated heterozygous DQ2 alleles. From 69 children with AITD and without CD, only 3 patients (4%) presented heterozygous DQ2 haplotype predisposing for CD. The rest of 66 patient (96%) associated nonDQ2/DQ8 alleles. From 92 children with IDDM and negative results for CD screening, 25 patients (27%) associated homo or heterozygous DQ2 and DQ8 alleles. The rest of 67 patients (73%) did not present characteristic genetic background for CD. There were significantly more cases with IDDM without CD but with predisposing haplotype for CD (27%) compared to the number of patients with AITD seronegative for CD and with DQ2/DQ8 alleles (4%) p<0,005. ***Conclusions:*** Recommending AITD and IDDM as selection parameters for CD screening in asymptomatic children is justified by the high frequency of gluten enteropaty obtained in this study (7% and 6% respectively). HLA assessment can not highlight a significant role of a certain allele in the pathogenesis of autoimmune comorbidity AITD/CD or IDDM/CD. DQ2 and DQ8 alleles are mandatory but insufficient for CD development. The intervention of environmental factors is very important. Performing as first line approaching HLA typing in asymptomatic at risk children may be a valuable proposal. A negative result for DQ2 or DQ8 alleles will render CD highly improbable and there will be no need for subsequent CD antibodies testing in such cases.

Keywords: celiac disease, children, autoimmune thyroid disorders, insulin-depended mellitus diabetes

Introduction:

Gluten intolerance is defined by the presence of three major features: malabsorption, atrophic changes in the structure of the intestinal mucosa and clinical and morphological response following the exclusion of gluten from the diet. Nowadays, the current trend is to replace the concept mentioned above with a new one - gluten-sensitive enteropathy, which is defined as an exaggerated immune response of intestinal mucosa to gluten protein. This response occurs only in genetically predisposed subjects. Histological it can be translated by a great variety of morphological abnormalities: from a discrete intraepithelial hyperlymphocytosis to total villous atrophy. (1)

Recent research demonstrated that the classical definition of the disease is limited to 30% of patients with genetic susceptibility and morphological changes and does not include the vast majority of subjects with gluten sensitivity, which have minor villous injuries. Most cases of celiac disease (CD) present as atypical, silent or latent form of disease, without clinical manifestations. This model was described by Richard Logan in 1992 as the celiac iceberg. (2) Nowadays, celiac disease is defined as an immune-mediated enteropathy caused by intolerance to gluten in genetically susceptible individuals (HLA DQ2 or DQ8). CD has a low incidence estimated at about 1% of the general population. This disease occurs in subjects presenting gastrointestinal and extradigestive symptoms. Also it can occure in some asymptomatic subjects affected by autoimmune or genetic diseases (insulin dependent diabetes mellitus - IDDM, autoimmune thyroid disorders-AITD , Turner syndrome, Down syndrome, Williams syndrome), patients with selective IgA deficiency and first-degree relatives of patients with CD.

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Several classifications of CD have been used. Classical CD includes chronic diarrhea, abdominal distension and failure to thrive. Atypical form of CD can associates one or more of the following: constipation, iron-deficiency anaemia, short stature/growth failure, increased level of liver enzymes, ameoreea s.a. Silent CD is defined as the presence of positive CD-specific antibodies, HLA and small-bowel biopsy findings that are compatible with CD but without sufficient symptoms and signs to warrant clinical suspicion of CD. Latent CD is defined by the presence of compatible HLA but without enteropathy in a patient who has had a gluten-dependent enteropathy at some point in his or her life. The patient may or may not have symptoms and may or may not have CD-specific antibodies. Potential CD is defined by the presence of CD-specific antibodies and compatible HLA but without histological abnormalities in duodenal biopsies. The patient may or may not have symptoms and signs and may or may not develop a gluten-dependent enteropathy later.(3)

Serological screening of CD in a population with associated risk factors is now considered the most efficient strategy, taking into account cost-effectiveness. The efficiency of this serological screening is to identify the cases with atypical or oligosymptopatic forms of CD in the study group. The benefits are prevention of clinical expression of silent CD and ability to take specific remedial measures - gluten-free diet.

The prevalence of various comorbidities association with CD can vary from one study to another. Recent data show that the prevalence of autoimmune diseases among patients with CD is proportional to period of time they have been exposed to gluten. (4). IDDM is reported to be present in patients with CD in a proportion of 3.5% to 10% (5), AITD in celiac population appear in a proportion of 4% to 8% (6), the presence of rheumatoid arthritis is cited in 1.5% to 7.5% of CD patients (7), autoimmune hepatitis is found in a proportion of 6% to 8% (8), Sjögren's syndrome appears to have a prevalence ranging between 2% and 15% of the CD patients (9), selective IgA deficiency occurs in 7% - 9% of all patients with gluten enteropathy (10) and dermatitis herpetiformis is reported in 20% - 25% of patients with CD. (11)

Objectives:

The aims of this study were to perform a serological screening in a pediatric population from the Western part of Romania with autoimmune diseases associated (AITD and IDDM) considered risk factors for CD and to asses the prevalence and the clinical forms of gluten enteropathy in this population comparing with a control group. We also analyzed the HLA DQ polymorphism in children with autoimmune thyroiditis, diabetes and autoimmune comorbidity CD- thyroiditis, CD - diabetes and in control group.

Material and methods:

We developed a descriptive, prospective study in 1st Pediatric Clinic of Emergency Children Hospital, "Louis Turcanu" Timisoara. The serological screening for CD was performed in all the patients diagnosed with AITD and IDDM admitted to the Endocrinology Department and in all subjects from the control grup without gastrointestinal, autoimmune or genetic disorders.

Autoimmune thyroiditis is considered risk factor for CD. All children diagnosed with Basedow Graves disease and Hashimoto's autoimmune thyroiditis were screened for CD. Hashimoto thyroiditis was defined by the presence of thyroid antibodies: anti-tireoglobulin (anti-Tg) and anti-tiroid peroxidase (anti –TPO) and hyper, euthyroidism or hypothyroidism (low, normal or high TSH). The majority of cases with Hashimoto's thyroiditis associated clinical or subclinical hypothyroidism. Overt hypothyroidism was defined by low fT4, high TSH level and subclinical hypothyroidism was defined by normal fT4 and TSH levels. Patients with Basedow Graves and goiter associated high level of tiroid stimulating immunoglobulins antibody (TSI), anti-Tg anti –TPO, low TSH level and high fT3 and fT4 values.

The patients with AITD and IDDM and those from the control group were all tested for CD using IgA/IgG combined assessment for anti tissue-transglutaminase and deaminated gliadin peptide antibodies (IgA/IgG tTG/DGP) and IgA anti-endomysial antibodies (EMA).

For IgA/IgG tTG/DGP combined assessment, we used Quanta Lite h-tTG/DGP Screen kit, based on an enzyme-linked immunosorbent assay (ELISA) for semi-quantitative detection of IgA and IgG antibodies to synthetic DGP and human tTG in serum. This test allows detection of celiac serological markers even in patients with selective IgA deficiency.

Anti-endomysial antibodies (IgA EMA) were assessed using indirect immunoflorescence method on monkeys' esophagus smooth muscle using ImmuGloTM Anti-Endomysial Antibody (EMA) test kits.

Intestinal biopsy was performed to the patiens with at least one positive test. 4 biopsy samples were obtained for each patient during upper gastrointestinal endoscopy from second part of the duodenum. Histological interpretation of the intestinal samples was performerd by an experienced pathologist using Marsh classification modified by Oberhuber.

All the patients enrolled in this study were haplotyped for the detection of HLA DQ2/DQ8 alleles. The HLA DQ2/DQ8 detection was performed to the control group also. We usued QIAamp DNA Blood Mini kit (Qiagen) for the extraction and isolation of the genomic DNA. An optimal concentration of genomic DNA (50 ng/µl) was required, in order to obtain an efficient PCR amplification. The isolated genomic was analysed using PCR-SSP (polimerase chain reaction sequence specific primers) method for the quantification of HLA DQ2 and DQ8 haplotypes. AllSet Gold HLA DQA1 (32 mix), AllSet Gold HLA DQB1 02/04 şi AllSet Gold HLA DQB1 03, Dynal – Invitrogen were used for this purpose. The interpretation of the results was done according to the specific Worksheet - Gel Documentation Form associated to the primers kit used which contained all the possible alleles combinations.

The study was approved by Ethical Committee of the host institution, Emergengy Children Hospital "Louis Turcanu", Timisoara.

Statistical analysis was performed using specific informatic applications - R statistic soft program version 2.7.1 Data were analyzed by chisquare test. For all statistical analyses, a two-tailed p value <0.05 was considered significant.

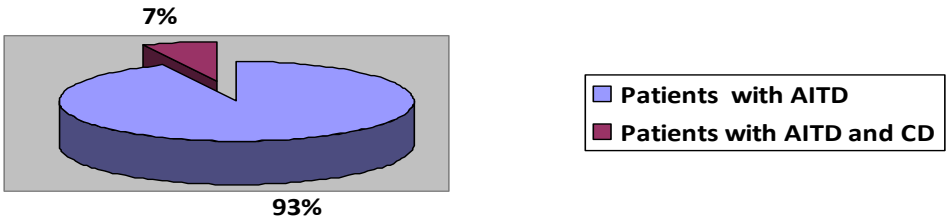

Figure 1: Frequency of CD cases in lot I

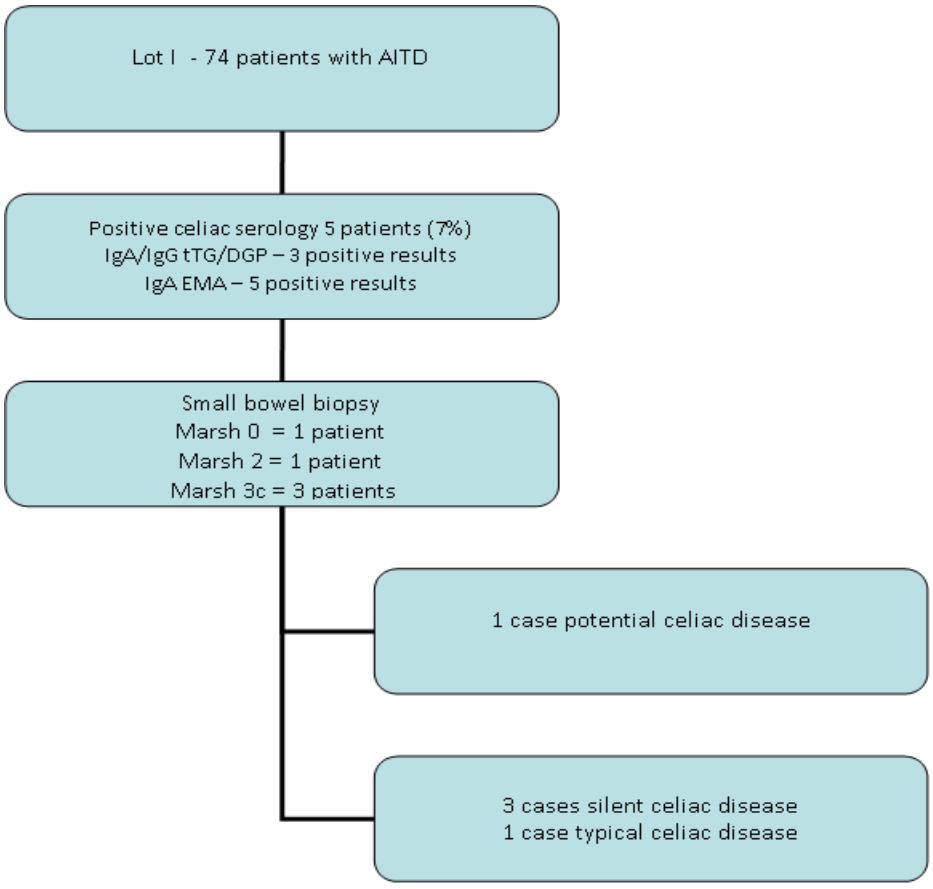

Figure 2: Flow chart of AITD/CD patient recruitment

Results and discussions:

During the study period (Octomber 2009 – December 2012), 74 patients diagnosed with AITD from the first, 98 patients with IDDM from the second lot and 80 healthy patients form the control group were screened for CD.

From the 74 patients with AITD screened, 16 patients had goiter associated with hyperthyroidism as Basedow Graves' disease and 58 had Hashimoto's thyroiditis associating subclinical and overt hypothyroidism.

The term autoimmune thyroid disorders (AITD) encompasses a number of different entities characterized by varying degree of thyroid dysfunction and the presence of serum auto-antibodies against thyroid tissue-specific components, such as thyreoglobulin (Tg) and thyroid peroxidase (TPO). Goiter accompanied by hyperthyroidism (due to Basedow disease or Hashimoto's autoimmune thyroiditis) is described in some studies to be associated with celiac disease. Biological, the hormonal status in these two entities presents with elevated FT3 and FT4 levels and low value of TSH, with anti-TPO antibodies and increased anti-thyreoglobulin level. As a marker of differentiation, thyroid stimulatory immunoglobulin (TSI) in high titer is specific for Basedow disease.

5 patients (7%) from the first lot were diagnosed by screening with CD, having at least one positive serologic test. 4 of them associated villous lesions and one child had normal intestinal morphology (Marsh 0). He was classified as having latent celiac disease because he presented positive IgA/IgG tTG/DGP and positive IgA EMA, associated with a genetic background predisposing for CD - HLA DQ2 heterozygous. None patient from those with Basedow's disease had positive serological tests for CD. All 5 patients diagnosed with gluten enteropathy had Hashimoto thyroiditis with overt or subclinical hypothyroidism. Prevalence of CD confirmed histologically after screening in patients with AITD from group I was 7%, taking into account the case with potential CD.

The distribution of clinical forms of CD was: a case of potential CD, 3 cases of silent CD asymptomatic but with positive serology and characteristic histology and a case with classical form of CD, associating chronic diarrhea, malnutrition, serological and histological markers suggestive of gluten enteropathy.

The screening results from the first group of patients with AITD are described in Figure 2.

From 74 cases with AITD screened in this study, CD was confirmed in 5 patients (7%), a higher value compared to similar adults reports. A pediatric study published by Larizza and collaborators described a similar prevalence of CD - 7.7% among children with AITD (12).

Collin et al screened 83 Finnish patients with autoimmune thyroid disease for CD and he found 3 asymptomatic celiac patients which, with one previously diagnosed CD patient, obtaining an overall frequency of 4.8%. In contrast, one (0.4%) out of 249 age and sex matched blood donors was found to have CD.(13) Sategna-Guidetti et al found that 5 of 152 patients with autoimmune thyroid disease (3.3%) also had CD using IgA-EmA and confirmed on duodenal histology. Only one patient presented with gastrointestinal symptoms.(14) Valentino et al screened 150 newly diagnosed patients with autoimmune thyroid disease using EMA and found 5 celiac patients (3.3%).(15)

6 children (6%) out of 98 patients with IDDM from the second group were diagnosed with CD having at least one positive serologic test and different degrees of villous lesions suggestive for gluten enteropathy. The prevalence of histologically confirmed CD after screening in the second lot was 6%.

All cases with CD diagnosed by screening in the second group presented as silent forms of disease.

The screening results in the second group of patients with IDDM are described in Figure 4.

The association of CD and type I diabetes has been the subject of several studies. Recent studies showed a low prevalence of symptomatic CD (0.7%) at the onset of diabetes, underlining the increased prevalence of CD up to 10% in patients with diabetes in the first 2 years after diagnosis. (16) Most forms of CD associated with type I diabetes may be subclinical, silent or latent forms. This is the reason why screening for gluten enteropathy is recommended at the onset of the disease and during the first 2 years after the diagnosis of diabetes. The prevalence of CD in children with type I diabetes is about 10 times higher compared to the prevalence of this disease in the general population. (17) This prevalence of gluten enteropathy in patients with insulin-dependent diabetes varies between 5 and 10%. (18). The percent of 6% cases with CD in all children diagnosed with diabetes encountered in this study was similar with the results of other pediatric studies.

In the control group none positive serological test was detected, so the detection rate of CD in this group was 0%.

There were not statistically significant differences between the prevalence of CD in the first group with AITD (7%) versus the prevalence of CD in the second group with IDDM (6%), $p > 0.05$.

We compared separately the two subgroups of children with autoimmune comorbidities (AITD and IDDM respectively) and CD. The distribution of the clinical forms of gluten enteropathy is shown below:

The combined analysis of the patients with autoimmune comorbidities (AITD / IDDM) and CD demonstrated the predominance of silent form of disease in children with autoimmune diseases that were tested. From 11 children diagnosed with CD (7 males and 4 females, mean age 6.5 yrs, range 1-18 yrs), 9 patients (82%) had silent form of CD, significantly more than those with the classic form - 1 patient (9%) or potential CD - 1 patient (9%) $p < 0.005\%$.

DQ2 and DQ8 haplotypes were identified as class II HLA genetic determinants of gluten sensibility. HLA-DQ2 heterodimer is encoded by alleles DQA1 0501 and DQB *0201 in cis form by DR3-DQ2 haplotype. HLA-DQ2 heterodimer can be encoded in trans position by the alleles DQA1*0505 and DQB *0202 in the DR5-DQ7/DR7-DQ2 haplotype. HLA DQ8 heterodimer is encoded by alleles DQA1*0301 and DQB1*0302 in cis conformation by DR4-DQ8 haplotype. (19)

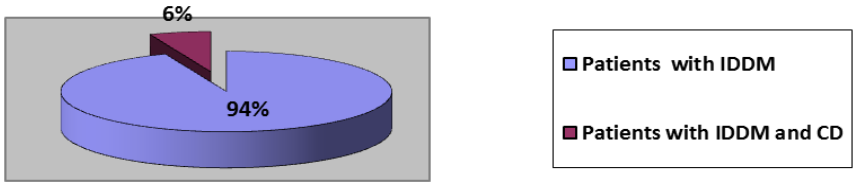

Figure 3: Frequency of CD cases in lot II

The haplotype has become an important first step in screening candidates with risk for CD and monitoring these patients later on. Its important role can be noted in seropositive cases with normal intestinal architecture, when it can be use to exclude this disease. The presence of HLA-DQ2 or DQ8 haplotype is highly sugestive for the potential form of CD, excluding false positive serological results. Some authors have proposed for the diagnosis of CD the histological aspects of the intestinal villous and the detection of HLA DQ2 or DQ8 in these patients. In this cases, the molecular typing of the HLA has no additional diagnostic value if serological tests are positive. (19)

There are multiple evidences that HLA typing for DQ2/DQ8 molecules plays a role in the case-finding strategy in subjects with autoimmune conditions considered risk factors for CD. The coexistence of CD and autoimmune disease is thought to be partly due to a common genetic predisposition. HLA-DQ2 and DQ8 haplotypes are over-represented in many autoimmune diseases. The inheritance of these haplotypes and the associated immunological phenotype may explain the link.(20)

In this study we performed molecular typing for HLA-DQ2/DQ8 in all patients included in the first and the second lot and in the control group.

All 5 children diagnosed with CD from the first group with AITD had HLA-DQ2 heterozygous haplotypes. Out of the remaining 69 children without CD, only 3 (4%) had HLA-DQ2 heterozygous haplotype and the rest (96%) associated other HLA alleles, non DQ /DQ8.

Out of the 6 patients diagnosed with CD after screening from the second group with IDDM, one case presented HLA-DQ8 haplotype, 2 children had HLA-DQ2 homozygous haplotype and 3 cases had heterozygous HLA-DQ2 haplotype.

The rest of 92 patients with IDDM and without CD associated the following haplotypes: 21 (23%) had HLA-DQ2 heterozygous haplotype, 3 (3%) had HLA-DQ2 homozygous haplotype, one patient (1%) had HLA-DQ8 heterozygous haplotypes and the rest (73%) were non DQ2/DQ8.

In the control group (80 subjects enrolled), there weren't any CD cases diagnosed by screening. 16 subjects (20%) had predisposing genetic background for CD (HLA DQ2 heterozygous haplotype) and the rest (80%) associated other non DQ2/DQ8 HLA combinations.

These results are similar with those reported in the medical literature highlighting the fact that the presence of HLA-DQ2 or DQ8 haplotypes is required, but not enough for the disease to become manifest. The development of CD is multigenic, in which the presence of HLA-DQ2 or DQ8 heterodimers is essensial. The HLA-DQ2, DQ8 haplotype are characterized by high sensitivity and low specificity, which gives them a low positive predictive value, with a high negative predictive value for the diagnosis of celiac disease. The absence of these molecules had a negative predictive value of 100% for the diagnosis of celiac disease. (20)

The majority of cases with autoimmune disease and negative serologic markers for CD showed non DQ2/DQ8 haplotype.

Among those 69 patients with AITD and without CD associated, the percentage of those with predisposing haplotype for CD (HLA-DQ2) was significantly lower (3 patients - 4%) compared with those with nonDQ2/DQ8 alleles (66 patients - 96 %) $p < 0.05$.

From 92 patients with IDDM and negative results at CD screening, 67 patients (73%) had non DQ2/DQ8 alleles, significantly more than those with characteristic genetic background (DQ2 or DQ8 HLA) and without CD (25 patients - 27%) $p < 0.05$.

Comparing the percentage of children with IDDM /without CD, DQ2/ DQ8 positives (27%) with the percentage of children with AITD/without CD, DQ2/ DQ8 positives (4%), a statistically significant difference ($p<0.005$) can be noted. The higher number of patients with diabetes and typical HLA haplotypes characteristic for CD, without developing gluten enteropathy can be explained by a more pronounced genetic similarity between IDDM and CD compared to the relationship between the AITD and celiac disease. Despite this, there weren't any differences between the frequency of CD diagnosed by screening in lot I (7%) and II (6%) respectively, as shown.

In this study, the percentage of children with AITD and without CD who had HLA compatible with CD was low, only 4% - 3 patients from 69.

Comparing this result with other published reports, the results are contradictories.

A study conducted by Valentino showed that 10 (71%) of 14 patients with Hashimoto's thyroiditis had genotypes compatible with CD (3 patients had DQ heterodimer A1*0501, B1*0201, 6 had DRB1*04 and 1 had A1*0101, B1*0501). Six of these 14 patients showed intestinal histologic alterations typical of CD. Among 4 of these 6 patients were described HLA genotypes associated with CD

(3 with DRB1*04, DQB1*03 and 1with DQA1*0501, DQB1*02). (21) In contrast, Larizza screened 90 children and adolescents with autoimmune thyroid disease and showed 7 cases to have CD (7,7%) , indicating a prevalence of 1 in 13 pediatric patients. All 90 patients were typed for HLA antigen class I and II and for HLA-DQA1 and DQB1 heterodimers. Celiac disease and DQA1*0501, DQB1*02 were found only in 7 (7.8%) patients.(12)

The pathogenesis of co-existent autoimmune thyroid disease and CD is not known, these conditions may share similar HLA haplotypes and more important, are associated with the gene encoding cytotoxic T-lymphocyte-associated antigen-4. HLA-DQ2 and DQ8 show a weak association with Hashimoto's thyroiditis, although HLA-DQ2 association is less clear in Graves' disease.(22)

It is important to highlight the fact that in this study in both lot I and II there were patients with autoimmune comorbidities AITD/CD and IDDM/CD respectively, with typical histological finding for CD, but with negative serology for IgA/IgG tTG/DGP combined assay. Only IgA EMA antibodies were positive. All these children had predisposing genetic background for CD, encoding DQ2 or DQ8 alleles. Using the new combined assay IgA/IgG tTG/DGP for CD screening in pediatric patients at risk may provide negative results. Therefore, performing as first line approaching HLA typing in asymptomatic at risk children may be a valuable proposal. A negative result for DQ2 or DQ8 alleles will render CD highly improbable in these children and there will be no need for subsequent CD antibodies testing in such cases, due to the high negative predictive value of HLA typing.

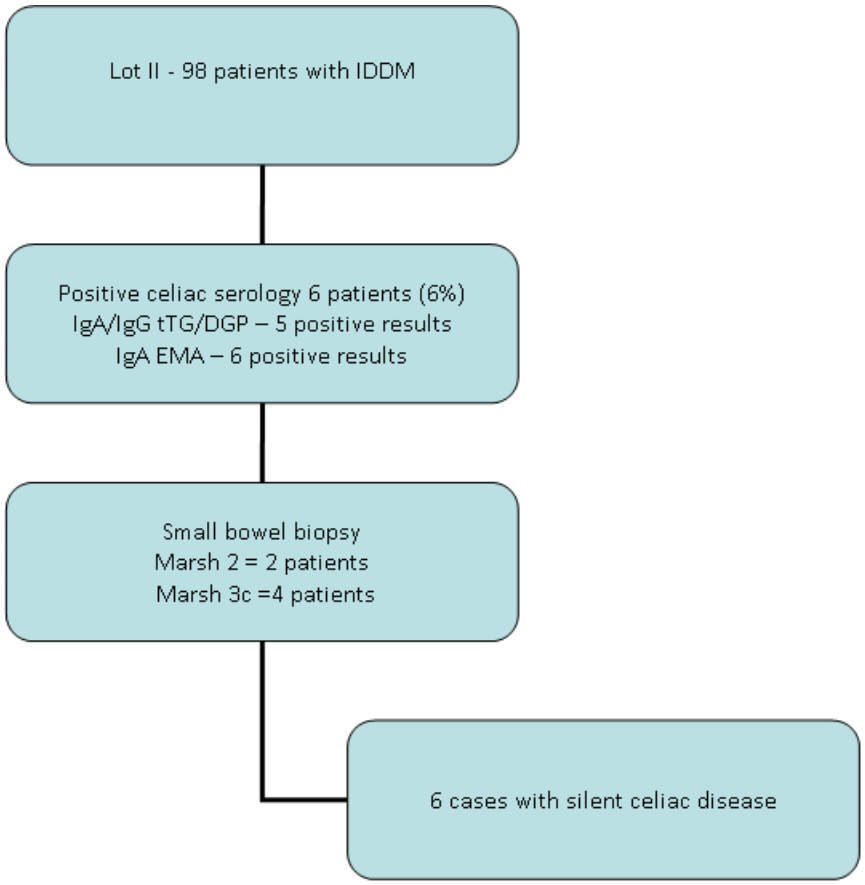

Figure 4: Flow chart of IDDM/CD patient recruitment

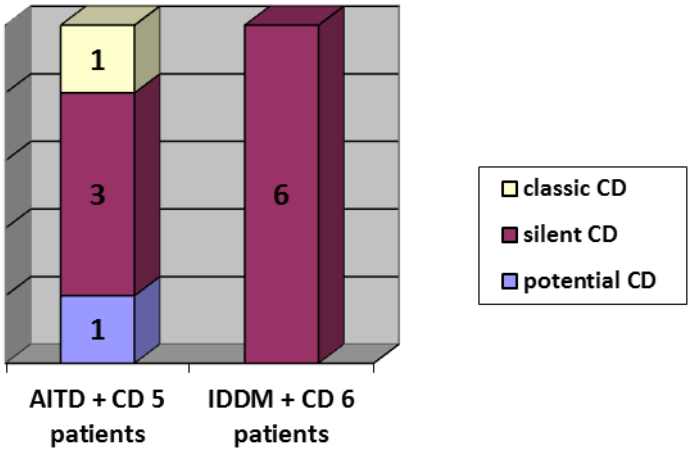

Figure 5: Distribution of CD clinical forms in each group of patients with comorbidity
AITD – CD and IDDM – CD respectively

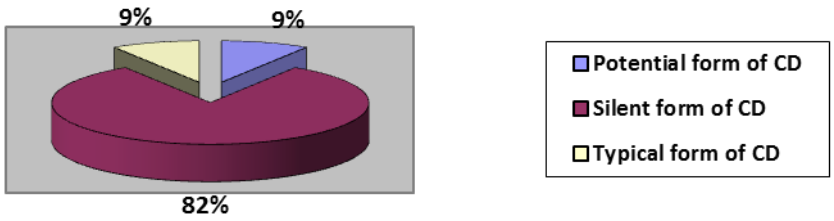

Figure 6: Repartition of clinical forms of celiac disease among children with autoimmune disorders reffered to screening.

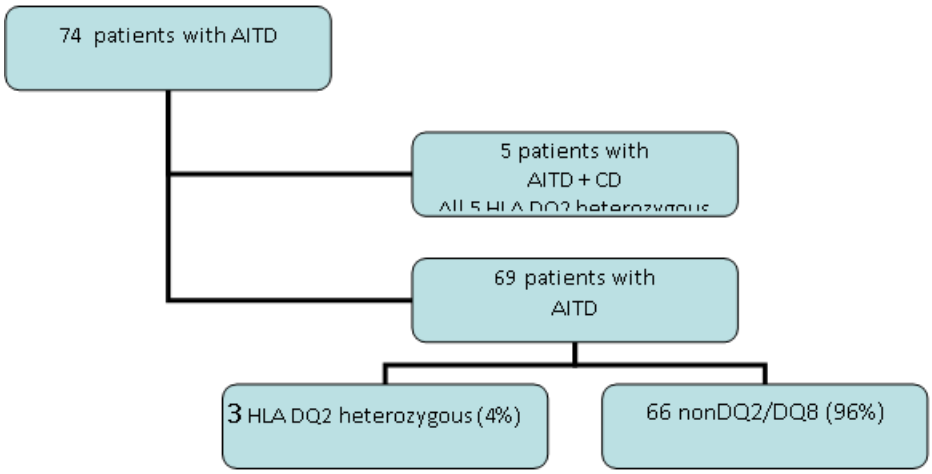

Figure 7: Distribution of HLA DQ alleles in patients from lot I

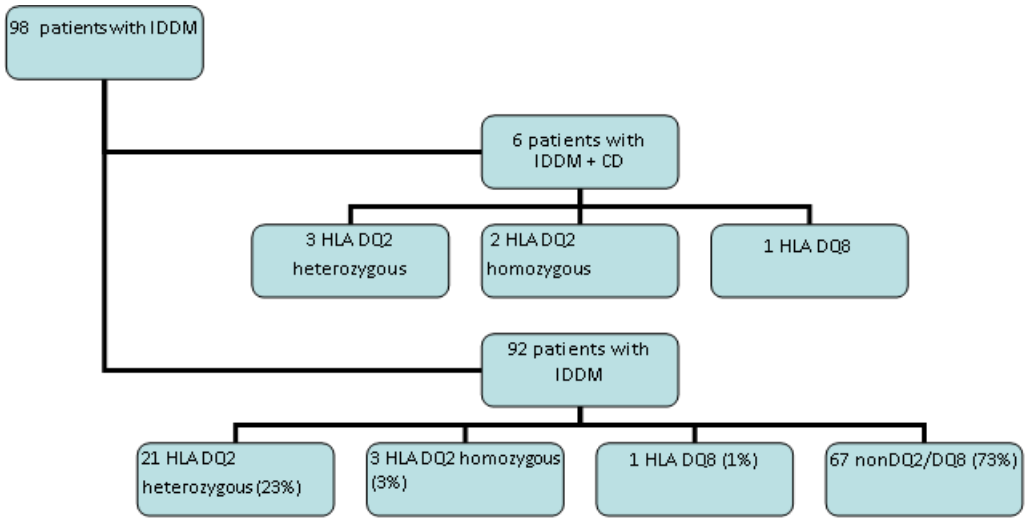

Figure 8: Distribution of HLA DQ alleles in patients from lot II

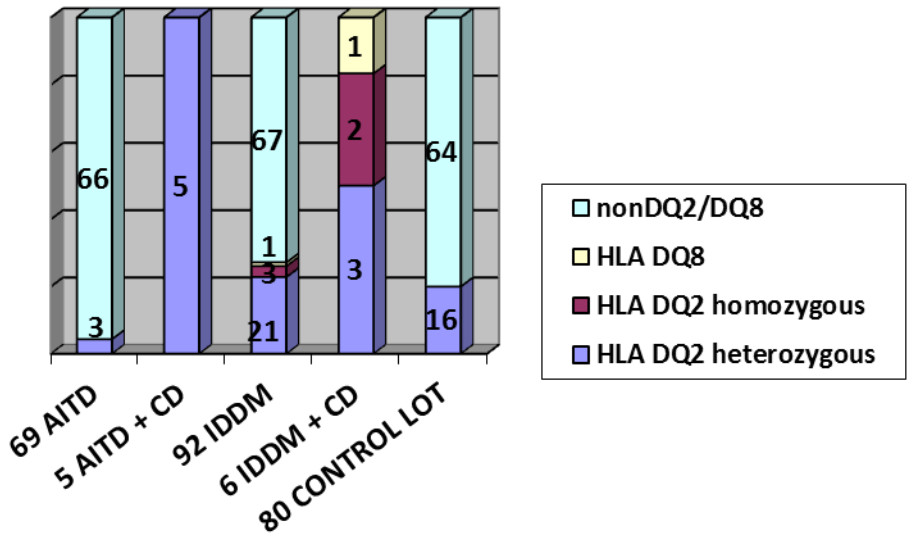

Figure 9: Alelles distribution in each lot of study

Conclusions:

Recommending AITD and IDDM as selection parameters for CD screening in asymptomatic children is justified by the high frequency of gluten enteropaty obtained in this study (7 % and 6% respectively).

The availability of serological tests for CD screening and the posibility to prevent severe complications such as malabsorption, grow impairment and intestinal lymphoma among undiagnosed cases underline the importance of screening patients with autoimmune thyroiditis or diabetes even in the absence of suggestive symptoms.

Haplotypes assessment can not highlight a significant role of a certain allele in the pathogenesis of autoimmune comorbidity AITD/CD or IDDM/CD. DQ2 and DQ8 alleles are mandatory but insufficient for CD development. Except the haplotype, genetic and environmental factors play a major role in an individual with an autoimmune condition for the initiation and the maintenance of the autoimmune response

Serologic screening performed only once in life is not sufficient to detect/rule out the presence of CD in subjects with high risk of autoimmune disorders. Performing as first line approaching HLA typing in asymptomatic at risk children may be a valuable proposal. A negative result for DQ2 or DQ8 alleles will render CD highly improbable and there will be no need for subsequent CD antibodies testing in such cases.

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IS INSULIN RESISTANCE MORE FREQUENT IN CHILDREN BORN SGA?

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Abstract

Introduction: Rapid increase in weight during early childhood, "catch-up growth" phenomenon, in children born small for gestational age (SGA) has been strongly linked with insulin resistance (IR), which may be a risk factor for type 2 diabetes mellitus and cardiovascular disease. IR occurred in the prenatal period has a protective role, that of intrauterine survival in conditions of malnutrition. In the postnatal period, early onset IR becomes a risk factor for metabolic syndrome and its components correlated with normal (or excessive) nutritional intake. ***Material and methods:*** A retrospective observational study was carried out on long-term metabolic complications in children born SGA, which were admitted to our hospital over a 5 year period from 2007 to 2011. 517 patients (mean age 12 years±0.6, aged between 6 - 18 years) were divided in two study groups, following the statistical processing of data sheets, as follows: 410 obese patients that were born appropriate for gestational age (AGA) (79,30 %) and 107 obese patients that were born SGA (29,69 %). Baseline glucose and insulin levels of the patients were measured and IR index was assessed by homeostasis model assessment (HOMA). A cut-off HOMA level of >2.5 in the prepubertal period and of > 3.5 for adolescents was used to identify an IR status. ***Results:*** IR was found in 20% of obese AGA children and 25,3% of obese SGA. Rate of IR in patients born SGA was greater compared to obese children born AGA and had a significant statistical difference (P = 0.03, mean 2,95229 AGA versus 3,72778 SGA group and SD 1,7 versus 2,6).***Conclusion:*** Increased prevalence of IR patients born SGA compared to AGA indicates that being born SGA appears to be an additional risk factor in the developement of IR. IR met in a high percentage among obese patients born SGA, allows us to affirm that the cardiovascular risk in these patients as well as the risk of developing type 2 diabetes is higher. Monitoring, periodic evaluation and appropriate dietary therapy in the case of obese children born SGA is crucial in preventing early onset cardiovascular disease.

Key words: Small for gestational age, obesity, insulinresistance

Introduction:

About 3-5% of neonates are born small for gestational age (SGA). 85-90% of them recover weight up to 2 years of age, majority of which become obese up to 4 years of age, later on developing components of the metabolic syndrome (MetS).The rapid “catch up” growth during the cell division period up to 2 years of age leads to hyperplastic obesity (1,2). These children have a high risk of developing MetS with all its components: obesity, impaired glucose tolerance, insulin resistance with subsequent development of diabetes, arterial hypertension, dyslipidemia. There is also a risk of developing adrenocortical pathology and reproductive pathology (3,4,5,6).

Rapid increase in weight during early childhood, "catch-up growth" phenomenon, in children born small for gestational age (SGA) has been strongly linked with insulin resistance (IR), which may be a risk factor for type 2 diabetes mellitus and cardiovascular disease. IR occurred in the prenatal period has a protective role, that of intrauterine survival in conditions of malnutrition. In the postnatal period, early onset IR becomes a risk factor for metabolic syndrome and its components correlated with normal (or excessive) nutritional intake. (7,8,9,10)

Whilst several epidemiological surveys have confirmed the association between metabolic disturbances in adulthood and low birth size, few and conflicting data exist for childhood . The potential impact of the early recognition of altered insulin sensitivity in clinical practice is high, because it might prompt the establishment of appropriate hormone-, diet-, or lifestyle-based strategies to prevent the long-term metabolic consequences of intrauterine growth retardation.

Material and methods:

A retrospective descriptive study was conducted over a period of five years, between January 2007 and December 2011, on cases of obesity in children diagnosed at the Emergency Hospital for Children "Louis Ţurcanu" Timişoara in the departments of Diabetes and Nutritional Diseases, Endocrinology and Cardiology.

Children were considered obese on the basis of age specific BMI reference guidelines from Centers for Disease Control and Prevention Child Growth Standards 2000 (above 95th percentile).(11) When defining SGA, growth nomograms and charts proposed by Niklasson (12) are being used; newborns weighing less than 2 standard deviations (SD) from the average for gestational age, we considered as being SGA.

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Antropometric and metabolic characteristic of the study group

	AGA						SGA					
total number	410						107					
	prepubertal		pubertal		adolescents		prepubertal		pubertal		adolescents	
total number	165		150		95		42		46		19	
residence urban/rural	95(57%)/70(43%)		106(70%)/44(30%)		56(59%)/39(41%)		23 (55%)/19 (45%)		28(60%)/18(40%)		12(63%)/7(27%)	
gender male/female	105(64%)/60(36%)		90(60%)/60(40%)		38(40%)/57(60%)		23 (55%)/19 (45%)		19(41%)/27(59%)		7 (37%)/12(63%)	
	Mean ± standard deviation	range	Mean± standard deviation	range	Mean± standard deviation	range	Mean± standard deviation	range	Mean± standard deviation	range	Mean± standard deviation	range
Age (years)	7.35±1.922	5 10	12.35±1.04	11 14	16.25±1.2	15 18	7.45±1.867	5 10	12.28±1.096	11 14	15.79±0.83	15-18
Anthropometric data												
Weight (kg)	39.34±14.5	10.3 82	66.72±16.63	45-112	84.57±20.3	49-142	36.5±18.63	10.5-105	63.64±17.9	41-105	73.9±26.95	53-143
Height (cm)	126±0.2	67-164	155.7±0.09	127-177.5	166.28±10.35	150-190	129.5±18.29	90-145	152.82±10.8	131.2-180	157.41±15.43	116-177.5
BMI (kg/m2)	23.88±6.3	14-34	27.23±5.37	16-48.9	30.44±6.29	19.5-44.9	38±2.96	13.4-120	26.9±5.557	19-43	29.31±8.3	19-54
Biological data												
Baseline glucose (mmol/l)	4.55±0.533	2.91-5.75	4.55±0.71	3.9-5.5	4.667±0.63	3.9-6.21	4.8±0.6	3.6-5.6	4.65±0.533	3.9-5.5	4.4±0.22	3.9 - 5.1
Baseline insulin (uui/l)	10.29±6.62	2 35	15.57±9.41	2-45.1	18.62±15.7	3.3-88.5	12.6±8.64	1.86-35.3	21.7±17.13	2-74.9	13.45±9.16	2-37.3
HOMA	2.4±1.57	0.34-8.2	3.6±3.17	0.38-23	3±2.28	0.4-9.2	3.32±1.65	0.66-7.31	4.57±3	0.39-11.78	4.22±3.35	0.72-20.82

Table 1. Antropometric and metabolic characteristic of the study group

		Prepubertal		Pubertal		Adolescents		Total	
		AGA	SGA	AGA	SGA	AGA	SGA	AGA	SGA
IR+	No(%)	27 (16.3%)	8(19%)	32(21.33%)	14 (30%)	22(23%)	5(26.3%)	81 (20%)	27(25.3%)
IR-	No(%)	138(83.6%)	34(81%)	118(78.66%)	32(70%)	73(77%)	14(73.6%)	329(80%)	80(74.7%)

Tabel 2- Presence of IR in AGA and SGA children according to age: prepubertal, pubertal, adolescents

Basal glucose and insulin levels of the patients were measured and IR index was assessed by homeostasis model assessment (HOMA- fasting glucose in mmol/l multiplied by baseline insulin in microunits per milliliter, divided by 22.5). A cut-off HOMA level above 2.5 in the prepubertal period and of > 3.5 for adolescents was used to define an IR status.

Exclusion criteria were evidenced for syndromal, chromosomal, or infectious etiology of low birth weight;endocrine or syndromal disorders, systemic disease or acute illness.

Thus, the result was an extended batch of 517 patients diagnosed with obesity, including 410 patients AGA and 107 patients SGA. Obese AGA and SGA patients were distributed into subgroups by age, namely prepubertal (5-10 years), pubertal (11-14 years) and adolescent (15-18 years). We divided children into two categories according to their HOMA values: children with IR (IR+) and children without IR(IR-).

The data are expressed as means± standard deviation pr as frequencies. We used the unpaired t test (with a confidence interval of 95 percent) to evaluate the differences between the two groups SGA vs. AGA.

Results

Clinical and metabolic characteristics of the study groups are shown in Table 1.

The study group has been homogeneous regarding BMI with one exception prepubertal AGA subgroup comparing to prepubertal SGA subgroup (mean 23.88±6.3 vs. 38±2.96).

The distribution of the 517 patients from the original study group according to gestational age, resulting in two

groups, obese AGA patients and obese SGA patients is shown in Figure 1. As expected, it appears that the SGA group is smaller than the AGA group, representing about a third of it:AGA-410 (79%), SGA-107 (21%).

The presence of IR among AGA and SGA are illustrated in Table 2. IR was found in 20% of obese AGA children and 25,3% of obese SGA. IR increases by age: prepubertal group 16.3% in AGA group and 19% in SGA group adolescent group: 23% AGA group and 26.3% SGA group. We found a higher prevalence IR in the pubertal SGA group 30%. Figure 2a, 2b, 3.

Discussions:

Rate of IR in patients born SGA was greater compared to obese children born AGA and had a significant statistical difference (P = 0.03, mean 2, 95229 AGA versus 3,72778 SGA group and SD 1,7 versus 2,6).

Baseline glucose levels were almost similar in all the 6 subgroups. A difference in baseline insulin has been noticed. Higher levels of insulin have been observed in the patients born SGA (table 2) in all the three subgroups prepubertal, pubertal, adolescents. We speculated that an early phase of increased insulin level during childhood might precede the onset of insulin resistance in young adult SGA subjects.

Several reports suggest reduced insulin sensitivity in SGA children, to date very few strict case-control studies have been carried out. Gray and colleagues studied 100 premature and/or small for gestational age infants (age range: 1-65 days). Fasting and postprandial glucose and insulin levels were measured. SGA neonates had higher 60-minute insulin levels than AGA neonates despite similar glucose levels.(13)Yanjnik and colleagues performed a glucose tolerance test in 379 4-year-old low birth weight Indian children. 30 minutes after an oral glucose load, subjects with lower birth weights had higher plasma glucose and insulin levels, irrespective of their current size.(14). Those findings coincide with the conclusions drawn in the present study.

As far as we know, our study is the first study in obese children analyzing the impact of former SGA status in order to set up the prevalence of IR. We consider important establishing an appropriate period for screening the former SGA to prevent cardiovascular disease.

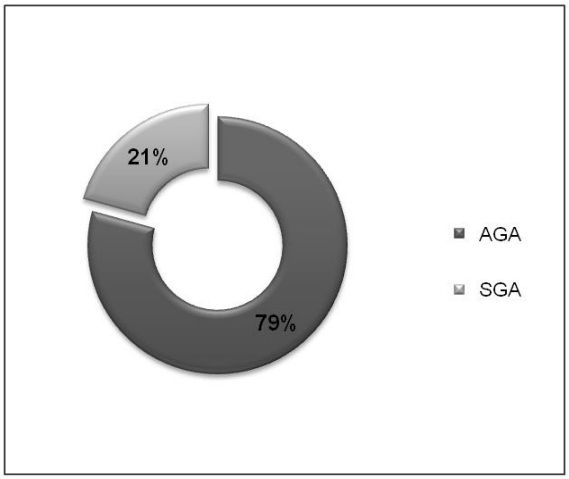
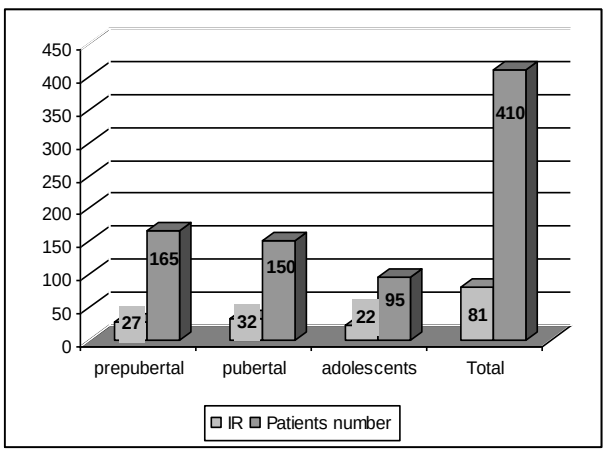
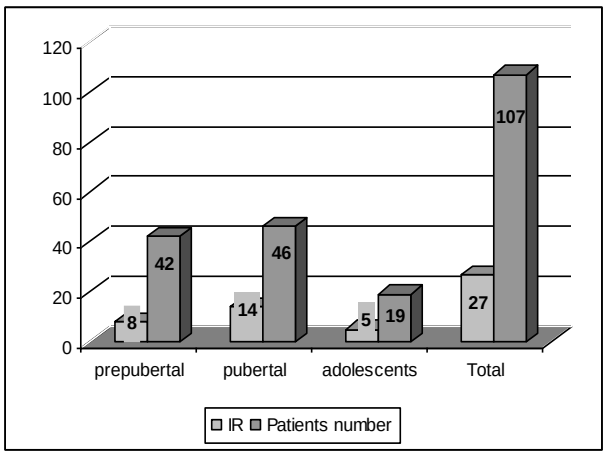


Figure 1: Percentage distribution of study groups according to gestational age

AGA=appropriate for gestational age, SGA=small for



a. AGA group



b. SGA group

Figure 2- Distribution of IR in a. AGA group and b. SGA group according to age

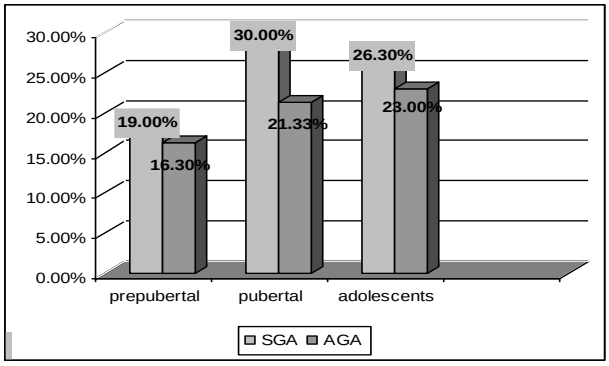


Figure 3 Percentage distribution of IR in AGA vs. SGA group according to age

Conclusions:

Metabolic impairment in SGA children is amplified by weight gain and influenced by fetal programming; developing intrauterine IR as a prenatal surviving mechanism is a risk factor for postnatal MetS and cardiovascular disease. Influence of SGA on developing IR increases gradually with age.

Increased prevalence of IR patients born SGA compared to AGA indicates that being born SGA appears to be an additional risk factor in the developement of IR. IR met in a high percentage among obese patients born SGA, allows us to affirm that the cardiovascular risk in these patients as well as the risk of developing type 2 diabetes is higher. Monitoring, periodic evaluation and appropriate dietary therapy in the case of obese children born SGA is crucial in **preventing early onset cardiovascular disease**.

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OVERWEIGHT PATHOLOGY IN CHILDREN FORM TIMIS COUNTY

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Abstract:

Introduction/background: The constant global rise in the occurrence of overweight and obesity among all ages is accompanied by a higher incidence in serious health risks, such as type 2 diabetes, asthma, and the growth of cardiovascular diseases, which is now potentially present at an early age. ***Aims:*** To examine correlation and differences of overweight in school-aged children (10-13 years old-yo) according to their health lifestyle factors and depending on demographic repartition in our district, using two materials (Raport DSP 2008-2009 and Timiș Save the children survey 2010-2011). ***Material and methods:*** A cross-sectional survey including pupils (n= 1003, 7-17 yo) from the Timis county was carried-out. Height and weight were measured and a questionnaire regarding nutritional behavior was completed. Results were compared in terms of Rural/Urban appurtenance by sex and age compared with the median 10-13 yo from our group (585 children) and Timișoara 6th grade pupils (1220 children). We use CDC Atlanta BMI charts and Excel analysis. ***Results:*** From rural group, girls medium height was 1.51 m and medium weight 46.6 kg and for boys 1.49 m and 44.2 kg, comparative with the urban group, girls medium height was 1.55 m and medium weight 44.9kg and for boys 1.54 m and 46.6 kg. Rural: 15.04% are overweight, 14.36% obese; urban: 17% overweight/obese from which 4% obese. ***Conclusions:*** Rural SC Timiș survey: 15.04% overweight, 14.46% obese, the difference boys-girls=3.71% statistically significant, pupils percentage with a BMI over 85 percentile (overweight and obese) for the urban group is 17%. Girls in urban group 13% are overweight or obese and 4% obese.

Background

Obesity involves multiple interactions between genetic, social, behavioral, metabolic, cellular and molecular factors because of which changes in energy balance occur (1). Increasing global prevalence of obesity and overweight is due, on one hand, to the increasing intake of energy, particularly high callories-density foods, rich in fats, sugar, and on the other hand the decrease in activity due to the increased sedentary individuals. The risk of becoming obese adults of children who developed obesity in the early years of life is 80% for those with both parents obese and 40% for children with one obese parent.(2,3) The World Health Organization (WHO 1986) defines health as a resource to live a productive life, and absence could obstruct achieving goals in life.

Obesity in children and adolescents is a risk factor for cardiovascular disease, hypertension, type 2 diabetes, sleep apnea, depression and some other forms of disease. (4, 5). In a study conducted in our teritory (15) it was demonstrate that lifestyle and food behaviour it represents predictors for early onset of coronary diseases.

According to the current consensus, as for adults, also for children was adopted, the case definition of obesity based on body mass index (BMI = weight in kg / height in m square, Quetelet index). Also according to the new proposed definition of obesity in 2007 by an expert committee of the American Medical Association's Department of Human Health and the Center for Disease Control (Center for Disease Control - CDC), this also includes the severity of the disease. Thus, a BMI value between 85-95 percentile defines overweight, a BMI between 95-99 percentiles defines obesity, a BMI above the 99th percentile represents severe obesity and a characterized BMI> 40 kg/ m signifies morbid obesity. (6)

Aims

To examine correlation and differences of overweight in school-aged children (aged 10-13 years old-yo) according to their health lifestyle factors and depending on demographic repartition in our district using two materials (Raport de cercetare al DSP 2008-2009 and Timis Save the children survey 2010-2011).

Material and methods

A cross-sectional survey including pupils (n= 1003, 7-17 yo) from 9 rural Timis county settlements was carried-out. Height and weight were measured and a questionnaire regarding nutritional behavior and physical activity was completed. Results were compared in terms of Rural/Urban appurtenance by sex and age oriented on comparison with the median 10-13 yo from our group (585 children) and Timisoara 6th grade pupils (1220 children). We use CDC Atlanta body mass index (BMI) charts and Excel data analysis.

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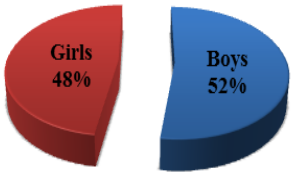
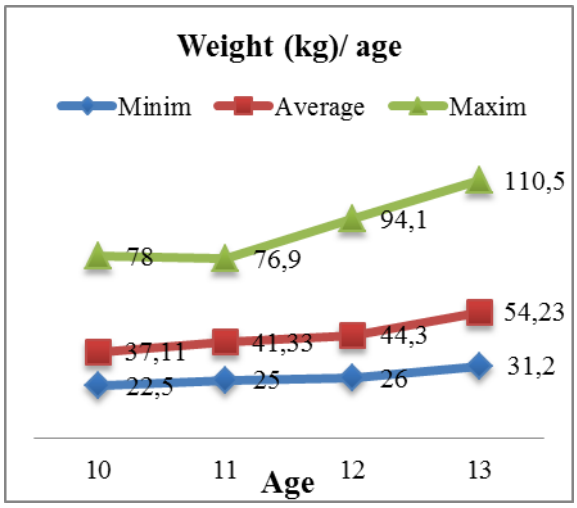
		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	F	478	47.7	47.7	47.7
	M	525	52.3	52.3	100.0

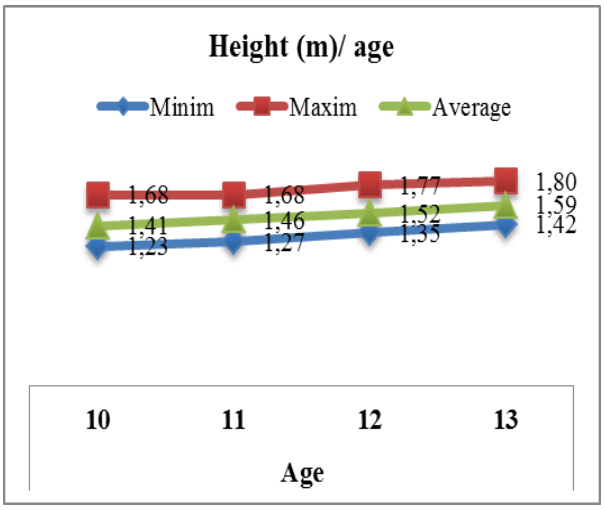
Table 1. Cohort distribution by sex

Graph 1. Sex repartition

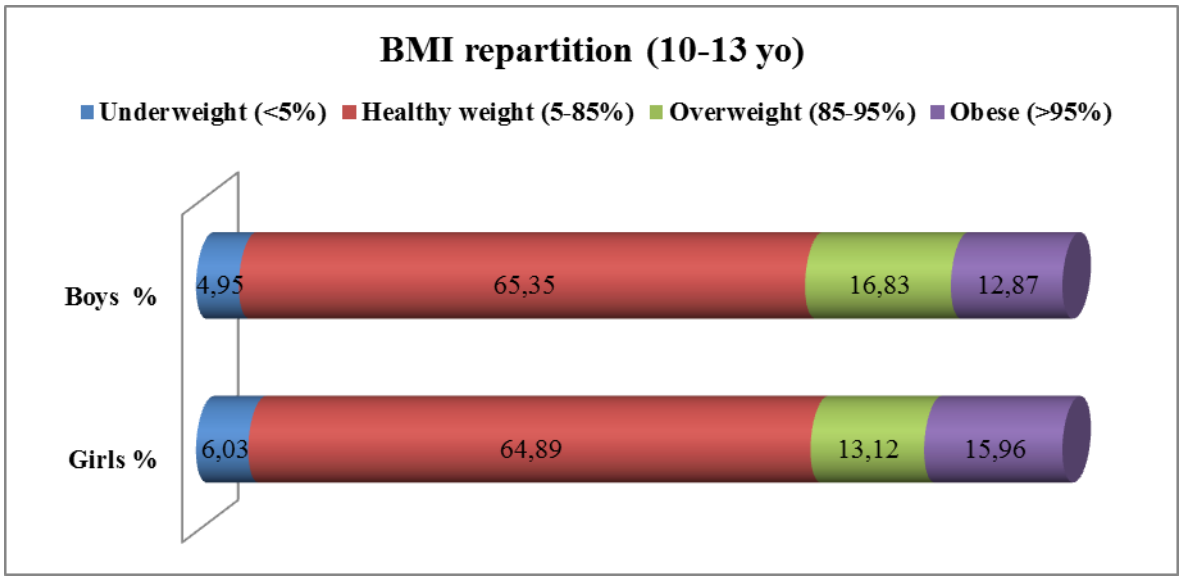




Graph 2. Weight values/ age



Graph 3. Height values/ age



Graph 4. BMI repartition in rural lot (10-13 yo)

Results

Whole rural lot- descriptive statistics

The analysis group in terms of sex, we obtained the following: 525 male subjects and 478 girls valid for analysis. Boys are a percentage of 52.3% of the population and girls 47.7%, the balance is tilting in favor of boys. (table 1)

For an accurate comparative study with the urban Timisoara cohort, we selected from our whole lot, children with between 10-13 years old.

10-13 years old group parameters

From rural group, girls medium height was 1.51 m and medium weight 46.6 kg and for boys 1.49 m and 44.2 kg, comparative with the urban group, girls medium height was 1.55 m and medium weight 44.9 kg and for boys 1.54 m and 46.6 kg.

In the study group the average of girls BMI is different from the boys. To determine the statistical difference was applied Student t test, the value of p was 0.02. With reference $p < 0.05$ and the hypothesis H0: Mean BMI girls differ significantly from the average BMI of boys. The result was a statistically significant difference in the value of $p = 0.02$. So the two groups separately, with the criterion of sex differentiation and CDC graph as a reference for age and sex data were obtained:

- rural: 15.04% are overweight, 14.36% obese;
- urban: 17% overweight/obese from which 4% obese .

In rural lot, the proportion of healthy BMI is almost the same on girls and boys, girls are more underweight than boys and more boys (29.7%) are overweight or obese than girls (29.08%), but without a significant difference.

We applied a questionnaire regarding the children life style and sweet food/soft drinks consumption in our rural cohort and for Timisoara lot it was a vast and detailed list of items (both for pupil and parent) that we can compare in a large disscusion. We resume that on one fact –that the correlation of soft drinks consumption by categories of gender overall results showed that boys drink more than girls, for example, in the frequency of 3-4 times a week there is a difference of 3.51% in favor of boys, and about every day drinking, a difference of 4.81%. (graph. 5)

Discussions

The prevalence of obesity and overweight in children is increasing alarmingly in North America, in Europe, but recently in Australia, China, South America and North Africa. The prevalence varies considerably between different regions and countries, from under 5% in Africa and some parts of Asia, more than 20% in Europe and 30% in America and some countries in the Middle East. (7)

In the past 30 years, according to data from NHANES prevalence of obesity has tripled: in children aged 6-11 from 6.5% in 1980 to 19.6% in 2008, and in adolescents 12 to 19 years from 5 % to 18.1 %. (Kuczmarski, 2008)

In Romania, according to a study in the west of the country, in 1980, on a sample of 5250 children 3 months to 16 years, there has been a prevalence of obesity of 14.7%, ie 18.6% in infants 15% to preschool and 14.2% in school, with a predominance for girls. (1)

The first research HBSC (Health Behaviour in School-aged Children) in Romania took place in 2005-2006 (study published in a report by IASO, London, 2009), in children a11 ged to 15 years old showed that the prevalence of overweight was 14.7% in girls and 8.7% for boys. (8)

A study performed in ClujNapoca (2009) schowed that 8.29% of school children were obese, while 12.84% of them were overweight, using also CDC Atlanta growth reference charts, boys were more likely to be obese or overweight than girls (9).

According to data from the National Center for Evaluation and Promotion of Health in Romania (CNEPSS), the prevalence of obesity in children 3-16 years increased from 2004 in 2010 from 0.7% in rural areas and 1.6% in the urban to 1.5% and 3.1%.

In Romania (Craiova), during 2008-2010 was made a research aimed to pursuit the correlations between obesity, overweight and the children's lifestyle and a better understanding of the clinical and etiopathogenic aspects of obesity in children. From 166 scholar children aged 6-14(75 girls and 91 boys) 26.69% were overweight, 40.96% were obese and 34.33% had normal weight. From the girls 15.66 % were overweight, 9,63% were obese and 19.87% normal. From the boys 9.03% were overweight, 31.32% were obese and 14.45% normal. These numbers show semnificative differences for overweight between girls (15,66%) and boys (9,03%) and for obesity between boys (31.32%) and girls(9.63%). (8)

Previous studies showed that social status has a inverse relation with obesity in childhood period, a fact that is presumable in the results of this present study were overweight it was much higher in the rural areas that in the urban group of pupils.(11)

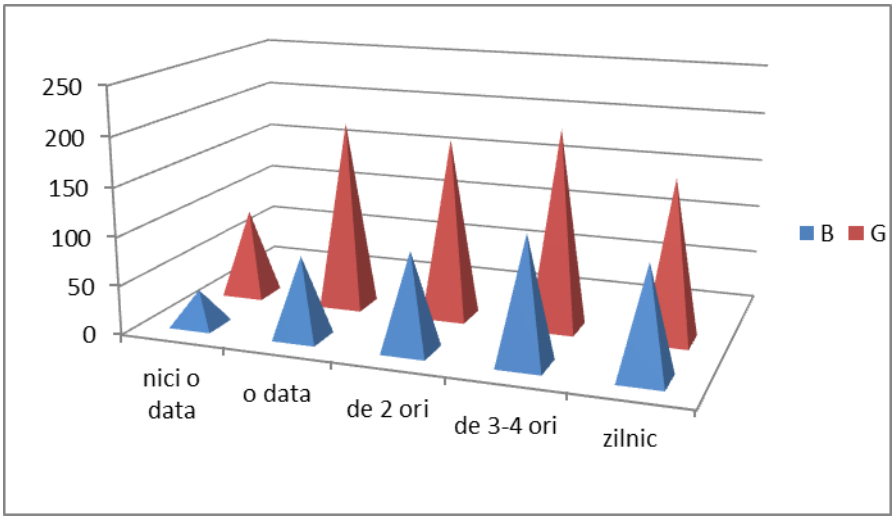
In the largest study from our county (12) using two groups from urban and rural areas we report associations between obesity and drinking of sweet beverages (1 of 4 children drink this every day), and no corelation with fast-food intake. We must agree that this became a major issue because in US the soft drink consumption increased by 300% in 20 years, with heavy consequences on teenagers health.(16)

Conclusions

Rural SC survey showed 15.04% children with overweight, 14.46% obese, the difference boys-girls=3.71%, that is statistically significant. Pupil's percentage with a BMI over 85 percentile (overweight and obese) for the Timisoara urban group is 17%. In the girls from urban group they found 13% with overweight or obese and from those - 4% were obese. So it is obvious that in the low social status from villages in Timis county we have much more overweight pathology that in the main city (despite the fact that children from villages do more physical activity). We can presume that is linked with low economic profile but for a comprehensible position we need to solve the limitations of the studies (with same frame and tools doubled by obtaining the precise age using the date of birth on the database).

Urban study results	Girls %	Boys %	Total
Numar de copii evaluati	618	530	1148
Underweight (<5%)	4,00	3,00	3,00
Normal weight (5-85%)	84,00	75,00	80,00
Overweight (85-95%)	11,00	15,00	13,00
Obese (>95%)	2,00	7,00	4,00

Table 2. BMI repartition in urban lot (10-13 yo)



Graph 5. Rural cohort-soft drinks consumption comparison (boys-B vs girls-G)

In the final conclusion we must quote from AMERICAN ACADEMY OF PEDIATRICS (16) recommendation that suits just right in our region - Pediatricians should work to eliminate sweetened drinks in schools; they must promote literacy, better school meals, and consumption of fruits and vegetables. Without further changes in society, any actions may not be enough to prevent childhood obesity. Pediatricians should advocate for the formation of a school nutrition advisory council comprising parents, school officials, and food service representing persons, other physicians, nurses, dietitians, dentists, and other health care professionals.

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THERAPEUTIC APPROACH IN PRADER-WILLI SYNDROME

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Abstract

Prader-Willi syndrome (PWS) is a genetic disorder characterized by absence of the active genes on chromosome 15. Symptoms appear since intrauterine development with decreased fetal movements, low birth weight and persist after birth with hypotonia, feeding difficulties and failure to thrive in the neonatal period. From infancy until adulthood, patients have short stature, become severely obese, with an insatiable appetite and food-seeking behavior. They also have psychiatric disorders, behavioral problems and learning disabilities. Treatment of these patients is multidisciplinary and several drugs have been studied in order to control appetite and reduce the morbidity of obesity, including cardiovascular and metabolic side-effects. The following paper offers an insight in the difficult management of the co-morbidities of Prader-Willi syndrome.

Keywords Prader-Willi syndrome, obesity, growth hormone, therapy

Introduction

Prader Willi syndrome (PWS) is the most common syndromic form of obesity. Its early description dates from 1887 when Langdon-Down described a girl with probable Prader Willi syndrome during adolescence, with mental impairment, short stature, hypogonadism and obesity. In 1956 Prader and his colleagues mentioned several other patients with similar phenotypes. In 1981, Ledbetter et al, described the microdeletions within chromosome 15 as site for PWS. PWS affects between 350 000 and 400 000 individuals worldwide and affects both sexes.

The diagnosis of PWS is suspected in patients who have characteristic clinical features and is confirmed by genetic testing. Affected pregnancies often exhibit reduced fetal activity with polyhydramnios and breech position. In 1993, Prader et al, developed clinical diagnostic criteria1, listed in Table 1. For children three years of age and younger, the diagnosis of PWS is highly likely if five points are scored among these criteria (four from major criteria). In children older than three years of age, eight points are required (five or more from the major criteria). Neonatal hypotonia is defined as the hallmark feature of this disorder and it is also a major cause of death because of asphyxia. Hypotonia determines also feeding difficulties with poor suck and failure to thrive. Soon after it was demonstrated that these criteria were too exclusive and they might have missed the diagnosis of PWS in patients with positive molecular testing. In 2001, Gunay-Aygun et al2 proposed a lower threshold for diagnostic DNA testing in patients with clinical features specific for their age, independent from the Prader criteria, as follows: neonates and infants up to two years old presenting hypotonia with poor suck; children between two and six years of age with hypotonia with history of poor suck and global developmental delay; children between six and twelve years old with history of hypotonia and poor suck, global developmental delay, hyperphagia with obesity if food is uncontrolled; children thirteen years old through adulthood with cognitive impairment, excessive eating, hypothalamic hypogonadism and/or typical behavior problems (temper tantrums, obsessive-compulsive features).

Prader Willi syndrome is the first genetic disorder attributed to genetic imprinting, meaning that the expression of genes depends on the gender of the parent donating the gene. PWS is caused by the absence of expression of the paternal active genes from the long arm of chromosome 15q11.2-13, either due to deletions of these regions from the paternal chromosome (approximately 78 percent of cases), maternal disomy (28 percent of cases) or rarely (fewer than 1 percent) defects in the imprinting center which determines a greater risk of recurrence in future siblings (up to 50 percent). Despite these defects, most of the cases of PWS arise sporadically. A standard diagnostic panel for PWS involves karyotype, fluorescence in-situ hybridization (FISH) followed by methylation studies and then micro-satellite probes to detect maternal uniparental disomy (UPD).

FISH analysis detects deletions, trans-locations or rearrangements on the chromosome 15q11.2-13. A negative FISH or karyotype analysis does not exclude the diagnosis of PWS and further investigations are needed.

Molecular analysis in PWS is highly sensitive and detects up to 99 percent of the cases and has become the "gold standard" technique to both confirm and reject the diagnosis of PWS. Methylation detects abnormal parent specific methylation imprinting within the PWS critical region on 15q11.2-13, the SNURF-SNRPN locus. This can be done by the Southern method using a methylation sensitive probe (SNRPN or PW71B) or by polymerase chain reaction (PCR) using parent specific primers.

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If only a maternal pattern is present after methylation, PWS is confirmed. A positive DNA methylation analysis needs further investigations in order to distinguish between an imprinting defect or a maternal uniparental disomy. ***GH secretion in PWS patients***

Prader Willi syndrome is a complex and multi-systemic disorder and patients might exhibit endocrinopathies attributed to hypothalamic and pituitary dysfunction. Children with PWS have growth failure, altered body composition with increased in the fat mass, decreased lean body mass, reduced bone density with increased risk for osteoporosis, hypogonadism which might worsen the bone density, sleep disorders, behavioral and psychiatric problems and learning disabilities.

Intrauterine growth restriction is common, with a birth weight of -1.37 standard deviation (SD) score and median birth length of -0.46 SD score(3). After birth short stature is also a common feature, especially in the first two years of life and the average final height in adult PWS patients has been reported as 162 cm in boys and 150 cm in girls(4) . Growth hormone secretion is generally blunted in PWS patients and GH peak during pharmacological stimulation tests fails to rise above 10 μg/l. The exact mechanism responsible for the GH deficiency is unknown, and several hypothesis have been proposed. One of them is related to the ghrelin level. Ghrelin produced by the stomach when fasting, is an endogenous ligand for the receptor responsible for the growth hormone secretion, GH secretagogue receptor (GHS-R) from the hypothalamus and pituitary gland. An independent effect of ghrelin observed in rodents is that it induces adypogenesis and infusion of ghrelin enhances appetite and increases food intake. In obese patients, ghrelin levels are low while in patients with weight loss and anorexia nervosa, levels tend to be higher. Despite these observations, patients with PWS have extremely high levels of ghrelin via an unknown mechanism, which might be implicated in the pathogenesis of the hyperphagia, GH deficiency or the reduced levels of GHS-R (5). Hyperghrelinemia is not a consequence of GH deficiency since GH replacement therapy does not reduce the levels of ghrelin. Ghrelin is transported into the brain where stimulates neurones from the arcuate nucleus and thus makes part of a circuit involving the energy homeostasis, stomach and hypothalamus (6). However, other causes of growth failure should be excluded including hypothyroidism and under-nutrition (a young child who fails to thrive or in case of a restricted calorie diet).

Children with genetically confirmed PWS are candidates for treatment with GH which was approved by the United States Food and Drug Administration (FDA) in 2000 and has been approved for this use in most countries. It is generally not necessary to evaluate formally for growth hormone deficiency before considering treatment (3). Growth failure is typically defined as decreased linear growth velocity or decreased height in comparison with the mid-parental height (MPH) prediction. Measurement of insulin-like growth factor-1 (IGF-1) and insulin-like binding protein-3 (IGFBP-3) are sometimes used to appreciate the correct growth hormone dose.

Treatment with GH has beneficial effects on linear growth, body composition, osteoporosis and bone mineral density along with language acquisition, gross motor skills and cognitive scores (7). The optimal age to begin treatment, dosing and duration of therapy have not been established but there is increasing evidence that early initiation of GH treatment, before two years of age, improves clinical outcomes (8). Initiation before the age of 18 months old was associated with accelerated acquisition of mobility skills compared to controls of the same age, improvement in behavior with lack of behavioral deterioration during adolescence (9). The response to growth hormone treatment is greatest in the first 12 months and persists for as long as five years. Even with long term GH treatment, body composition is not completely normalized and adult PWS subjects, especially men, failed to improve bone mass with GH treatment for two years in a recent study (10). Regarding the final height after treatment with GH, the results are astonishing in the Kabi International Growth Study (KIGS) database (11) and show that children treated with GH for 6.9 years reached the adult height within MPH.

Because of several reports(12) of unexpected deaths coinciding with the use of exogenous GH, FDA has added labeling to GH products stating that they are contraindicated in high risk PWS patients with severe obesity (weight > 225 percent of ideal body weight), diabetes, respiratory compromise or severe sleep apnea. The deaths were mostly associated with respiratory problems and most occurred within the first nine months of treatment, with a median of three months and supported the hypothesis that GH might have a possible role in worsening respiratory complications at the start of treatment (12). Growth hormone has mixed effects on breathing problems especially during sleep; it may worsen obstructive apnea by stimulating adenotonsillar hypertrophy. Otherwise, GH has direct effects on hypothalamic function improving the central hypoventilation. Unexpected deaths were also reported in children with PWS without GH treatment suggesting that PWS patients have an increased risk of death independent of treatment with GH products, most of the deaths being related to a complicated respiratory tract infection, hypoventilation, obstructive sleep apnea, chocking episodes, acute gastric distension/rupture and necrosis, septicemia or cardiac events. In the same review, Tauber et al(12) found that the ratio between males and females was 2:1 suggesting that boys with PWS are at greater risk of death.

Before starting GH treatment, patients should be evaluated for upper airway obstruction or apnea (with the use of polysomnography), glucose intolerance and scoliosis because of the possibility of aggravation of these conditions.

For all these reasons, it is advised to start treatment with a low dose, 0.25-0.3 mg/m2/day or 0.009-0.012 mg/kg/day, increasing during the first weeks and months to reach the standard replacement dose. The currently recommended dose is 1.0 mg/m2/day or 0.035 mg/kg/day (3) and the dose should be adjusted with changes in body weight during the course of therapy. The dose might be adjusted to achieve IGF-1 levels in the normal range to optimize linear growth and minimize risks of adverse

metabolic side effects. It is recommended to avoid high IGF-1 levels, especially if there are clinical suspicions of overtreatment (edema, worsening of snoring, headache, acromegalic clinical features) (3). Children with abnormal polysomnograms should be followed up monthly and the treatment should be ceased if they develop intercurrent respiratory tract infections and increased obstructive symptoms. Careful monitoring is recommended for infants who are at greater risk of respiratory compromise because of the general hypotonia. They should have a constant monitorization of the oxygen saturation during sleep for the first one to two months after starting treatment.

Cessation of GH treatment is also recommended if the patient presents uncontrolled progression of obesity despite controlled food intake, worsening of glycemic control despite diabetic medication and attainment of adult final height.

It has not been established whether continuation of GH treatment in adulthood has beneficial effects, but the modest benefits in body composition, cognition, quality of life and peak bone mass raise the possibility of continuation of GH treatment even after epiphyseal closure.

Obesity and hyperphagia treatment

In an extensive cohort study, Jennifer Miller et al(13), demonstrated that PWS is characterized by several gradual nutritional phases. Phase 0 occurs in utero with reduced fetal movement and growth restriction, with a mean body weight of 2.8 kg at term, often associated with polyhidramnios. Phase 1 consists of severe neonatal hypotonia, hyporeflexia, without onset of obesity. Subphase one requires frequent assisted feeding for up to 3-4 months of age because of poor suck with or without failure to thrive. Subphase two is characterised by a normal development, a normal growth and a steady weight curve. Starting nutritional phase two, which usually starts at a mean age of 2 years, weight slowly increases. In subphase one the total body weight increases without increasing calorie intake and appearance of food cravings. It has been shown that at this point, with early counseling, calorie restriction and dietary recommendations, it is possible to maintain a normal weight reported to height. In subphase two, the child starts to develop abnormal interest in food which serves to a worsening of their existing obesity, but without unrelenting appetite. Phase three is the most aggressive nutritional status in PWS patients and has been described from 3 up to 15 years of age, with a median age of onset of 8 years old. It is the classical phase with hyperphagia, increased calorie intake, aggressive food seeking, reduced energy expenditure and satiety. A restrictive food environment is highly recommended, with food storage being locked, access to food or money to buy food being forbidden and constant supervision employed whenever possible(3). Some adults progress to a phase 4 when the insatiable appetite disappears and the patient regains his satiety sensation.

A major concern in PWS patients has been the motor performance. Even though at birth newborns are severely hypotonic, after several months of life the muscle tone improves but still they suffer from muscle weakness and delayed motor development. Persistence of these problems has been reported in childhood and adulthood, with decreased physical activity and low scores on standardized performance tests (14). The cause of these abnormalities is unknown but it could be related to the abnormal body composition and neuromuscular functioning. It has been thought that muscle hypotonia might be due to a central nervous system abnormality, but Sone(15) suggested that there is a primary muscle pathology with muscle fiber immaturity and abnormal muscle fiber type distribution.

Studies of body composition with the aid of body dual-energy X-ray absorptiometry (DEXA) have demonstrated that despite their adiposity, patients with PWS have decreased visceral fat, which protects them from the negative effects of the metabolic syndrome: type 2 diabetes, insulin-resistance and dislipidemia. Adipose tissue is thought to be an endocrine organ capable of producing a variety of cytokines and hormones, of interest being adiponectin. Adiponectin has antidiabetic and antiatherogenic properties and thus, obese patients with type 2 diabetes or cardiovascular diseases usually have hypoadiponectinemia. Kennedy et al (16) has shown that levels of adiponectin are lower in PWS patients compared to lean subjects but are higher than control obese patients. A variety of gastrointestinal peptides have been studied among patients with PWS: pancreatic polypeptide, cholecystokinin and ghrelin. The mechanism that causes impaired satiety and hyperphagia is not completely understood though the role of ghrelin as a primary or secondary factor in satiety defect is unclear. Some authors proposed that a surge in ghrelin might precede the hyperphagia and obesity observed in older children(16). As pharmacoherapy, somatostatin analogs suppress plasma ghrelin concentrations in PWS patients but fail to reduce the appetite and further studies showed no benefit of chronic administration of these agents (17).

Traditionally, the mainstay of management has centered on early institution of a low-calorie diet with regular exercise, rigorous supervision, restriction of food and money, and appropriate psychological and behavioral counseling for the patient and family, often in the context of group homes for PWS adolescents and adults(3).

Pharmacological treatment in PWS patients, especially children is not an accepted choice of treatment since there there is little evidence that these drugs have specific effects on binge eating or weight gain. Different drugs have been tried, like selective serotonin reuptake inhibitors (SSRIs) or topiramate, a novel anticonvulsivant, which did not decrease appetite, food intake or weight status although it decreased self-injurious behaviors, such as skin-picking.

Since dietary restriction or appetite suppressing agents are ineffective, surgical weight loss procedures have been also tried but there are scattered case reports, most with follow-up of less than 2 years and results seem to be inconsistent.

Patients that qualify for bariatric surgery are those with a BMI over 40 kg/m2 with medical conditions or those with a BMI of over 50 kg/m2, children who have reached their physical maturity (Tanner stage 4 or 5), emotional and cognitive maturity and those who have been unable to loose

weight by all other measures. Guidelines recommend against bariatric surgery for prepubertal children, untreated psychiatric conditions, Prader-Willi syndrome or eating disorders(18). Bariatric procedures for weight loss are divided in malabsorbtive, restrictive or a combination of both. Surgical procedures that restrict the stomach may be particularly risky for patients with PWS as there are reports of gastric dilatation and necrosis. A variety of bariatric techniques have been implemented but the ideal procedure is still controversial(19). Since ghrelin is involved in hyperphagia and the lack of satiety, surgical procedures reducing its levels proved to be efficacious in reducing body weight at the expenditure of malabsorbtion, diarrhea, vitamin B12, iron and folate deficiency, bone demineralization and osteoporosis, hypoalbunemia and protein malnutrition(20). Even though, reports have shown a little reduction in body weight but an improved quality of life. A recent clinical report(21) on three patients with PWS treated with laparoscopic mini-gastric bypass (LMGBP) and laparoscopic sleeve gastrectomy (LSG) demonstrated significant reduction of body weight and serum ghrelin after a follow up of 33 months. The main advantage of these procedures is that ghrelin serum level is reduced by removal of gastric fundus and reduction of ghrelin apparently corrects hormonal abnormalities in PWS patients.

Steroid treatment and puberty induction

Hypogonadism in PWS patients has four phenotypes characterized by the analysis of FSH and Inhibin B, which suggest both a hypothalamic and a peripheral cause(22): primary hypogonadism, central hypogonadism, partial gonadal and central dysfunction, mild central and severe gonadal dysfunction; testosterone levels are usually low and estrogen levels are in the normal range of the follicular phase. Hypogonadism manifests early in infancy by genital hypoplasia in females, micropenis and/or cryptorchidism in boys, for which they generally need correctional surgery in the first year of life; the Committee on Genetics, American Academy of Pediatrics recommends an initial course of medical treatment with human chorionic gonadotropin (hCG) before surgery, in order to avoid general anesthesia which might aggravate respiratory infections due to hypotonia(23). Besides descent of the testes, hCG treatment also contributes to the normal development of the scrotum and has a good prognosis on the final penile length.

Major criteria (1 point each)
Neonatal and infantile central hypotonia, gradually improving with age
Feeding problems in infancy with need for special feeding techniques and poor weight gain/failure to thrive
Excessive weight gain between 12 months and 6 years of age; central obesity in the absence of intervention
Characteristic facial features (three or more of the below) Dolichocephaly (infancy) Narrow face or bifrontal diameter Almond-shaped eyes Small-appearing mouth with thin upper lip - *(Figure 1)* Down-turned corners of mouth
Hypogonadism, with any of the following Genital hypoplasia (hypoplasia of labia minora) Delayed or incomplete maturation with delayed pubertal signs in the absence of intervention after 16 years of age (amenorrhea after age 16)
Mild to moderate mental retardation or learning problems in older children (QI= 69)
Hyperphagia/food foraging/obsession with food
Deletion 15q11-13 (or other cytogenetic/molecular abnormality of the Prader-Willi chromosome region)
Minor criteria (1/2 point each)
Decreased fetal movement or infantile lethargy or weak cry in infancy, improving with age
Characteristic behavior problems–temper tantrums, violent outbursts, and obsessive-compulsive behavior; tendency to be argumentative, oppositional, rigid, manipulative possessive, and stubborn; perseverating, stealing, and lying (5 or more of these symptoms required)
Sleep disturbance and sleep apnea
Short stature for genetic background by age 15 (in the absence of growth hormone intervention)
Hypopigmentation—fair skin and hair compared with family
Small hands (<25th percentile) and/or feet (<10th percentile) for height age – *Figure 1*
Narrow hands with straight ulnar borders
Eye abnormalities (esotropia, myopia)
Thick viscous saliva with crusting at corners of the mouth – *Figure 2*
Speech articulation defects
Skin-picking

Table 1. Diagnostic criteria for Prader-Willi syndrome. Major criteria are weighted at one point each and minor criteria are weighed at one half point. Major criteria must comprise ≥ five points of the total score (Holm *et al* [1], 1993).

Premature pubarche has been described, due to an early maturation of zona reticularis, but it is not sustained and it does not need treatment with GnRH analogs. Obese PWS girls may have pseudo-pubertal development with vaginal bleeding mimicking monthly menses but without ovulation. This is due to aromatization in the adipose tissue of adrenal steroids to estrogens which determine endometrial estrogenisation and breakthrough bleeding. LH levels in PWS patients are low and this explains the injury of the germ cells and defects in the spermatogenesis. Correction of the gonadal axis may be achieved with a course of treatment with clomiphene citrate which raises testosterone and both serum and urinary gonadotropin levels.

Treatment of hypogonadism in PWS is still controversial and there is no consensus for the management of this condition. At some point they will need sexual steroid replacement therapy regardless of their mental retardation, especially if there are signs and symptoms of hypogonadism: lack of sexual secondary development, amenorhea/oligomenorrhea or decreased bone density. Replacement doses should be titrated to the individual's response since there are concerns about effects on mood and behavior. Care should be given to females with menses since hygiene issues might be difficult to manage. Transdermal estrogen preparations are well tolerated despite the skin picking. For testosterone replacement therapy both transdermal and intramuscular preparations are a good choice of treatment. The dose should be lower than the normally recommended (one third to one half) and titration is important to prevent the aggressive behavior occasionally seen in some individuals. PWS girls with regular menses and sexual maturation should benefit from sexual counseling and appropriate contraceptive treatment because even though they are sterile, pregnancies have been reported(24); specialists usually advise against conception due to the high risk of recurrence of the disease in the offspring (3). Paternity in PWS patients has not yet been reported. Because of their hypogonadism and increased risk for osteoporosis, yearly evaluation of BMD by dual-energy X-ray absorptiometry (DEXA) is recommended(3).

As mentioned, PWS patients have hypothalamic dysfunctions therefore the clinical manifestations of pituitary hormone deficiency are expected. Under normal conditions, the secretion of cortisol is controlled by the adrenocorticotropic hormone (ACTH). Clinical manifestations of adrenal insufficiency are uncommon in PWS patients but various dynamic tests demonstrated that patients with PWS cannot provide a stress induced rise in cortisol similar to a normal person. A study from 2008, reported a 60% prevalence of central adrenal insufficiency (CAI) in children with PWS(25). Based on similar reports, it has been suggested the treatment with hydrocortisone during acute illness unless CAI has been ruled out.

Orthopedic treatment

Frequently observed in PWS patients are severe deformities of the spine in both frontal and sagittal plan. Scoliosis is one of them, its incidence is 30-70%(26) and it increases with age. Because of their obesity, a clinical diagnosis of scoliosis in PWS patients is sometimes difficult so radiographic evaluation is needed. A risk of aggravating the scoliosis was thought to be the height velocity in patients treated with growth hormone, but recent studies have not confirmed this suspicion(27). Scoliosis is frequently associated with kyphosis which explains the risk for development of severe progressive cervical thoracic kyphosis in those treated surgically.

Bracing, as a treatment, is controversial because moulding is difficult especially in those with severe obesity and lack of compliance. Remodeling is therefore often necessary in about 15-20% of patients, especially in those with unbalanced and progressive curves, respiratory dysfunctions and cardiocirculatory restrictions. Retrospective studies have shown that growing spinal implants are safer and produce less complications (delayed wound healing, temporary paraplegia, deep infections, pseudoarthrosis), in the treatment of early-onset scoliosis (28). Nevertheless, there is no consensus on the management of scoliosis and the ideal remodeling surgical procedure.

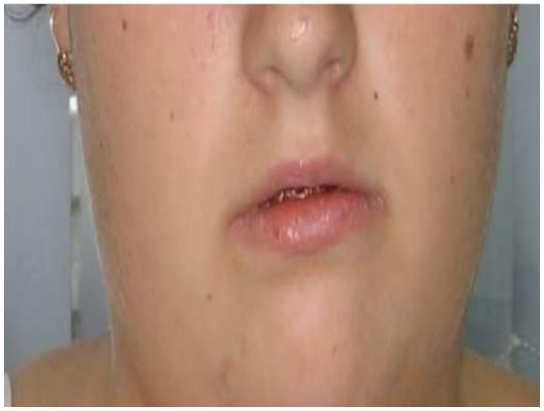

Figure 1. *Small-appearing mouth with thin upper lip and thick viscous saliva with crusting at corners of the mouth in a 16 years old girl with PWS*

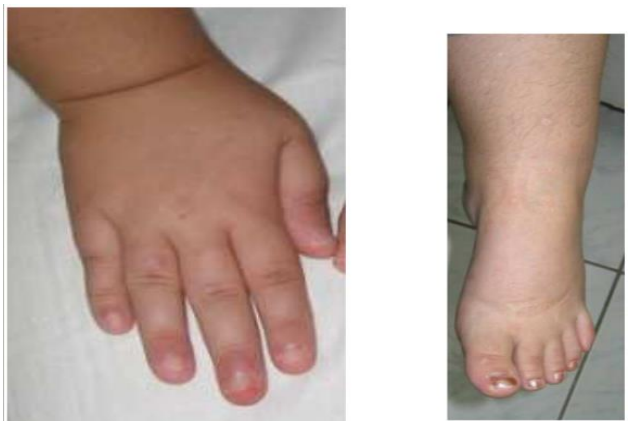

Figure 2. *Small hands (<25th percentile) and/or feet (<10th percentile) for height age from the same 16 years of age girl with PWS*

Sleep apnea and respiratory dysfunctions

Patients with PWS are at increased risk of sleep disturbances including central apnea, obstructive apnea and narcolepsy. Obstructive sleep apnea is caused by adenotonsillar hypertrophy, kyphoscoliosis, thick and sticky saliva, hypotonia of the respiratory muscles and also by the narrow upper respiratory airways. Sleep disordered breathing occurs in at least 70% of children and young adults with PWS, and is associated with increased daytime sleepiness, behavioral problems, increased risk for cardiovascular complications, cor pulmonale or pulmonary hypertension, aggravation of arterial hypertension or diabetes mellitus. It is recommended to monitor all patients with PWS for sleep related disturbances, snoring, apnea for more than five seconds or daytime sleepiness, particularly during intercurrent respiratory infections. Patients with severe obesity and clinical symptoms of sleep apnea should be further evaluated for adenotonsillar hypertrophy and also referred to a polysomnogram. In patients with severe obstructive sleep apnea, tonsillectomy, adenoidectomy or tracheostomy placement may be necessary.

Psychiatric treatment

PWS patients are well known for their reduced Intelligence Quotient (IQ) but despite this, they have a good developed long term memory, visual spacial performances and they also may have a high interest in puzzles. Scientists have identified a characteristic pattern of behavior and psychiatric problems. The cardinal aspect in PWS is the hyperphagia and all the preoccupations regarding food: stealing money to buy food, hiding food, scavenging, eating raw, spoiled or frozen food and sometimes having picas. Besides this, PWS patients exhibit other behavioral problems, temper-tantrums, emotional lability, impulsiveness, aggressiveness, bipolar disorders, compulsive behavior and physical injury such as skin-picking which is present in up to 96 % of patients and is generally related to boredom and anxiety (3). Since the etiology is elusive, the management of these disorders is usually environmental and behavioral. There are few studies regarding safety of psychiatric medication for PWS patients except from antidepressants and antipsychotics which are a better choice than mood-stabilizing medication (29). As described above, medical treatment has little or no effect on hyperphagia and insatiable appetite but reduces the self-injurious behavior (skin-picking).

Conclusions

Since there is no cure for Prader Willi syndrome, the major interest in the management of this disorder is the development of sensitive genetic testing modalities to allow early diagnosis and intervention to improve the quality of life of both the patients and their families and reduce though, the high risk of morbidities and mortality. PWS patients need a multidisciplinary team and pharmacological, surgical and environmental treatment. Despite the reported side effects, growth hormone still plays an important role in the management of these patients, and early use helps them to achieve their final adult height, improves the body composition with reduction of the adipose tissue and increase of the lean mass. Anorexigenic agents failed to treat hyperphagia and treatment of obesity sometimes needs restrictive bariatric surgery along with a better food control, restrictive calorie diet, physical activity and rigorous supervision. There are still unknown mechanisms implicated in the pathophysiology of this syndrome, so further studies are needed to establish the exact cause of the signs and symptoms of PWS in order to develop target pharmacological treatment.

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CONTROVERSIES IN MANAGEMENT OF GROWTH DISORDERS IN JUVENILE IDIOPATHIC ARTHRITIS

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Abstract

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood and is responsible for many growth disorders. Abnormalities of growth and development in JIA can be attributed to a combination of factors, as disease process (with enhanced pro-inflammatory cytokines production), perturbation of the growth hormone (GH) - insulin-like growth factor (IGF-1) axis, and glucocorticoid treatment. The aim of study was to assess the IGF-1 level in JIA patients and to evaluate correlation between IGF-1 levels and parameters of disease activity. IGF-1 serum concentration was measured using chemiluminescent immunoassay method. We found lower IGF-1 serum levels in polyarthritis and systemic JIA comparative with control group, but with normal mean IGF-1 values in oligoarticular and enthesitis-related arthritis, respectively. Weak to moderate negative correlations were found between IGF-1 levels and disease activity parameters. These results arise a few controversial questions: should we treat certain JIA types with GH to maintain normal growth, to prevent potential growth deterioration or to catch up growth delay? Or, perhaps a good control of disease activity in juvenile arthritis would be enough to avoid or to correct abnormalities of growth and development?

Key-words: insulin-like growth factor, juvenile idiopathic arthritis

Introduction

Juvenile idiopathic arthritis is a heterogeneous group of diseases with chronic joint inflammation as common characteristic. Abnormalities of growth and development are frequent complications of chronic arthritis or its treatment. Growth disorders due to chronic inflammatory diseases can be attributed to a combination of systemic factors that includes disease process, poor nutrition, enhanced catabolic activity, excess of glucocorticoids, and defect in growth hormone (GH) secretion or action (1,2). In JIA patients abnormalities of growth vary from general growth retardation to local acceleration of growth in the affected limb.

In juvenile arthritis, growth disorders are correlated to an increased production of pro-inflammatory cytokines, such as interleukin (IL) -1, IL-6, and tumor necrosis factor alpha (TNF-α). Pro-inflammatory cytokines may act individually or in combination to impair child growth through systemic mechanisms and/or a local action (3). Thus, cytokines may affect growth through systemic mechanisms that alter the GH-insulin-like growth factor I (IGF-1) axis by playing a paracrine/autocrine role in GH regulation in the pituitary independently from the intracellular pathways of the GH secretagogues (4). Whereas IL-6 affects growth mainly via systemic mechanisms altering growth hormone secretion, IL-1 and TNF-α can directly affect growth plate chondrocyte dynamics as well as longitudinal bone growth (5). Growth-inhibitory effects of TNF and IL-1 are due to a combination of effects on matrix synthesis, chondrocyte proliferation and a reduction in the hypertrophic zone, with hypertrophic chondrocytes which are the principal determinant of longitudinal bone growth (6).

Two of the most important and studied regulators of postnatal bone growth are GH and IGF1. The dual effector theory of GH/IGF-1 action on the growth plate proposes that GH acts directly on germinal zone precursors of the growth plate to stimulate the differentiation of chondrocytes and then increases local IGF-1 synthesis, which will induce in turn the clonal expansion of chondrocyte columns in an autocrine/paracrine manner (7). Although liver-derived IGF-1 is the main determinant of serum IGF-1 levels, it is less important for postnatal growth than locally derived IGF-1 (8).

Material and method

Study cohort consisted of 39 patients with JIA, admitted and assessed in First Pediatric Clinic, Timisoara, Romania. Diagnosis and classification were concordant to International League Against Rheumatism (ILAR) criteria. A control group (n=13), matched for age and sex, with no musculoskeletal complaints, was evaluated as well. Assessment of study cohort included: 1) clinical examination with a 27 joint count for tender or swollen joint; 2) acute phase reactants determination (erythrocyte sedimentation rate= ESR, C-reactive protein= CRP); 3) patient assessment of well-being, measured on visual analogue scale (VAS), where 0= very well and 10= very poor; and 4) measurement of IGF-1 levels in serum.

Children's height from both groups (JIA patients and control group) was plotted on the growth references from World Health Organization (WHO) 2007, and expressed as height percentiles. Children with height situated below 3thd percentile were noted as on percentile 3.

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Composite disease activity score (JADAS) was calculated as the linear sum of the scores of its components: 1) physician global assessment (VAS), 2) parent or patient global assessment (VAS), 3) active joint count (swollen joint count and tender joint count), 4) normalized ESR (range 0 to 10).

IGF-1 levels were measured in serum by using a chemiluminescent immunoassay (CMIA) method. Detection limit of the method was 20 pg/mL3 and referential values were according to age.

Statistical analysis was performed using statistical package SPSS 17. We expressed the data as frequencies or means ± standard deviations, as appropriate. Student's t-test was used to compare the JIA patients with the control group. Regression analysis was performed to evaluate relationship between IGF-1 serum levels and other clinical features and biomarkers.

The study was approved by the ethics committees of the institution. Informed consent was obtained from parents or guardians of all participating children.

Results

Descriptive characteristics of the JIA cohort are presented in table 1. IGF-1 mean level in JIA group was 281ng/ml ±102.56 (mean ±standard deviation) and was not found significantly differences between genders (p=.032). Mean IGF-1 level in female patients was 297.68 ng/ml ±116.779 and in male children 264 ng/ml ±83.85. Median IGF-1 level in control group was 242.92 ng/ml ±84.42 and we found no significant differences (p=.861) in comparison with study group.

Comparison of IGF-1 levels between subtypes of JIA group revealed statistical significance (p=.011). Multivariate analysis showed a statistical significant (p=.045) difference in IGF-1 levels between children with oligoarthritis and patients with systemic JIA (mean difference=171ng/ml), in favour of oligoarticular type. Difference in IGF-1 serum levels in patients with polyarthritis in comparison with oligoarthritis was close to statistical significance (p=.06) with a mean difference of 114.6ng/ml favourable to polyarthritis.

Multiple comparison of mean IGF-1 levels in JIA subtypes, and control group respectively was performed using statistic ANOVA test (Boferroni option). IGF-1 serum levels in both polyarthritis (mean difference=168.5ng/ml) and systemic arthritis (mean difference=225.5ng/ml) were found significantly lower in comparison with control group (p=.001, and p=.007 respectively) (table 2 and figure 1).

Correlations between IGF-1 levels and clinical parameters

Evaluating association of IGF-1 levels with height percentiles, we found in both arthritic and control group a positive moderate correlation (rho=.556, p=.005) (figure 2).

Positive moderate correlation (rho=.583) with statistical significance (p= .01) was found between IGF-1 level and the age of disease onset (years) in children with juvenile arthritis (figure 3). We found no correlation between IGF-1 levels and duration of chronic arthritis (rho=-.122, p=.569) illustrated in figure 4.

Type of JIA (number)	Median ESR (mm/1h)	Median CRP (mg/dl)	ANA+ (no cases)	Anti-CCP+ (no cases)	Median JADAS
Systemic (3)	49.8±12.7	12.2±5.7	0	0	19.8±3.5
Oligo (15)	25.5±11.2	7.49±3.2	2	0	5.9±2.4
RF+ Poly (4)	47.1±18.6	14.2±2.9	0	2	17.5±4
RF- Poly (9)	30.8±11.6	12.6±2.8	2	2	12.9±2.6
ERA (8)	16.1±7.4	4.8±2.1	0	1	10.7±4

Table 1. Descriptive characteristics of JIA cohort

(A) Control group	(B) Type of arthritis	Mean difference (A-B)	Standard error	Significance
Control group	Oligoarthritis	53.900	41.702	1.000
	Polyarthritis	168.500	37.260	0.001
	Systemic	225.000	59.837	0.007
	ERA	89.900	33.545	0.117

Table 2. Multiple comparasion between mean IGF-1 levels of JIA subtypes and control group

Correlations between IGF-1 and disease activity

Spearman's test was used to evaluate correlations between IGF-1 levels and other parameters which characterized the group of children with chronic arthritis. We found no association between IGF-1 levels and children's VAS score of pain (rho=-.146, p=.496).

IGF-1 levels were inversely correlated (rho=-.436, p=.033) with the number of active joints (swelling or/ and tenderness) (figure 5). Similar association (rho=.456, p=.025) was found between IGF-1 levels and the number of joints with radiological evident lesions (joint space narrowing or/and erosions) (figure 6).

Analyzing the correlations between IGF-1 serum levels and inflammatory biomarkers in patients with chronic arthritis, we found a negative association (rho=-.426) with statistical significance (p=.038) between ESR values and IGF-1 levels (figure 7). Similarly, negative weak correlation (rho=-.356), but with no statistical significance (p=.088) was found between IGF-1 levels and CRP values (figure 8).

Evaluating the relationsheep between IGF-1 levels and the composite disease activity score (JADAS), there had been found a weak negative correlation (rho=-.341), but with no statistical significancy (p=.103) (figure 9).

Discussion

In our study we found no difference between mean IGF-1 levels in JIA patients and control group, but there were found significantly lower levels of IGF-1 in two subtypes of JIA: polyarthritis and systemic onset arthritis. Decreased IGF-1 levels in these two forms reflect reduced pituitary function with GH deficiency or insensitivity to GH due to chronic inflammation. In rheumatoid arthritis as well has been found a decrease in IGF-1 serum level in comparison with healthy subjects (9).

Even if it was not statistically significant in every case, our study showed a negative correlation of IGF-1 levels with the main parameters of disease activity: active joint number, ESR, CRP, JADAS score and number of joints with radiological evident lesions. Main limit of the study is the low number of cases, which could be responsible of the lack of significance. These results are in contradiction with the findings of some clinical studies performed in rheumatoid arthritis, which found no correlation between IGF-1 and CRP (10). Conversely, others studies showed that factors, which might contribute to growth suppression associated with childhood arthritis, include the degree, extent, and duration of disease activity (3).

IGF-1 is responsible for stimulating cartilage and bone extracellular matrix protein synthesis, thus decreased levels in juvenile arthritis could explain the growth disorders appeared in evolution of the disease (11). IGF-1 promotes muscle growth as well by stimulating muscle satellite cells and their differentiation. Conversely, when the levels of IGF-1 are insufficient or catabolic signals (e.g. glucocorticoids, cytokines) are increased, muscle wasting ensues (12).

In case of proved disturbance of GH-IGF-1 axis in polyarticular and systemic onset juvenile arthritis, the main controversial issue is the correct management of these JIA forms. Question is: is it enough to reduce disease activity, waiting the consequent correction of IGF-1 levels or should we intervene actively in IGF-1 produced bone and muscular growth disturbance by GH treatment? Two other questions arise further: is it efficient and is it safe to treat children with juvenile arthritis with growth hormone?

Growth hormone (GH) therapy proved to have many benefic effects in JIA: it has shown efficacy in controlling disease, positively influence body composition (increases bone mineral density and bone mass and changes bone geometry), accelerates growth velocity, increases height and promotes muscle mass recuperation (13). Despite benefic effects of GH therapy, there are, however, factors that may limit the statural gains achieved with GH, including severe inflammation, severe statural deficiency at GH therapy initiation, long disease duration and delayed puberty (13). In a four years long controlled study, Bechtold and co. showed that the mean improvement in height in the GH treated group was 1 SD, whereas the JIA patients of the control group lost 0.7 SD. Disease activity markers correlated significantly with the mean growth velocity standard deviation score. They concluded that children with mild or moderate disease and lower comedication grew and responded better to growth hormone therapy than those with active disease (14).

An earlier study of Davies and co. showed a significant increase in height velocity in almost all children during GH treatment. Children with mild to moderate disease activity grew at a better rate than those with very active disease, and children with polyarticular disease responded better than those with systemic JIA (15).

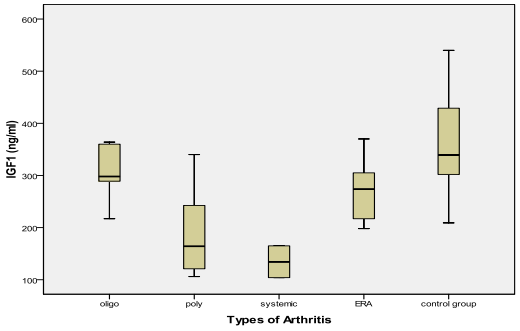

Figure 1. Comparison between IGF-1 levels in JIA subtypes and control group

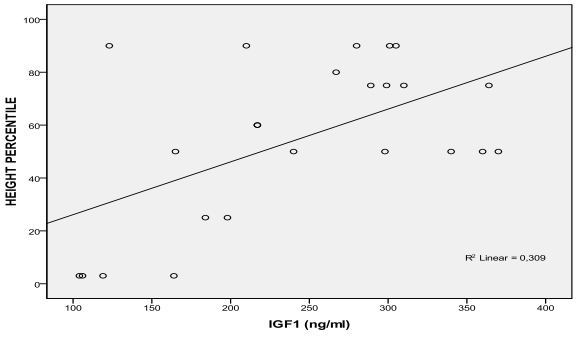

Figure 2. Correlation between IGF-1 levels and height percentiles

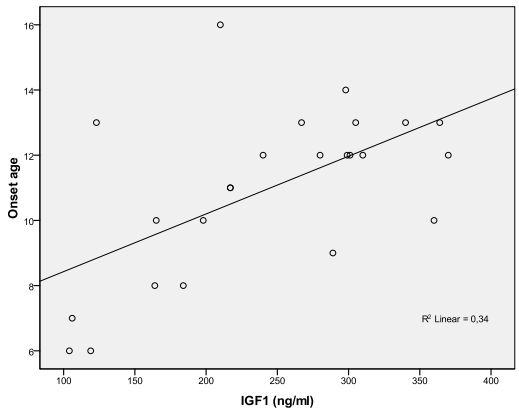

Figure 3. Correlation between IGF-1 levels and age of disease onset (years)

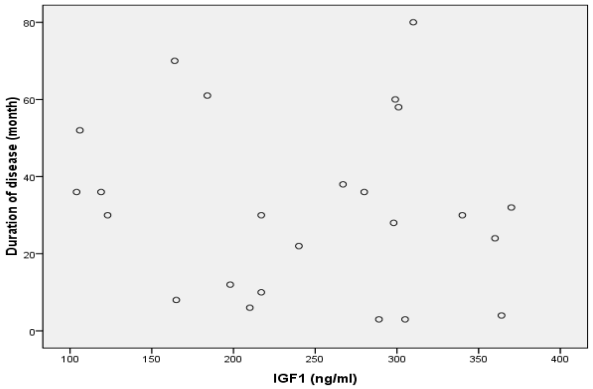

Figure 4. Correlation between IGF-1 and duration of disease (months)

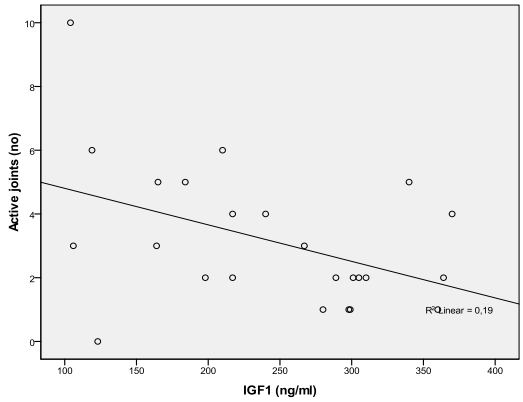

Figure 5. Correlation between IGF-1 level and active joint number

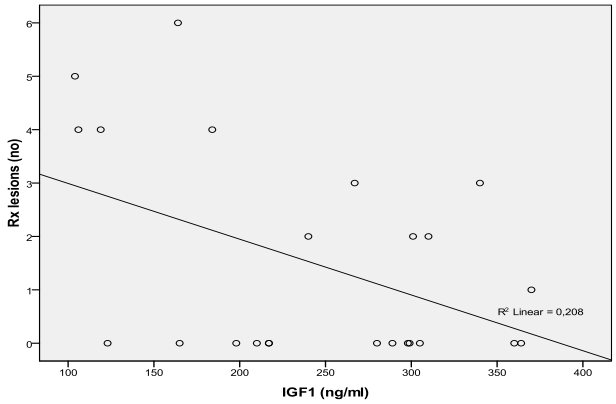

Figure 6. Correlation between IGF-1 level and Rx lesions

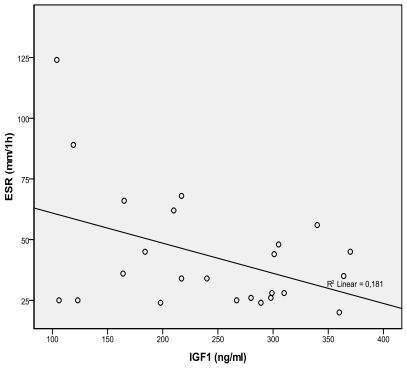

Figure 7. Correlation between IGF-1 levels and ESR

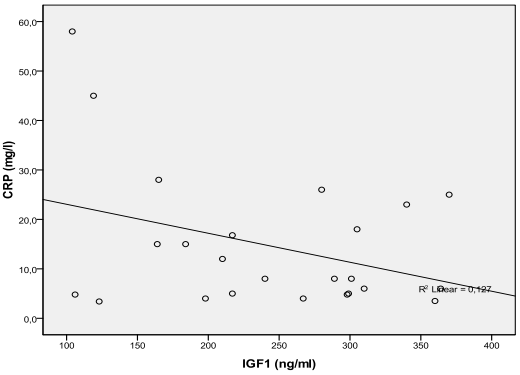

Figure 8. Correlation between IGF-1 levels and CRP values

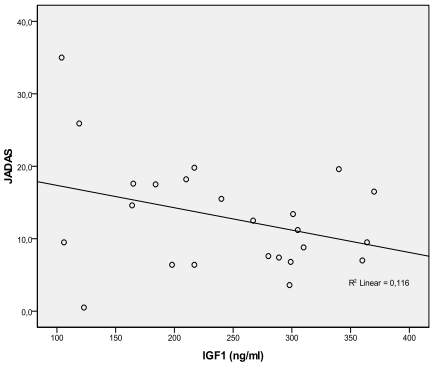

Figure 9. Correlation between IGF-1 levels and JADAS score

Davies highlighted that children receiving high dose GH grew significantly more than those on the low dose regimen. Saha and co. found a significant response to GH treatment, compared with placebo in most children (16). They treated 25 prepubertal children with severe growth retardation due to JIA with GH (6 months) and placebo (6 months afterwards).The median height velocity standard deviation score was +2.09 during the 6 month period of GH therapy and -1.11 during placebo treatment ($p = 0.0002$). The median height standard deviation score increased from -2.08 to -1.79 during GH treatment and from -2.18 to -2.02 during placebo ($p = 0.0268$). Saha and co. concluded that GH may be of benefit in the treatment of severe growth retardation in children with JIA, the response was seen after only 6 months and was independent of initial growth hormone status of the child (16).

GH treatment in children with chronic arthritis was proposed especially in cases treated with glucocorticoids. Simon and co. showed that GH treatment markedly increased growth velocity in JIA patients receiving steroid therapy, but had a minor effect on SDS height suggesting that these children will remain short at adult age (17). The study concluded that using GH earlier in these patients during the course of their disease may prevent growth deterioration and metabolic complications induced by chronic inflammation and long-term steroid therapy. Results of other studies suggested that GH may partially counteract the adverse effects of glucocorticoids on growth and metabolism in patients with chronic inflammatory disease (18). Mauras study showed that both GH and IGF-I may decrease the catabolic effects of chronic steroid use in humans, particularly by enhancing lean body mass accrual and, in children, by increasing linear growth (19). Ahmed and co. highlighted that both glucocorticoids and pro-inflammatory cytokines can adversely affect a number of components of growth plate chondrogenesis, and these effects can be ameliorated by raising local IGF-I exposure (1). However, this intervention does not lead to complete normalization of the growth plate. In children with chronic inflammation, the cornerstone of improving growth remains the judicious use of glucocorticoids while ensuring effective control of the disease process (1).Studies proved that GH treatment can normalize growth velocity and prevent the severe loss of height, however, catch-up growth markedly varies with the severity of the disease activity and the steroid doses used during GH treatment. Recently, early institution of GH treatment has been shown to maintain normal growth in children with JIA and has been proved its utility in preservation of long-term growth during disease progression (20).

Safety of GH treatment

Most of the studies proved no side effects due to GH therapy in JIA (14,16). However, GH treatment in JIA children can decrease insulin sensitivity but had only modest effects on glucose tolerance. Close monitoring by oral glucose tolerance testing is crucial before and during GH treatment, particularly during puberty and relapses (21). Available data on growth hormone therapy in glucocorticoid-treated children with JIA suggest a satisfactory safety profile. There have been few reports of adverse effects on the course of the joint disease (e.g., inflammatory flare-ups or osteoarticular complications). Despite strong concern that combined glucocorticoid and GH therapy might impair glucose tolerance, this has been uncommon in clinical trials (13). Davies and co. found that bone maturation did not exceed chronological age in GH treated JIA chidren (15).

The major objective in juvenile arthritis management is optimal disease control while maintaining normal growth. ACR recommendations are helpful guidelines in JIA treatment (22). Savendahl sustains that specific immunomodulatory therapy that targets the actions of TNFα is at least partially effective at rescuing linear growth in many children with JIA (23). Patients who do not respond to anti-TNF treatment may be candidates for therapeutic agents that target other pro-inflammatory cytokines and for GH intervention. Most of the physicians recommend close monitoring of growth velocity and bone mass accrual, and in some patients indicate additional medications such as growth hormone (24).

Timing of GH therapy initiation is also important because the extent of recovery following cytokine exposure of growth plates depends on the duration of exposure, and may be incomplete following longer periods of exposure (6). Early recognition of patients who develop prolonged growth disturbances and altered body composition is important as these abnormalities contribute to long-term morbidity and need to be addressed both diagnostically and therapeutically when treating children with JIA (25).

Although JIA is not an approved pediatric indication for GH treatment, it represents a promising area of investigation (26).

Conclusions

GH-IGF-1 axis is disturbed in polyarthritis and systemic JIA. In juvenile arthritis, IGF-1 serum levels appears to be inversely correlated to disease activity.

Careful monitoring of growth in children with JIA, especially in systemic and polyarticular forms, is mandatory. The main objective in juvenile arthritis therapy is represented by disease control through an efficient reduction of inflammatory process. However, GH therapy before onset of severe growth delay could be useful in maintaining normal growth and in preventing potential growth deterioration. Furthermore, in JIA children with growth disturbances, GH therapy could be a useful tool in the growth catch-up process.

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ENDOCRINE POLYMORPHISM OF CHILDHOOD NEURIFIBROMATOSIS

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Abstract:

Introduction: Neurofibromatosis (NF) is an autosomal dominant disorder with a multisystemic involvement and a variety of problems presented in childhood. ***Objectives:*** The authors aimed to evaluate the endocrine pathology associated to patients diagnosed with NF. ***Material and method:*** Patients (0-18 years old) diagnosed with NF and admitted to the Endocrinology Departament of "Louis Turcanu" Children Emergency Hospital were studied over a period of 5 years from 2007 to 2012. The study protocol consisted in the family and patients' history, physical examination and anthropometric measurements. Serum levels of TSH, FT4 and FT3, GH, LH, FSH, testosterone or estradiol, DHEA, 17 OH progesterone, cortisol, adrenaline and prolactin were measured. The imagistic examination depended of cases and consisted in radiography, pelvic ultrasound or head MRI. ***Results and discussions:*** Our study lot comprised 12 patients (3 months to 18 years and 6 months) diagnosed with NF (type I - 91.6%) with a sex ration male: female 1:2. 33.4% children had a parents known with NF. Regarding of endocrine pathology associated, 58.4% of them had short stature secondary to GH deficiencies and one boy had gigantism caused by optic pathway gliomas responsible for GH hypersecretion. Half of the girls had abnormal menses due to the polycystic ovary syndrome. No cases of hypothyroidism or pheochromocytoma was encountered. ***Conclusions:*** Although NF pictures are characteristic, other rare conditions including endocrine pathology can be associated so clinical clues should be always sought and investigation should be performed for in these circumstances.

Introduction:

Neurofibromatosis (NF) is an autosomal dominant disorder, a heterogeneous multisystemic neurocutaneous disorders involving both neuroectodermal and mesenchymal derivatives, probably of neural crest origin, which can involve any organ system. The National Institutes of Health Consensus Development Conference has defined 2 distinct types: neurofibromatosis type 1 (NF1), or von Recklinghausen disease, which affects 85% of patients, and neurofibromatosis type 2 (NF2), or bilateral acoustic neuromas/vestibular schwannomas, which affects 10% of patients.

The manifestations of NF1 are the result of a mutation in or deletion of the NF1 gene responsible for the production of neurofibromin. Its role consists in tumor suppressor while its decreased production is associated with clinical manifestations. The NF2 gene product known as merlin serves as a tumor suppressor. Decreased function or production of this protein results in a predisposition to develop a variety of tumors of the central and peripheral nervous systems .

Multisystemic involvement is common, and a variety of problems may present in childhood. Some frequent pathology associated are optic and acoustic involvement, intracranial and spinal tumors, and an increased incidence of malignancies, endocrine disorders, autonomic involvement, GI tract involvement, hypertension, and vascular anomalies .

Objective:

The authors aimed to evaluate the endocrine pathology associated to patients diagnosed with NF .

Material and metod:

Patients (0-18 years old) diagnosed with NF and admitted to the Endocrinology Departament of "Louis Turcanu" Children Emergency Hospital were studied. Out study took place on a period of 5 years from 2007 to 2012. All these patients presented to our departments for other complaints and not those characteristic for NF. They were diagnosed with NF according to the following criteria :

1. Six or more café-au-lait macules, the greatest diameter of which is >5 mm in prepubertal patients, and >15 mm in post-pubertal patients
2. Freckling in the axillary or inguinal region
3. Two or more neurofibromas of any type or one plexiform neurofibroma
4. Two or more Lisch nodules in the iris
5. Optic glioma
6. A distinctive osseous lesion such as sphenoid dysplasia or pseudoarthritis
7. A first-degree relative with NF1 diagnosed according to the preceding criteria

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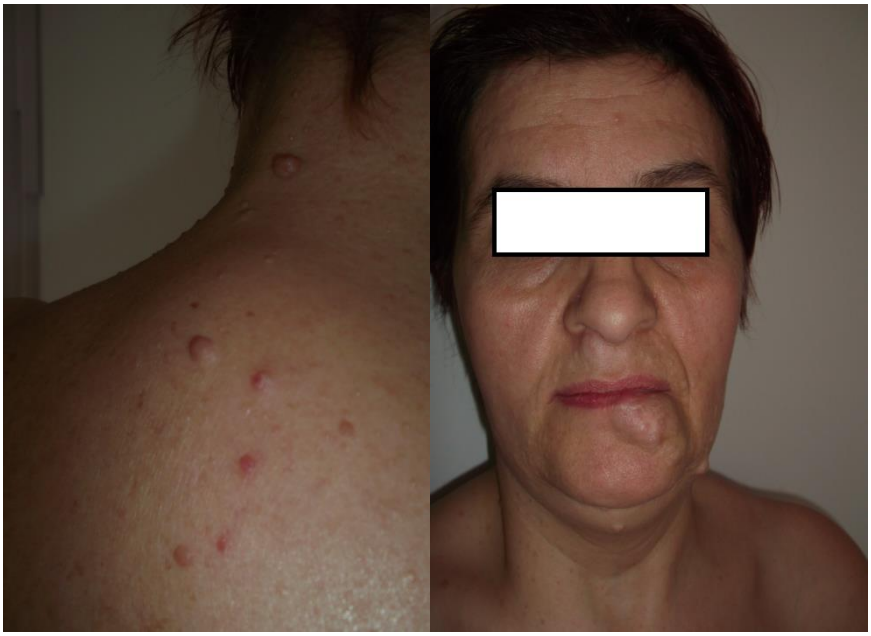

Figure 1 and 2: Clinical aspects of parents of RR child with NF

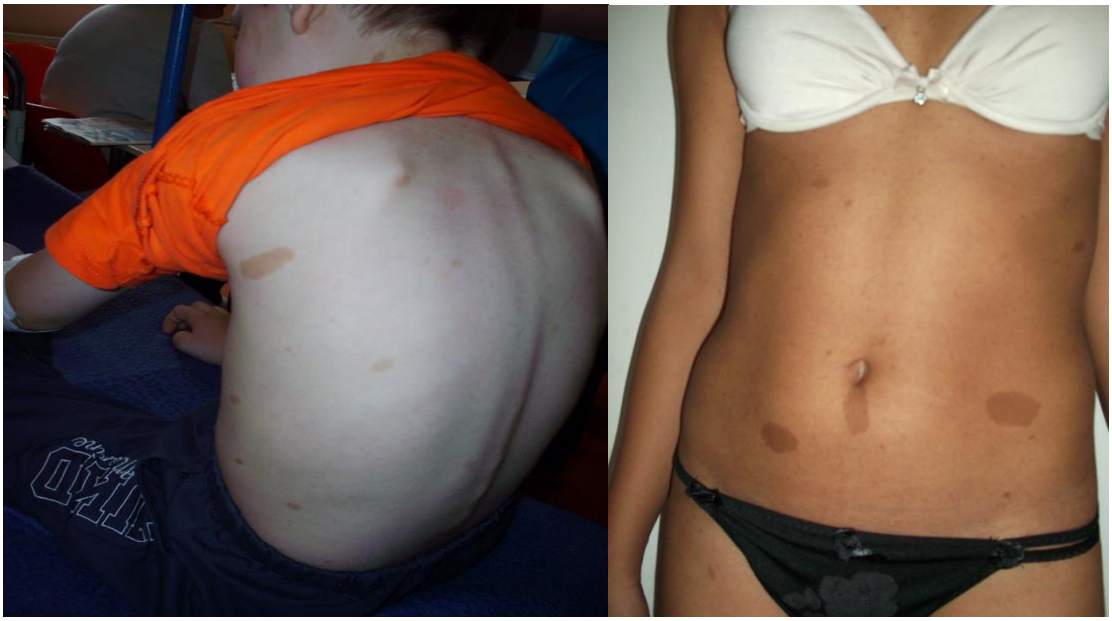

Figure 3 and 4: Clinical aspects - café-au-lait macules in IV boy 8 years old and RR 15 years old

Family's and patients' medical history were noted. They were clinical examined and anthropometric data (height, height standard deviation score, weight, body mass index, growth velocity) were measured clinically. Also it was noted the stage of pubertal development according to the Tanner criteria. Blood pressure was measured periodically and Holter examination performed in selected cases.

Serum levels of thyroid stimulating hormone, free T4 and T3, lutheinizing hormone, follicle stimulating hormone, testosterone or estradiol, DHEA, 17 OH progesterone , cortisol, adrenaline and prolactin were measured in all patients periodically. Catecholamine, metanephrine and vanillylmandelic acid levels in the 24-h urine collection were tested in order to diagnosed pheochromocytoma. The pituitary growth hormone reserve and the stimulating

growth hormone test and the serum level of IGF1 was assessed in patients with height deficiency.

Bone age determinations were performed at every year in selected cases. Other imagistic evaluation consisted in pelvic transabdominal ultrasounds and head MRI scan in cases with neurological symptoms.

Data were statistically analyzed using SPSS version 16.00. This study complied with the Declaration of Helsinki and has been approved by our institutional Ethics Committe somatostatinergic tone, increased GH release and loss of pulsatility . Specific tumor therapy is not indicated for this patient in the absence of mass effect or visual disturbance, but when these manifestations are presented, surgery, radiation, and/or chemotherapy should be done. Medical literature recommended the treating of GH excess with somatostatin analogue (Octreotide). Sometime, precocious puberty can developed as a side effect of this treatment . Unfortunately his parents refused any treatment and other medical advices because they belong to specific religious group.

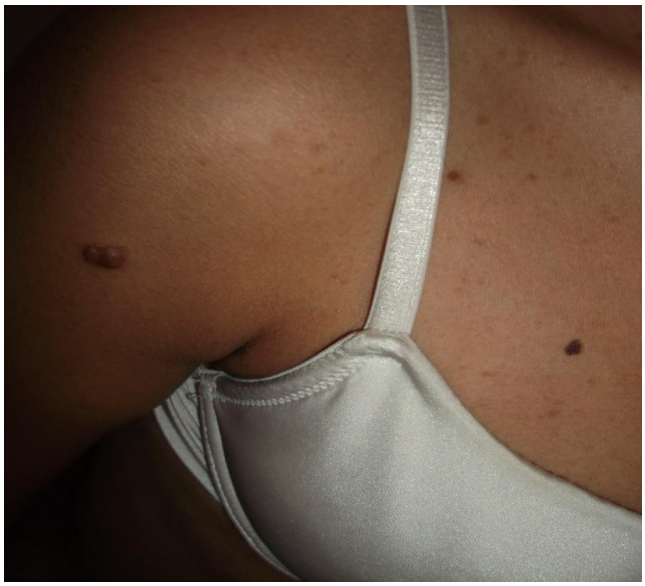

Figure 5: RR 15 years old clinical aspect – neurofibromas

Results and discussions:

Our study lot comprised 12 patients diagnosed with NF with a sex ration male: female 1:2. The patients' age ranged between 3 months to 18 years and 6 months. Only 4 children had their parents known with NF (Figure 1 and 2).

All the patients fulfilled the needed criteria, the majority of them being diagnosed as type I of NF (91.6%).

Regarding the anthropometric data, the majority of patients had short stature (58.4%) for their age as presenting in figure 6.

These patients with short stature (defined as a height that is equal to or more than 2 standard deviations below the population mean) had lower values of basal and stimulated GH (using clonidine or insulin-induced hypoglycemia as GH secretagogues) secondary to GH deficiency. (Figure 7). It is well known that short statute a feature of NF1, affecting approximately 13% to 24% of prepubertal patients and >40% of adults . In our study the prevalence of short stature was higher. Short stature associated with NF1 usually affects the skeleton symmetrically but scoliosis or deep plexiform neurofibromas, or the use of psychostimulant medications for the treatment of attention deficit disorder characteristic to the NF can interference with the normal skeletal development , . In our cases, 4 patients associated mild form of scoliosis with good evolution and without the need of surgical treatment.

One boy was diagnosed with gigantism secondary to the GH hypersecretion. Elevated serum level of prolactin was observed also. His MRI revealed the presence of optic pathway gliomas responsible for this hypersecretion. The mechanism consisted in the infiltration of the somatostatinergic pathways by the tumor leading to loss of

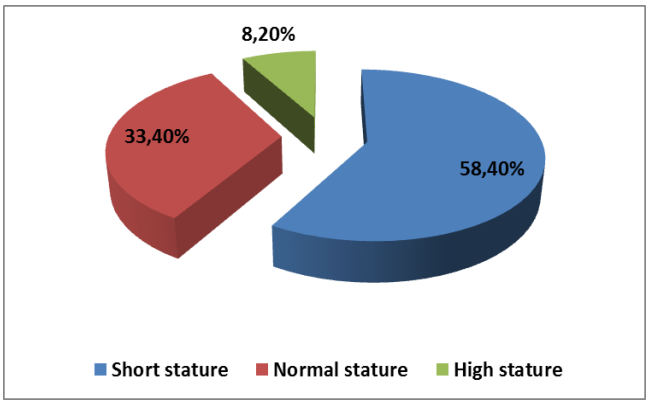

Figure 6: Distribution of patients studied according to their height

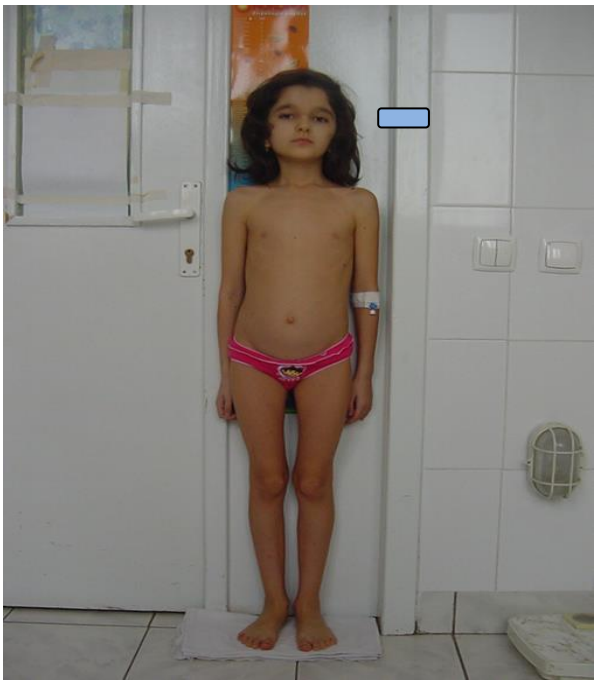

Figure 7: AD 19 years with NF and short stature

In children with NF, the most prevalent hormonal disorder is central precocious puberty, with a frequency of 3% compared to 0.06% in the general pediatric population . Half of the girls had polycystic ovary syndrome suggested by abnormal menses, increased values of DHEA, 17 OH progesterone and characteristic aspects at transabdominal pelvic ultrasound.

Pheochromocytoma is the most common endocrinopathy in adults with NF1, occurring in approximately 1% of adult patients and 0.1%-5.7% in children , but we have encountered no patients with such pathology in this study. Four children with NF had increased values of blood pressure at Holter examination, but their laboratory data were normal and no other suggestive clinical signs or symptoms were presented.

Conclusions:

NF is one of the most common phakomatoses encountered worldwide. Although its clinical pictures is characterized by the associations with intracerebral tumours, in specific scenario, other rare associations including endocrine pathology should be kept in mind, and clinical clues and investigations should be always sought for in these circumstances.

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A RARE CASE OF FAILURE TO THRIVE IN INFANTS: MALIGNANT INFANTILE OSTEOPETROSIS

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Abstract

Background: Malignant infantile osteopetrosis (MIOP) is a rare autosomal recessive bone disease, characterized by reduced or dysregulated osteoclastic activity and increased bone mass. Major consequences include bone marrow failure and nerve compression. Chronic anemia, feeding problems caused by bulbar nerve involvement and recurrent infections as well as bone growth in diameter and not length leads to failure to thrive (delayed growth, weight gain, and development), seen in many osteopetrotic children. The pericentric inversion of chromosome 9 is the most frequently found in general population and has a role in abnormal phenotype development. ***Material and methods:*** Case report of a 6 months old boy with 3 admissions, first at the age of three months for hypocalcemic seizures. Based on the dysmorphic phenotype,presence of anemia, severe hypocalcemia, hepatosplenomegaly, failure to thrive, mental retardation, ventriculomegaly, optic nerve atrophy and the typical radiological images diagnose of MIOP complicated by rickets was established. Failure to thrive was defined based on persistent weight and waist below the 5th percentile. Genetic evaluation for chromosome abnormalities revealed apericentric inversion of chromosome 9. ***Conclusions:*** MIOP is a rare disease which can present with nonspecific symptoms; therefore it has to be considered in case of craniofacial bones abnormalities, severe hypocalcemia, anemia and early onset failure to thrive. The association of osteopetrosis complicated by rickets and chromosome 9 inversion led in our case to severe dysmorphic features and severe growth restriction.

Key word: osteopetrosis, failure to thrive, chromosome 9 inversion

Introduction

Osteopetrosis, also referred to as 'marble bone disease', is an inherited disease characterized by failure of osteoclasts to resorb bone making bones abnormally dense and prone to fracture. Impaired bone modeling and remodeling and defect in bone turnover result in skeletal fragility despite increased bone mass and may also lead to insufficient hematopoietic activity. The disease was firstly described by Albers-Schönberg in 1904 1. To date, researchers have described at least eight types of osteopetrosis in humans distinguished by their pattern of inheritance and by by the severity of their signs and symptoms (4). Autosomal dominant osteopetrosis (ADO), also called Albers-Schönberg disease, with onset in late childhood and adolescence. It is the most common form with good prognosis (5) and an incidence of 1: 20-500.000 children. Autosomal recessive osteopetrosis (ARO) or malignant infantile osteopetrosis (MIOP) is the autosomal recessively inherited form. This form has an early onset , during infancy, and a poor prognosis. It this case the incidence is 1: 200.000 children. Although rare, MIOP should be considered in children with failure to thrive . A cause of short stature in children with MIOP is abnormal bone development, bone grows in width and not lenght.

Case report

The patient M.T., 6 month old male infant, with repeated admissions in our clinic, presented at the age of 3 months seizures due to severe hypocalcemia. At the first hospitalization, at the age of three months, during the physical examination, a dismorfic phenotype was observed: plagiocephaly (bilateral parietal and temporal flattening with prominent frontal and occipital regions), high forehead, frontal bossing, head circumference > 97th percentile, microretrognathia, asymmetry of the ears, the left ear inserted below, bulging anterior fontanelle with a diameter of 4.5 / 4 inches, sunsetting eyes sign, ogival palate. Further inspection detected a slightly flared thorax, distended abdomen,the liver with the inferior margin palpable at 4 cm below the costal margin and the spleen palpable at 2 cm below the costal margin. Based on the presence of anemia, hypocalcemia, hepatosplenomegaly, failure to thrive, mental retardation, ventriculomegaly, optic nerve atrophy and the typical radiological images diagnose of MIOP complicated by rickets was established.

Failure to thrive was defined based on persistent weight and waist below the 5th percentile. (Fig.1) Genetic evaluation revealed a pericentric inversion of the chromosome 9. Treatment with high doses of calcium (50 mg / kg / day) and active vitamin D (calcitriol-0, 3 ug / kg / day) showed a slow biological improvement. After 1 month of treatment, the vitamin D levels normalized while the PTH levels remained high.

Paraclinical findings showed abnormal hypocalcemia, anemia, low vitamin D levels and high PTH levels. 25-OH Vitamin D3 = 19.4 ng/l - 3 months; = 36,4 ng/l – 3 months 2 weeks; - .NV. > 30 ng/l (fig. 2, 3,4, 5, 6, 7)

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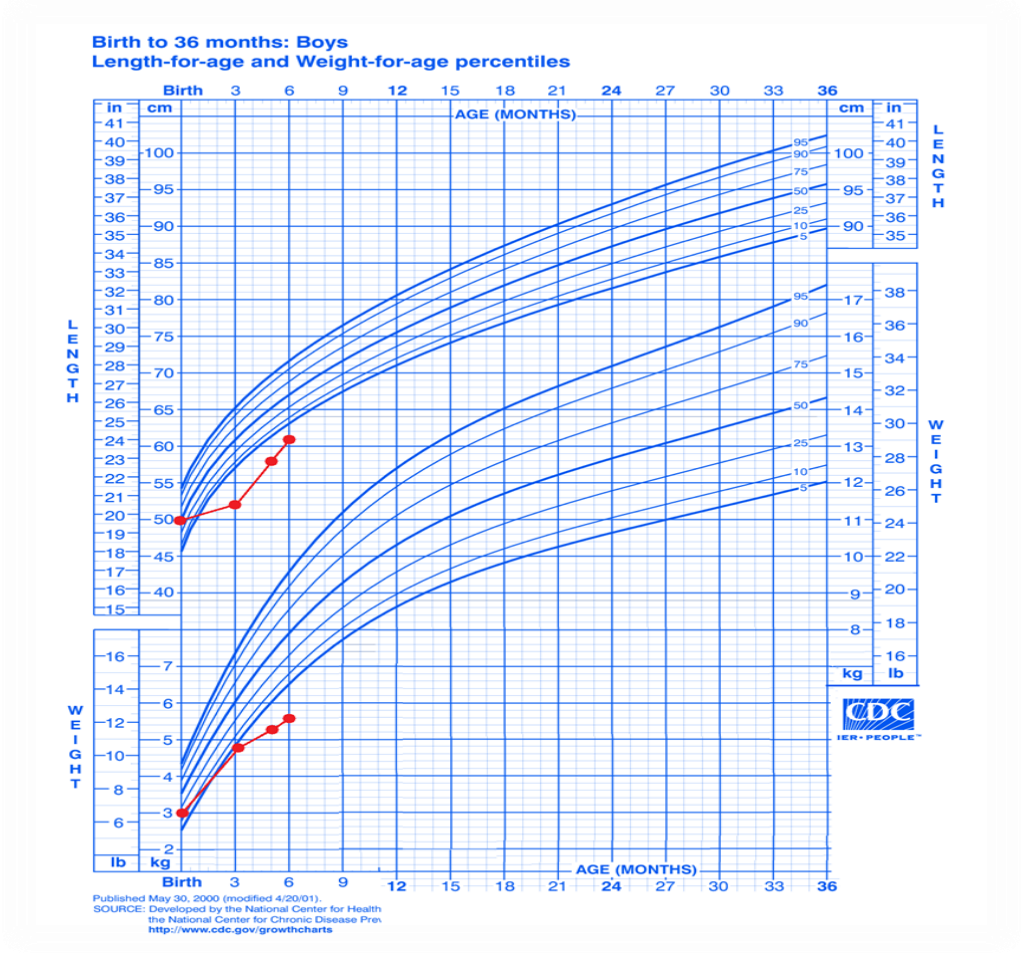

Fig. 1 Lenght and weight evolution of the patient at 3, 5 respectively 6 months.

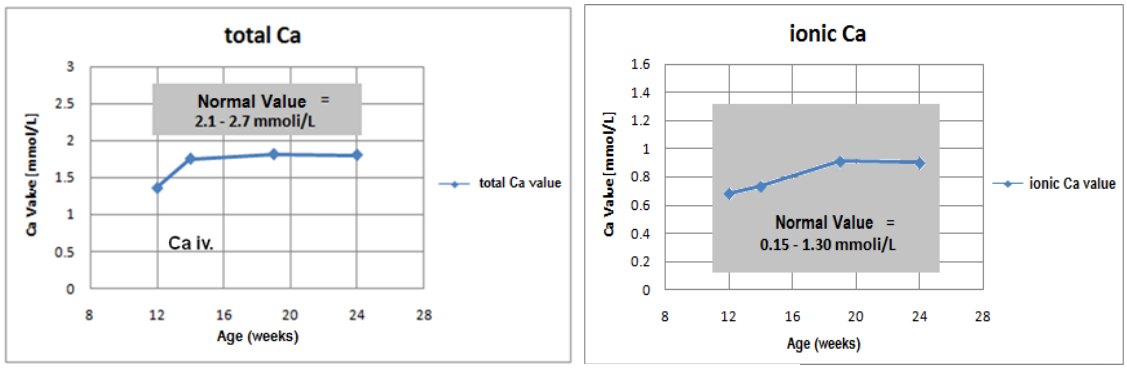

Fig. 2 Evolution of the calcium levels

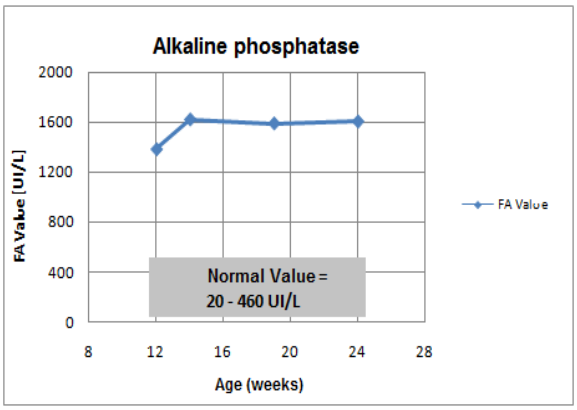

Fig. 3 Levels of alkaline phosphatase

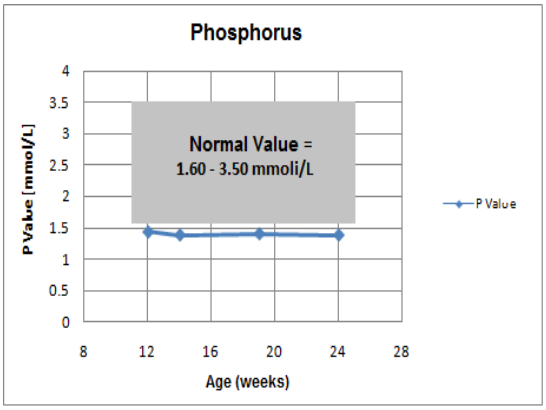

Fig. 4 Phosphorus values

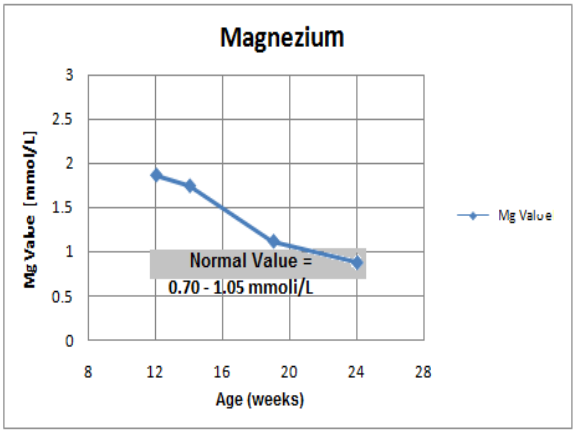

Fig. 5 Magnesium values

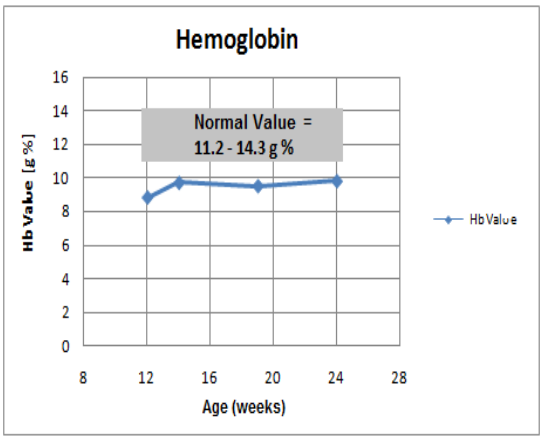

Fig. 6 Hemoglobin values

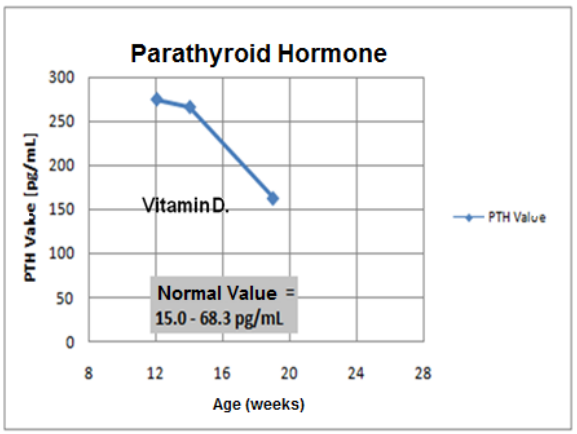

Fig. 7 Parathiroid hormone level

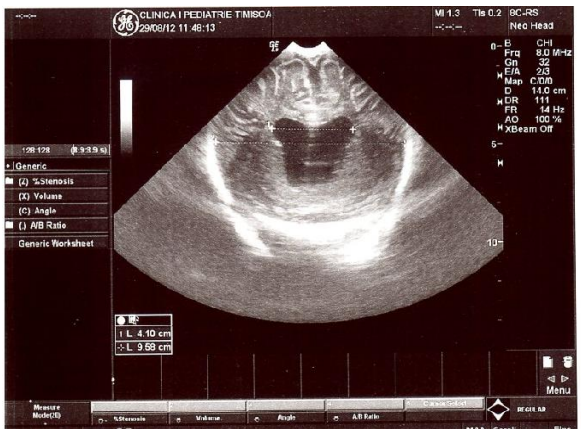

Fig. 8 transfontanelar ultrasound: Bilateral Ventriculomegaly

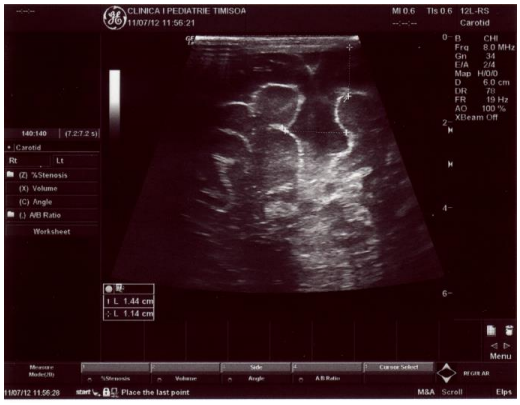

Fig. 9 Transfontanelar ultrasound: Mild cerebral atrophy

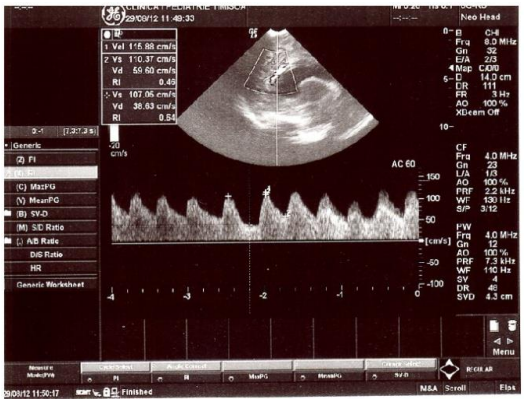

Fig. 10 Transfontanelar Doppler: Anterior cerebral arterial resistivity index (RI)

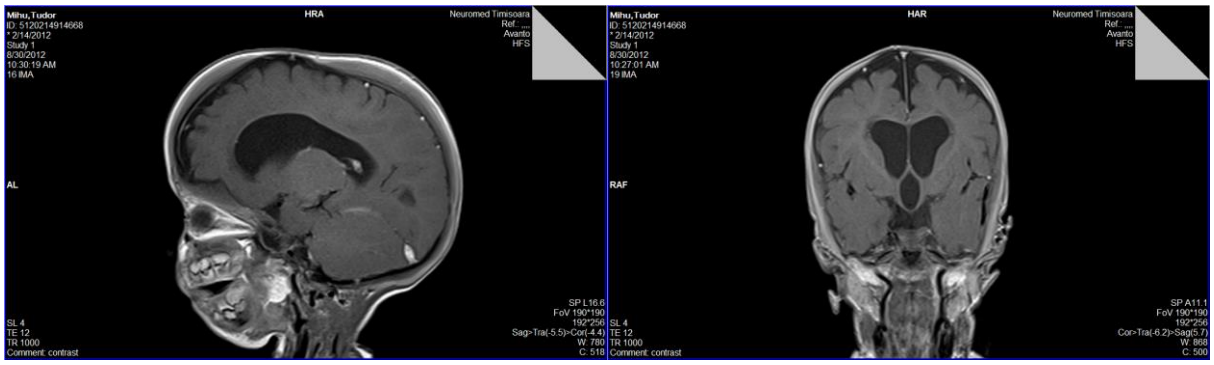

Fig. 10 MRI: Hypertrophy of the cranial bones Fig.11 MRI: Tricameral ventriculomegaly

Thoracic X-Ray showed rachitic cupes on the ribs and proximal humerus.

Imaging, transfontanelar ultrasound revealed ventriculomegaly and cerebral atrophy without signs of incrisead intracranian pressure (delta RI<15) (Fig.8, 9, 10)

MRI: Moderate tricameral ventriculomegaly, without signs of activity. Homogenous hypertrophy of the cranial bones, more pronounced at the bones of the base of the skull with secondary volume reduction of the cranial cavities. (Fig.11, 12)

Discussions

High Calcitriol doses stimulate the bone resorbing function of the osteoclasts, with slow biological improvements.

Levels of parathyroid hormone and alkaline phosphatase were raised in our patient. Elevated alkaline phosphatase is a sign of defective bone mineralization, while high serum levels of parathyroid hormone are caused by decreased calcium levels. Defectuous bone resorption due to damaged osteoclasts and vitamin D deficiency lead to severe hypocalcemia.

Vitamin D dosage and bone X-Ray images have revealed signs of rickets. The PTH levels decreased after the correction of the vitamin D deficiency, remaining at elevated levels.

Faliure to thrive occurs due to the dysfunctional osteoclasts resulting in bony overgrowth, bones that are abnormally dense and brittle. This defect prevents the normal development of marrow cavities, the normal tubulation of long bones and the enlargement of osseous foramina.

Conclusions

MIOP has a poor prognosis unless treated early with haematopoietic stem cell transplantation. It remains essentially unrecognized as a cause of neonatal hypocalcemia and often leads to diagnostic delays and confusion.MIOP should be considered in the differential diagnosis of idiopathic neonatal hypocalcemia refractory to treatment or requiring correction doses.

While it may seem a paradox, osteopetrosis and rickets, cases in literature are described as a complication, resulting from the inability of osteoclasts to maintain a balance of Ca-P in the extracellular fluid.

The association with chromosome 9 inversion accentuates the severe dysmorphic features, with no clinical significance in the disease progression.

Although rare, MIOP should be considered in children with failure to thrive . A cause of short stature in children with MIOP is abnormal bone development, bone grows in width and not lenght.

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PREDISCHARGE GROWTH PATTERNS IN VLBW INFANTS

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Abstract

Introduction: VLBW preterm infants with postnatal growth restriction have a higher risk of morbidity and mortality. ***Objectives:*** The goal of this study was to determine the degree of extrauterine growth restriction in selected VLBW infants admited during ianuary 2011-december 2012 in the Neonatal Ward. ***Methods:*** Z-scores for birth weight and discharge weight were computed using Fenton's reference. They were compared to the median weight of a fetus of comparable gestational age based on an intrauterine growth reference. ***Results:*** The studied newborns were delivered with birth weight ranging from 700g to 1480g (mean birth weight = 1200g) between 26 to 32 weeks (mean gestational age = 29.2 weeks). 33% were small for gestational age. Mean z-score at discharge (-1.4), was lower than the mean z-score at birth (-0.58). Twice as many babies (68% vs 33%) were growth restricted at discharge compared to at birth. 87% of these experienced feeding intolerance and acute infections therefore requiring parenteral nutrition and invasive procedures as part of their management. ***Conclusion:*** The majority of the studied VLBW infants experienced a growth lag during their stay in the Neonatal Ward mostly as a reflection of their feeding intolerance and concurrent morbidities.

Key words: preterm VLBW, z score, growth restriction

Introduction

Very low birth weight (VLBW) infants represent about 1–1.5% of all liveborn infants in developed countries [1], and they constitute the large majority of the population in neonatal intensive care units (NICUs). Infants born VLBW are at increased risk for impaired growth, due to certain prenatal factors [2] and to concurrent morbidities. The prevention of postnatal growth restriction of these infants is extremely important because of its impact on the subsequent psychomotor development [3], and still represents a challenge for neonatologists [4].

Objectives

The aim of the present study was to determine the prevalence and degree of predischarge growth restriction in selected VLBW infants and to identify the factors affecting growth.

Methods

We conducted this retrospective study on a number of 62 selected preterm infants with birth weight less than 1480g. Data regarding birth-weight, discharge-weight and morbidities was extracted retrospectively from neonatal database of VLBW infants admitted between 1/1/2011 and 31/12/2013 in the Neonatal Ward of the Children's Hospital "Louis Turcanu" Timisoara. Exlusion criteria included the presence of major chromosomal or congenital anomalies, necrotising enterocolitis and surgery within the first month of life. Z-scores for birth weight and discharge weight were computed using Fenton's reference. They were compared to the median weight of a fetus of comparable gestational age based on an intrauterine growth reference.

Results

The studied newborns were delivered with birth weight ranging from 700g to 1480g, with a mean birth weight of 1200g. The gestational age ranged between 26 to 32 weeks with a mean of 29.2 weeks. There was no significant gender difference in the prevalence: 57% were male and 43% were female.

One third of these infants were small for gestational age (SGA).

Detailed nutritional data were collected daily. Composition and volume of intravenous solutions, and type and volume of enteral feedings, including caloric additives, were recorded. The majority of infants weighing less than 1200g had difficulties regarding their digestive tolerance therefore requiring partial or total parenteral nutrition. Of those with enteral tolerance only approximately 42% received maternal milk accompanied by human milk fortifiers, the rest were fed with adequate artificial milk formulas for preterms.

Mean z-score at discharge (-1.4), was lower than the mean z-score at birth (-0.58). Twice as many babies (68% vs 33%) were growth restricted at discharge compared to at birth. 87% of those with postnatal growth restriction experienced feeding intolerance and acute infections therefore requiring parenteral nutrition and invasive procedures as part of their management (central venous lines, numerous venous blood samples, long-term use of broad spectrum IV antibiotics, endotracheal intubation and mechanical ventilation).

Discussions

Preterm infants are at risk for potential nutritional compromise due to their limited nutrient reserves, immature metabolic pathways, and increased nutrient demands that can rarely be met [5]. Extrauterine growth in VLBW infants begins with a period of weight loss usually up to 15% body weight, that will most commonly be regained in the next 14-21 days of life [5]. In our case the mean initial weight loss was ~ 13.7%, and it was regained in the first 17-24 days of life in the majority of cases.

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Implementation of early parenteral and enteral nutrition to low birth weight infants during the first 24 hours of life results in higher weight velocity, and earlier achievement of full enteral feedings [6]. However, this strategy is often limited by the infant's ability to metabolize the nutrients and by the potential complications that may arise from hyperhydratation (eg, the likelihood of patent ductus arteriosus or chronic lung disease that) [7,8]. In our Ward the tendancy was to avoid sodium administration in the first 24-48h, unless there were major electrolyte imbalances, in order to avoid delayed contraction of the extracellular fluid.

In the past the Lubchenco growth chart was the most commonly used in NICUs, which was not gender specific. Of late, the Fenton fetal-infant chart has received more attention, based on more recent infant data, from a more wider geographical area. Using this chart the preterm's growth can be monitorised up to 50 weeks postmenstrual age with better confidence in the extreme percentiles [9].

The recommended growth velocity of 15 g/kg per day is intended to approximate intrauterine growth rates [10]; however it is often not achieved [11].

Predictors of postnatal growth restriction in preterm infants include lower birth weight and gestational age at birth, illness severity at birth, nosocomial infections, prolonged respiratory support need [12] and feeding tolerance. The infants from the study with gestational age under 30 weeks were the most affected by postnatal growth restriction, as the majority of them associated feeding intolerance, infectious intercurrencies and the need for assisted ventilation. Feeding intolerance, recognized by the presence of gastric residuals, occurs frequently in very low birth weight infants [13]. The inability to sustain enteral feedings contributes to extended periods of parenteral nutrition, often requiring central venous access, and increasing the risk of infection [5]. However, tolerating adequate enteral nutrition is difficult due to the immaturity of the VLBW infants' gastrointestinal system [5]. In our case, the infants with gestational age above 30 weeks, that presented enteral tolerance, were initially started on nasogastric feeding, proceeding later on at botlle feeding as soon as they developed swallowing reflex and breathing-swallowing coordination (35-36 weeks postmenstrual age).

Mean z-score at discharge (-1.4), was lower than the mean z-score at birth (-0.58), with twice as many babies (68% vs 33%) being growth restricted at discharge compared to at birth. This may be due to the accumulation of significant energy, protein, mineral and other nutrient deficits during their hospital stay correlated to their concurrent morbidities.

However, in the vast majority of the cases, once they reached 2000g the growth velocity increased significantly.

Conclusion

Extrauterine growth restriction remains a serious problem in critically ill VLBW premature neonates.

The majority of the studied VLBW infants experienced a growth lag during their stay in the Neonatal Ward. The most important factors contributing to poor postnatal growth were low gestational age, the need for assisted ventilation, and concurrent morbidities such as anemia, sepsis and respiratory disorders (bronchopulmonary dysplasia).

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ENDOCRINE CHANGES IN A MECHANICALLY VENTILATED GIRL WITH ANOREXIA NERVOSA

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Abstract

Introduction: Anorexia nervosa (AN) is an eating disorder and also a psychiatric disorder, characterized by a weight well below the standard weight due to a distorted image of the body with obsessive fear of weight gain. ***Material and method:*** We present the case of a 10 years old girl weighing 16 kg (body mass index BMI = 8.16 kg/m2), who was hospitalized in the Pediatric Clinic for loss of appetite, inability to walk and maintain orthostatism, with motor deficit on the right side of the body. The onset was affirmative five months ago, after separation from the mother (gone abroad), the child being left in the care of a grandmother. Twenty-four hours after admission, the girl experienced periods of voluntary apnea, requiring endotracheal intubation and mechanical ventilation. ***Results:*** Endocrine balance showed in this case: elevated cortisol levels, low levels of follicle stimulating hormone (FSH), estradiol and testosterone; high levels of growth hormone (GH) and low levels of insulin-like growth factor (IGF-I); low levels of thyroid hormones (T3 and T4) and slightly decreased thyroid-stimulating hormone (TSH). During the 96 days of hospitalization, the patient required the placement of a tube tracheostomy to continue mechanical ventilation and a PEG (percutaneous endoscopic gastrostomy tube) for enteral nutrition. Weight gain was 4 kg. The patient died due to infectious complications after 6 months following hospitalization in another center. ***Conclusions:*** Endocrine changes that occur in AN are secondary to physiological adaptation of the body to a state of starvation. AN and the associated malnutrition that occurs through self-imposed starvation can cause severe organic and psychological complications and can even lead to death.

Introduction

Anorexia nervosa (AN) is an eating disorder, and according to ICD-10 (international classifications of disease), diagnostic criteria for AN are: (a) Body weight is consistently 15% less (or lower) than that expected for height and age, or body mass index is 17.5 or less. This can be due to either weight loss, or failure to gain weight during growth. (b) Weight loss is caused by the avoidance of foods. (c) Distorted body image perception driven by an intense, irrational fear of becoming fat, leads to the desire to remain at a low body weight. (d) Amenorrhea in women, and loss of libido in men. There may be changes in growth hormone, cortisol, thyroid hormone and insulin. (e) Puberty in girls and boys may be delayed if the onset of anorexia nervosa is prepubertal, but once recovery from the illness is made, it will often progress normally.

AN affects 0.3-0.6% of the female population worldwide (1) and has the highest mortality rate of any psychiatric disorder, between 5-18% (2,3,4). AN is more common seen in female patients between the ages of ten to thirty years, with the greatest incidence at seventeen to eighteen years of age (5).

Over the last few years, many epidemiological and risk factor international studies have provided solid evidence on the role that genetic factors play in AN as well as on the influence of socio-cultural factors (6,7).

Endocrine disturbances in AN are complex and aims the hormones secreted in pituitary –adrenal, –thyroid, and –gonadal axes and represent a body response to starvation. For a better understanding of the physiology of AN it is essential to understand the physiology of starvation (8). The starvation response consists of three phases (9,10). Phase one is short and represents the period when the consumed meal has been digested. In this phase glycogen is not stored for energy. Phase two appears when glycogen stores completely deplete and this stage is responsible for many of the physiological and biochemical alterations in the body. Increase in free fatty acids (FFA) lead to an increase level of fibroblast growth factor-21 who mediates growth hormone (GH) resistance and reduces (insulin-growth-factor-1) IGF-1 levels (11). Further, if starvation continues, the fat stores exhaust and the body enters phase three of starvation. During this phase, there is a breakdown of muscle tissue and the amino acids liberated are used in the formation of glucose for maintaining brain function. Therefore, adapting to starvation involves reducing energy expenditure by suppressing metabolic rate, body temperature and delaying growth (12,13).

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Table I. Summary of vital signs from the initial physical examination in ICU.

Initial vital signs	
Pulse (bpm)	120
Blood pressure (mmHg)	120/65
Breathing (bpm)	0
Weight (kg)	16
Height (cm)	140
BMI (kg/m2)	9.18
Body temperature (°C)	36.2

Table II. Summary of the initial laboratory screening.

Initial laboratory screening		Reference values
Hemoglobin (g/dL)	14.4	11.0 – 15.0
RBC ($x10^6$ mm^3)	4.6	4.0 – 6.0
WBC ($x10^3$ mm^3)	11.3	4.0 – 12.0
Platelets ($x10^3$ mm^3)	360	150 - 400
CRP mg/L	0.26	0 – 5
Sodium (mmol/L)	135	135 - 145
Potassium (mmol/L)	4.0	3.5 – 4.5
pH	7.20*	7.35 – 7.45
PaO2 (mmHg)	46*	80 – 120
PaCO2 (mmHg)	>115*	40 – 50
Base excess (mmol/L)	-18*	-2 – 2
Glucose (mg%)	178*	80 – 120
ASAT (U/L)	25	2 – 31
ALAT (U/L)	23	2 – 32
TP (g/L)	73.9	60 – 80
Creatinine (µmol/L)	18*	45 – 75
BUN (mmol/L)	3.27	1.4 – 8.3
Lipids (g/L)	3.8*	5.0 – 8.0
Triglycerides (mmol/L)	0.5*	0.7 – 1.7
Cholesterol (mmol/L)	3.0*	3.1 – 5.20

Table III. Endocrine status

Endocrine status		**Reference values**
Cortisol nmol/L	680 ↑	171 - 536
FSH mIU/ml	0.13 ↓	0.3 – 11.1
Estradiol pg/ml	4.6 ↓	6.0 – 27.0
Testosterone ng/ml	0.02 ↓	0.050 – 0.522
GH ng/ml	34 ↑	< 20
IGF-I ng/ml	60 ↓	88 - 452
T3 pmol/L	3.7 ↓	4.1 – 7.9
T4 pmol/L	10.2 ↓	11.6 – 21.5
TSH µIU/ml	0.60 ↓(slight)	0.66 – 4.14

↑ above normal ranges
↓ below normal ranges

The onset was affirmative five months ago, after separation from the mother (gone abroad), the child being left in the care of a grandmother. The girl derived from a disorganized family (the parents are separated) and had difficulty in adaptation to a new school and a new environment.

Case report

We present the case of a 10 years old girl weighing 16 kg (body mass index BMI = 8.16 kg/m2), who was hospitalized in the Pediatric Clinic for loss of appetite, inability to walk and maintain orthostatism, with motor deficit on the right side of the body. There were reports for 2 admissions in 3 month before hospitalization in our clinic. First, in the Pediatric Neuropsychiatry Clinic for motor coordination disorder, personality disorders and depression and she was on medication with carbamazepine. At that time, the girl was weighing 23 kg (BMI = 11.73 kg/m2). The second admission, in another Pediatric Clinic for somatization disorder reveal a weight of 18 kg (BMI = 9.18 kg/m2).

Twenty-four hours after admission, the girl experienced periods of voluntary apnea, requiring endotracheal intubation and mechanical ventilation and was immediately admitted to the intensive care unit (ICU). Her mental status was altered. There were clinical signs of mild dehydration and muscle atrophy. Her breathing was voluntary stopped, with sinus tachycardia and normal blood pressure (see Table I for a summary of the initial physical examination). Electrocardiography (ECG) showed no pathological arrhythmias or signs of ischemia. An initial arterial blood gas analysis displayed severe acidosis with hypercarbia. There were no signs of infection, renal, liver functions and electrolytes were normal. Hyperglycemia and low levels of fatty acids were found. (see Table II for a summary of the initial laboratory screening).

Endocrine balance showed in this case: elevated cortisol levels, low levels of follicle stimulating hormone (FSH), estradiol and testosterone; high levels of growth hormone (GH) and low levels of insulin-like growth factor (IGF-I); low levels of thyroid hormones (T3 and T4) and slightly decreased thyroid-stimulating hormone (TSH) (see Table III for endocrine status).

Brain Magnetic Resonance Imaging (MRI) was normal and spine MRI showed signs of osteoporosis.

In ICU, the patient was put on mechanical ventilation mode synchronized intermittent mandatory ventilation with pressure support SIMV-PS with minimal parameters (peak inspiratory pressure PIP = 20 cmH2O, positive end expiratory pressure PEEP = 5 cmH2O, respiratory rate RR = 15 bpm, inspiratory time IT = 1.2 sec, pressure support PS = 15 cmH2O, FiO2 = 0.35). A central venous catheter was mounted for parenteral nutrition. Due to the risk of re-feeding syndrome, the intake of calories was restricted to 500 kcal over the first 24 hours and then increased. The risk of re-feeding syndrome is especially high in patients with a BMI <16, recent weight loss, and electrolyte abnormalities (14). Remaining energy intake was administered on nasogastric tube as nutritional drinks with a balanced protein, fat, and carbohydrate content.

After 72 hours of mechanical ventilation the vital signs normalized and patient was extubated. Because the girl's mother did not come to see her in the hospital, the patient refused any cooperation on oral nutrition, mobilization and respiration and was placed back on mechanical ventilation. Psychiatric evaluation reveal an intelligence above average (QI Raven = 118). On examination, the girl is introverted, suspicious, depressed and shows emotional trauma and somatisation. Psychotherapy was started, but she still remains in a marked depressive state.

During the 96 days of hospitalization, the patient required the placement of a tube tracheostomy to continue mechanical ventilation and a PEG (percutaneous endoscopic gastrostomy tube) for enteral nutrition. Weight gain was 4 kg. The patient died due to infectious complications after 6 months following hospitalization in another center.

Discussions

The endocrinopathies associated with eating disorders involve multiple systems and mechanisms designed to preserve energy and protect essential organs.

Hypercortisolemia is common in AN. Elevated levels of cortisol can be found in multiple sites including the serum, urine, saliva (15,16). Some studies showed loss of normal diurnal rhythm, assessed by late-night and early-morning salivary cortisol levels (16,17). Hypercortisolemia with elevated corticotropin-releasing factor (CRH) is commonly seen in anorexic patients (18). CRH is elevated in cerebral spinal fluid (19), suggesting a central mechanism causing the elevated cortisol. Hypercortisolemia is associated with excessive fear, atherosclerosis, osteoporosis and decreased immune function (20). Possibly, the intense fear seen in AN can be explained by the rise in CRH and cortisol levels. Cortisol also regulates the negative feedback mechanism for CRH secretion.

Delayed puberty can appear if an individual develops AN during adolescence, and some girls with this disorder have primary amenorrhea (21). Low estradiol levels in AN are seen due to a lack of ovarian stimulation and altered metabolism. Amenorrhea is a predictor of osteopenia and osteoporosis with increased risk of fracture later in life. Secretion of androgens including in particular testosterone is deficient in this syndrome, suggesting that gonadal sources are compromised (22).

Growth failure has been reported and might be attributed to deficient concentrations of estrogen and IGF-I. Increased GH levels accompanied by decreased IGF-I suggest an acquired resistance to GH that reverses with refeeding (23). Acute starvation is known to block IGF-I production by the liver, and thus GH excess in AN is attributed in part to lack of IGF-I-mediated negative feedback because of low IGF-I levels (24). Potential consequences of GH resistance include muscle atrophy, growth failure and osteopenia

Malnutrition in AN is accompanied by characteristic changes in peripheral thyroid hormone values outlining an euthyroid sick syndrome. Characteristically, endogenous T3 and T4 levels are low (25). TSH levels are generally within the normal range, but there are reports of levels being lower than in healthy controls (26).

AN has a negative impact on bonn tissue. Most of the endocrinopathies described above likely contribute to the bone loss including low T3, estradiol, testosterone, IGF-I and high cortisol.

Very few studies have investigated the relationship between malnutrition and psychological symptoms in AN. Lucka I. analised a group of 30 children with AN (27) and anxiety disorders were observed in 16.7% patients; 40% of the investigated children suffered from separation anxiety in the past and depression was significantly frequent amongst children suffering from anxiety disorders and AN.

Conclusions

Endocrine changes that occur in anorexia nervosa are secondary to physiological adaptation of the body to a state of starvation. Anorexia nervosa and the associated malnutrition that occurs through self-imposed starvation can cause severe organic and psychological complications and can even lead to death.

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CLINICAL SIGNIFICANCE OF ANTI-CYCLIC CITRULLINATED PEPTIDE ANTIBODIES IN A COHORT OF JUVENILE IDIOPATHIC ARTHRITIS

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Abstract

Anti-cyclic citrullinated peptide (anti-CCP) antibodies are considered to be specific for rheumatoid arthritis. The aim of the study consists in assessment of prevalence and clinical significance of anti-CCP antibodies in a cohort of juvenile idiopathic arthritis (JIA). In 55 patients with JIA, and a age and sex-matched control group (21 children with no articular sign) IgG anti-CCP antibodies were measured in serum using a commercial chemiluminescent immunoassay (CMIA) method (Architect ABBOTT). Positive anti-CCP values (above the 5U/ml cut-off value of the method) were found in 5 patients (9.1%). Statistical significant positive correlation had been found between anti-CCP antibodies titer and acute phase reactants, disease activity score and radiographic damage, respectively. Reevaluation after 3 months of the anti-CCP antibodies titer revealed statistical significant change. Anti-CCP is less prevalent in JIA than in rheumatoid arthritis, but its positivity denotes an erosive course of disease.

Key-words: anti-CCP antibodies, juvenile idiopathic arthritis

Background

In order to diagnose an autoimmune disease, determination of autoantibodies in the serum of patients is a matter of course. However, most of the autoantibodies can be detected in other conditions also, therefore they are not specific. A typical example for this situation is the rheumatoid factor (RF), which is present in many inflammatory conditions. Nevertheless, there are antibodies which occurs specifically in a certain disease, giving the clinician a precise indication of the type of pathologic condition. For example, anti-double chained DNA antibodies are typically present in systemic lupus erythematosus, and the literature of the last decade confirms that there are autoantibodies which are linked almost exclusively to rheumatoid arthritis (RA). These RA-specific autoantibodies are the so called anti-citrullinated peptide/ protein (anti-CCP) antibodies.

Citrullination (deimination) consists in a post-translational modification of arginine into citrulline. During this oxidation process, the positively charged arginine becomes neutrally charged citrulline, which increases hydrophobicity and leads to alteration of the protein structure. Secondly, citrulline is not coded by DNA, and consequently is not included in protein synthesis. Thereby, deimination, through alteration of protein structure and protein unfolding, probably leads to aberrant recognition of the citrullinated proteins by the immune system (1,2). Citrullination is preceded and up regulated by inflammation, and possibly leads to activation of CD4+ T cells (3) and initiation of autoimmunity. Studies performed in animal models with collagen-induced arthritis, proved that the anti-citrulline IgG response targeted not only the altered protein, but also caused cross-reactivity to unmodified peptide (3).

The anti-citrullinated peptide autoantibodies positivity can be searched via the anti-CCP antibody test. The first generation CCP test (CCP1) contained a single cyclic citrullinated peptide derived from fillagrin as the substrate (4). Second generation CCP test (CCP2) incorporates numerous novel citrullinated peptides with epitopes for detection of anti-CCP antibodies. The anti-CCP2 test demonstrated an RF-like sensitivity (70-75%) with a very high (95-99%) specificity for RA (5,6).

Objective

The present study was undertaken to determine the prevalence of anti-CCP antibodies in a cohort of children with JIA, and to observe possible correlations of these antibodies with subtype of JIA, disease activity and joint lesions. Basically, the main objective of the study was to estimate the clinical and prognostic significance of anti-CCP antibodies in JIA.

Patients and Methods

A cohort of 55 patients with JIA was recruited from First Pediatric Clinic of "Louis Ţurcanu" Clinical Emergency Hospital for Children, Timisoara, Romania and participated in the prospective study. The JIA group consisted in 32 girls and 22 boys, with median age of 11.3 ± 1.2 years. Diagnosis and classification was performed according to International League Association for Rheumatology (ILAR) criteria. Figure 1 presents the distribution of patients in subtypes of JIA.

Control group consisted in 21 children with no articular symptom or sign, 12 girls and 9 boys, and median age of 12.1± 1.8 years.

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Measurement of disease activity

Acute-phase reactants, including erythrocyte sedimentation rate (ESR, mm/h) and plasma concentrations of C reactive protein (CRP, mg/dl) were determined both in children with JIA and control group. At the same time points, clinical examination of studied group included a 27 joint count for tender and swollen joints. Assessment with a global visual analogue scale (VAS with range 0 to 10cm) was undertaken both by physician and parents or patients according to the age of child with JIA. ESR value was normalized to a 0-10 scale according to the following formula: [ESR (mm/hour) – 20] divided to 10. Before performing the calculation, ESR values < 20mm/hour were converted to 0 and ESR values > 120 mm/hour were converted to 120 (7). The Juvenile Arthritis Disease Activity Score (JADAS) was calculated as the simple linear sum of the scores of its four components: physician global assessment (VAS), parent or patient global assessment (VAS), active joint count (swollen joint count and tender joint count), normalized ESR (range 0 to 10).

Immunological assessment

IgG rheumatoid factor (RF) were determined by a nephelometric commercial test. Presence of antinuclear antibodies (ANA) was tested by a standard indirect immunofluorescence technique on HEp-2 cells. ANA were considered positive at serum titers >1/40.

Anti-CCP measurement

IgG anti-CCP antibodies were measured in serum using a commercial chemiluminescent immunoassay (CMIA) method (Architect ABBOTT) with 5 units/ml cut-off value. In all JIA cases titer of anti-CCP antibodies had been reassessed after 3 months.

Imagistic

X-ray was performed in order to evaluate the radiographic damage (erosions or joint space narrowing) in the affected joints (no).

Ethics

The study was approved by the ethics committees of the institution. Informed consent was obtained from parents or guardians of all participating children.

Results and Discussions

Prevalence of anti-CCP antibodies

Positive anti-CCP values (above the 5U/ml cut-off value of the method) were found in 5 patients (9.1%) in the cohort with JIA (figure 3), in comparison with the control group, with negative anti-CCP in all children (figure 4).

In comparison with the prevalence of anti-CCP antibodies in rheumatoid arthritis, we found a much lower rate of positivity in our juvenile cohort. Most of the studies from literature confirm our data, that anti-CCP can be detected also in patients with JIA, but they are generally present at low levels and less common than in adults with RA (8,9). Prevalence of anti-CCP in JIA is still a controversial issue; Avcin and co. (8) found a lower prevalence (2%) than ours, while a recent study performed on a large cohort of JIA patients (334) showed a prevalence of 14% of anti-CCP positivity (10). However, the absence of anti-CCP antibodies in control group states the question of the anti-CCP antibodies pathogenic role in JIA.

If we try to conclude the answer to the question "Should we test currently JIA children for anti-CCP antibodies?" is important to study concisely the predictive value of anti-CCP antibodies for rheumatoid arthritis. Clinical research studies show that anti-CCP is present in serum of a portion (55%-69%) of patients with rheumatoid arthritis and has been identified at all stages of RA: preclinical, early and established. Furthermore, blood bank studies proved that anti-CCP antibodies are present in the serum of patients as many as 12 to 14 years prior to the development of RA (11-14). The length of time that anti-CCP antibodies are detectable in patient serum prior to disease onset appears to be age related (15). Anti-CCP antibodies are present in the serum of older patients well before the developmental of clinical symptoms, while in younger patients, the detection of anti-CCP occurs closer to the time of disease onset (16). Clinical research showed that a combination of anti-CCP antibodies and RF had a high specificity and positive predictive value for the development of persistent RA. This autoantibody combination can be used to identify patients with disease destined to develop RA who may be appropriate for very early intervention (17).The results of these researches highlight the importance of anti-CCP testing, in spite of the low prevalence of anti-CCP positivity in JIA.

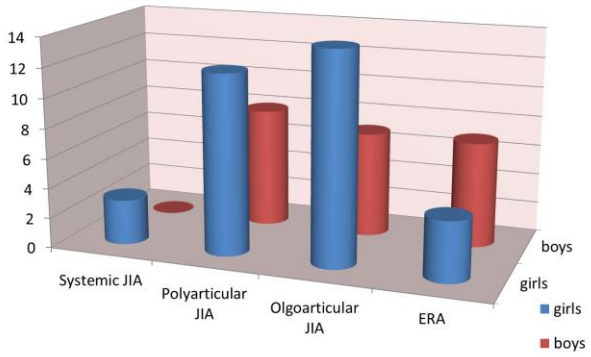

Figure 1. Distribution of cohort in types of JIA according to ILAR criteria

Distribution of anti-CCP positivity in JIA subtypes

In serum of 2 cases with extended ANA-positive oligoarthritis anti-CCP was found positive, but both cases were numbered into the polyarticular group, due to the extensive pattern of evolution. In 2 patients with seropositive (RF-positive) polyarticular onset JIA, we found positive anti-CCP antibodies, both with impressively high titers (≥200U/ml). Anti-CCP was not found positive in any case of persistent oligoarthritis or systemic JIA. In one case (1/11) with enthesitis-related-arthritis (ERA) anti-CCP titer was found higher than 5U/ml. Summarizing, in our cohort we found an association between anti-CCP positivity and a polyarticular course of disease (4/5, 2 seropositive, 2 seronegative), but the presence of anti-CCP antibodies was not exclusively linked to this subtype of JIA.

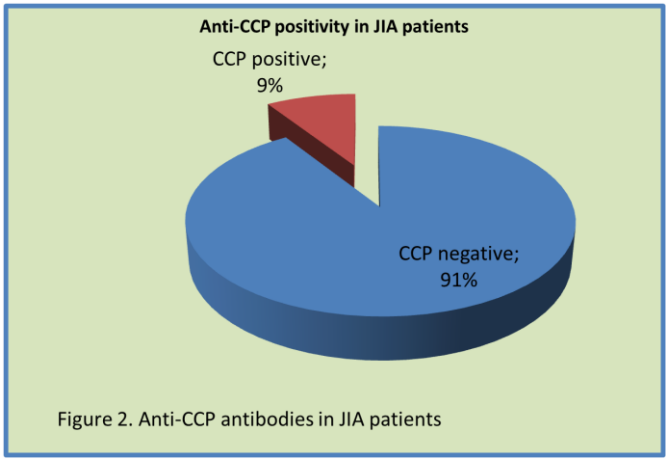

Figure 2. Anti-CCP antibodies in JIA patients

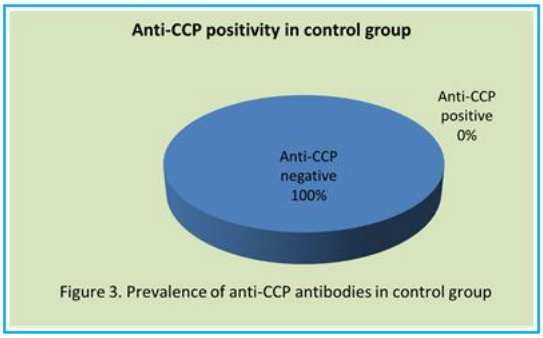

Figure 3. Prevalence of anti-CCP antibodies in control group

Type of JIA (number)	Median ESR (mm/1h)	Median CRP (mg/dl)	ANA+ (no cases)	Anti-CCP+ (no cases)	Median JADAS
Systemic (3)	49.8±12.7	12.2±5.7	0	0	19.8±3.5
Oligo (21)	27.5±11.9	7.35±4.3	2	0	6.3±2.9
RF+ Poly (6)	47.1±19.6	11.2±3.9	0	2	17.5±4
RF- Poly (14)	31.9±11.2	10.6±2.7	2	2	14.9±2.8
ERA (11)	20.1±7.1	4.8±1.3	0	1	11.7±4.7

Table 1. Description of clinical and paraclinical characteristics of the cohort

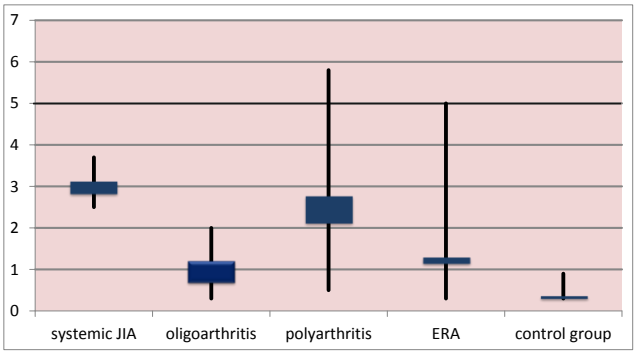

Figure 4. Median values of anti-CCP titers in different types of JIA and control group

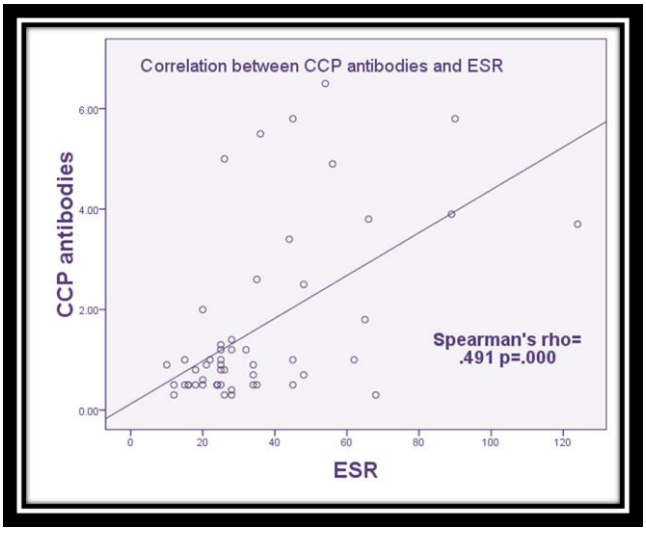

Fig. 5 Correlation between CCP antibodies and ESR

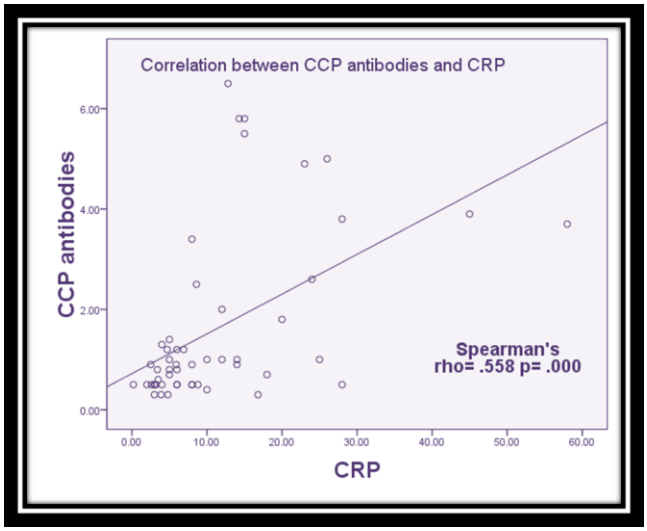

Fig. 6 Correlation between CCP antibodies and CRP

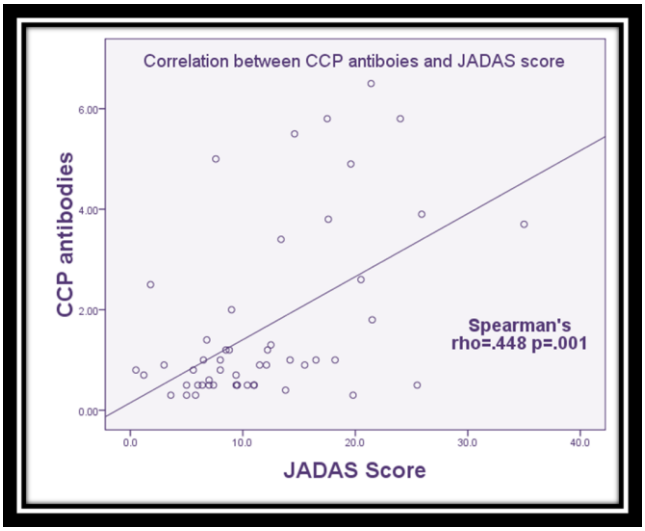

Fig. 7 Correlation between CCP antibodies and jadas SCORE

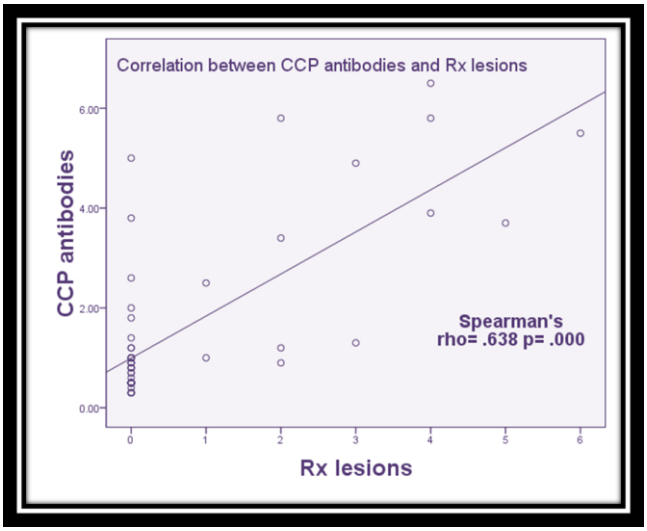

Fig. 6 Correlation between CCP antibodies and CRP

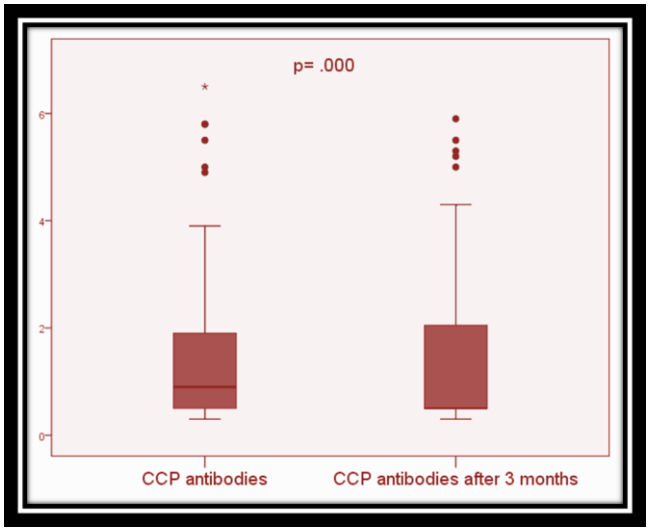

Fig. 7 CCP antibodies

Association between anti-CCP positivity and subtype of JIA is still debated. Habib and co. showed by his study that anti-CCP antibodies are detectable in a significant proportion of RF-positive patients with polyarticular-onset JIA, and are negative in patients with oligoarticular-onset and systemic-onset disease (18). Concordant with the previously mentioned study, Brunner found that anti-CCP antibodies are associated with RF-positive polyarticular course of JIA (19), they are not relevant for other subgroups of JIA, and therefore should not be investigated routinely. However, another important study (8) found no association between anti-CCP and disease subtype. Tebo and co. proved anti-CCP positivity in seronegative JIA patients as well, claiming that children with positive anti-CCP antibodies but negative RF are frequent, and may define a distinct subset of children with JIA (10). Similarly, clinical trials in adults suggest that anti-CCP antibodies are of particular diagnostic use in patients with rheumatoid arthritis who are negative for RF (20,21). Current research supports the hypothesis that rheumatoid arthritis patients who are negative or positive for anti-CCP antibodies may constitute two subsets of the disease with different clinical outcome (20). Therefore, testing of anti-CCP antibodies presence is mandatory in serum of all types of JIA patients.

Table 1 presents the median values of inflammatory biomarkers (ESR, CRP), the median disease activity score (JADAS), and the number of ANA, respectively anti-CCP positive cases severally for each subtype of JIA patients.

Disregarding the cut-off value of anti-CCP determination, we calculated the median titer for each type of JIA (figure 4), and the control group respectively. For a better analyze of the mean values, we excluded from the chart the two cases with high levels of anti-CCP (≥200U/ml). Figure 4 shows that in all types of JIA, the median anti-CCP titer was below the cut-off value of the commercial method, however permits a comparison between the median level of anti-CCP titer in JIA subtypes and the control group. We found a statistically significant difference ($p<0.005$) between median anti-CCP titer of all subtypes of JIA and anti-CCP values of control group.

These observations raise the issue of adjusted cut-off value in juvenile patients. The cut-off point should be calculated according to the mean value of anti-CCP titers of the control group. Similarly, in the study of Avcin and co. (8), the cut-off point was calculated as the mean plus three standard deviations of the values in the healthy children group (30 subjects matched for age and sex). In the assessment of rheumatoid arthritis also exists huge variation in cut-off values and performance characteristics of anti-CCP tests, highlighting the need for harmonization of these tests (15). There is a current effort at harmonization of anti-CCP tests in adult rheumatology, which includes the development of international reference reagents by the Centers for Disease Control and Prevention (20) and the Autoantibody Standardization Committee (22). Analogously, a standardization of the anti-CCP antibody cut-off value in juvenile arthritis would be mandatory. Perhaps, a lower cut-off level for anti-CCP antibodies in pediatric patients with an increased sensitivity would be more appropriate in JIA assessment.

Correlations between anti-CCP titer and disease activity

Using Spearman's test in order to investigate correlation between anti-CCP titer and the inflammatory biomarkers, we found a statistically significant moderate correlation between anti-CCP titer and ESR values (rho=0.491; p=0.000) (figure 5), and a good correlation between anti-CCP and CRP values (rho=0.558; p=0.000) respectively (figure 6).

Statistically significant moderate correlation was found between anti-CCP titer and disease activity score (JADAS) as well (rho=0.448, p=0.001) (figure 7).

In conclusion, our study found a positive correlation between anti-CCP titer and disease activity in JIA, which is not concordant with the results of the majority of published studies (8,9,11). This discrepancy may several explanations. First of all, all studies investigated the correlation between biomarkers of disease activity and exclusively the titer of anti-CCP which exceeded the cut-off point of the used method, reducing thus the number of tested patients. We searched the correlations disregarding the cut-off point of anti-CCP determination, including in trial all patients. Secondly, the two seropositive polyarticular cases with elevated titer of anti-CCP had a disease course with prolonged intense activity (high values of ESR, CRP). The low number of cases could be another reason of limitation. On the other hand, there are clinical trials which suggest that in patients with rheumatoid arthritis, anti-CCP positivity is associated with a more intense inflammatory response (15), synovial tissue from anti-CCP positive patients expresses higher concentrations of immune cytokines, has higher numbers of infiltrating lymphocytes (23). Berglin and his coworkers proved that anti-CCP levels are correlated to inflammatory activity (24).

Correlation between anti-CCP titer and radiographic damage

We counted the number of joints with radiographic lesions (erosions or joint space narrowing) at the time point of anti-CCP determination and investigated the correlations between them. A statistically significant good correlation (rho=0.638, p=0.000) was found (figure 8). Furthermore, all five anti-CCP positive cases presented severe radiographic damage, and the most dramatic joint deformations were found in the 2 patients with seropositive polyarticular JIA and impressively increased titers of anti-CCP antibodies (≥200U/ml).

This correlation is concordant with the results of most of the published studies (9,10,11,24,25). Gilliam and co. showed that JIA patients with radiographic damage had significantly elevated levels of anti-CCP antibodies in comparison with children with JIA, but no radiographic joint lesions. Similarly, several clinical trials have demonstrated a strong association between anti-CCP positivity and joint damage in rheumatoid arthritis (24-29). In a large, prospective study of rheumatoid arthritis patients, the positivity of anti-CCP was the most important single predictor of radiographic progression in patients with early RA, and patients with high levels of anti-CCP were especially prone to radiographic progression (30). Consequently, IgG anti-CCP antibodies have demonstrated increasing importance in assessment of both of rheumatoid arthritis and juvenile arthritis to determine which patients have or will have more aggressive or severe disease and to be a useful tool in therapeutic attitude to prevent joint damage and disability (31). Furthermore, in 2011 ACR Recommendations for the treatment of JIA included anti-CCP positivity as a feature of poor prognosis in the treatment group of JIA patients with history of arthritis of 5 or more joints (32).

Evolution of anti-CCP titer

Reevaluation of anti-CCP antibodies titer after 3 months revealed statistical significant change (figure 9).

In rheumatoid arthritis, evolution of anti-CCP antibody titer following therapy is still controversial. Some studies showed that anti-CCP antibody levels in RA patients following treatment tended to remain stable or decreased only slightly (11,33,34). Other studies proved an association between modification of anti-CCP antibody titer and the disease duration: only in patients with RA whose disease duration was less than one year, there had been observed significant reduction in anti-CCP levels following treatment (35, 36). Significant reduction of anti-CCP antibodies levels have been reported in RA patients with positive clinical response following treatment with TNF-α blockers (24,33-40). On the other hand, several studies have shown that treatment with TNF-α blockers in established RA patients produced a significant reduction of IgM rheumatoid factor

levels, while had significantly less effect on anti-CCP levels (41-44).

There are very few studies concerning profile of anti-CCP antibodies titer in patients with JIA following treatment. Syed and coworkers found no significant correlation between anti-CCP titer and disease activity, with no significant reduction of anti-CCP titer following JIA treatment (31). A possible explanation is that an analysis of a small number of individuals with positive anti-CCP antibodies decreases the possibility of obtaining statistically significant differences. We tested the outcome of anti-CCP titer disregarding the cut-off value of the used method (both anti-CCP positive and negative patients).

Researches in rheumatoid arthritis show that the baseline titer of anti-CCP antibodies was higher in patients with radiological progression and decreased significantly in those with response to therapy, titre of anti-CCP antibodies being related to disease severity (24).

Conclusions

Anti-CCP is less prevalent in JIA than in rheumatoid arthritis, but its positivity denotes an erosive course of disease. Therefore, anti-CCP determination is a valuable tool in JIA assessment and promotes a correct therapeutic attitude to prevent disability and joint damage. Anti-CCP concentration remains unchanged during the course of disease, with no role as indicator of response to treatment. Because of low number of cases, conclusions are limited.

Standardization of anti-CCP tests with adjusted cut-off value for children is required**.**

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THE TREATMENT OF AUTOIMMUNE THYROIDITIS IN ADOLESCENT– A CONTINUOUS CHALLENGE

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Abstract

Background: Autoimmune thyroiditis is the most frequent thyroid disorder in pediatric age, especially in females and puberty. ***Aim:*** The authors wanted to present the case of an adolescent girl diagnosed with autoimmune thyroiditis, describing all the difficulty encountered in the management of this pathology. ***Case presentation:*** We reported the case of 11 years old girl adolescent who was presented in 2011 into the Department of Endocrinology of " Louis Turcanu" Children Emergency Hospital, Timisoara for a tumor localized in the anterior neck. Her psychical examination revealed a well-developed adolescent, with enlarged and non-tender thyroid gland (stage II). Her laboratory assessment revealed thyroid-stimulating hormone level elevated and free thyroxine level suppressed with anti-thyroid peroxidase antibody and anti-thyroglobulin antibody increased. The patient was diagnosed with autoimmune thyroiditis with hypothyroidism and goiter and she initiated thyroid hormone replacement therapy at a dose of 25 µg/day. She remained euthyroid on a stable dose of Euthyrox without recurrences and normal growth and sexual development. In January 2013, the clinical examination was normal except the presence of dysphonia and an increased goiter. All the thyroid parameters were modified while the thyroid ultrasound identified multiples hypoechogenities in both thyroid lobes. The results of MRI and scintigraphy evaluations described a thyroid gland with increased size and decreased function, characteristic to the Hashimoto's thyroiditis. The cause of this thyroid dysfunction was the inappropriate administration of the hormonal treatment (at 12 o'clock, postprandial). ***Conclusions:*** The hormonal replacement therapy of hypothyroidism associated with autoimmune thyroid is permanent and should be monitoring although involve adolescents. The poor compliance to the hormone substitution is an important cause of treatment failure.

Key words: adolescent, autoimmune thyroiditis, hypothyroidism

Background

Autoimmune thyroid disease (ATD) is the most common autoimmune condition, affecting approximately 2% of the female population and 0.2% of the male population with its prevalence peaks in adulthood . It represents the most common etiology of acquired thyroid dysfunction (hypothyroidism) in pediatrics and the most common autoimmune disease in all ages, with a prevalence of 1.3 - 3.4% in children, depending on geographic location, type of study and gender of patients ATD is more common in females and usually occurs in early to mid-puberty .

The term thyroiditis is defined as evidence of "intrathyroidal lymphocytic infiltration" with or without follicular damage. Two types of AT (also defined as chronic lymphocytic thyroiditis) are causes of persistent hypothyroidism: Hashimoto's disease (goitrous form) and atrophic thyroiditis (nongoitrous form). Both are characterized by circulating thyroid autoantibodies and different degrees of thyroid dysfunction, differing only by the presence or absence of goiter. Transient thyroiditis seems to be a variant presentation of AT. It is characterized by an autoimmune-mediated lymphocytic inflammation of the thyroid gland resulting in a destructive thyroiditis with release of thyroid hormone and transient hyperthyroidism, frequently followed by a hypothyroid phase and full recovery.

Aim of study

The authors aimed to present the case of an adolescent girl diagnosed with autoimmune thyroiditis, describing all the difficulty encountered in the management of this pathology.

Case presentation

We reported the case of 11 years old girl adolescent who presented in 2011 into the Department of Endocrinology of Children Emergency Hospital, Timisoara for a tumor localized in the anterior neck. This has been observed since two months before medical presentation and it has been growing since then. She has no family history of endocrine or autoimmune disease.

Her psychical examination revealed a well-developed, well-nourished adolescent in no apparent distress. She had a normal blood pressure level of 110/68 mmHg and her pulse was increased (110 beats/minute). There was no lid lag or proptosis. Her thyroid gland was enlarged (stage II) and was non-tender at palpation. There was no cervical lymphadenopathy or appendicular tremor. The remainder of her physical examination was within normal limits. Her anthropometric data at the hospital admission are presented below.

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Chronological age=11 years and 1 month	Real weight=39kg	Real height=147 cm
Age-for-height=11 years and 9 months	Weight-for-height=46kg	Height-for-age=142±6.93 cm
	BMI=18.05 kg/m^2 (50th -75th percentiles)	Z score= +0.72

Tabel no. 1: Anthropometric measures at the diagnosis moment

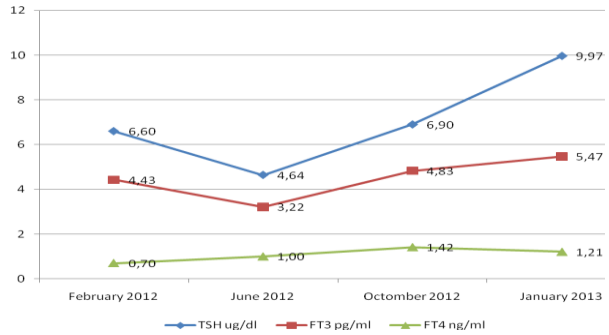

Figure no.1 Evolution in time of the values of thyroid hormones

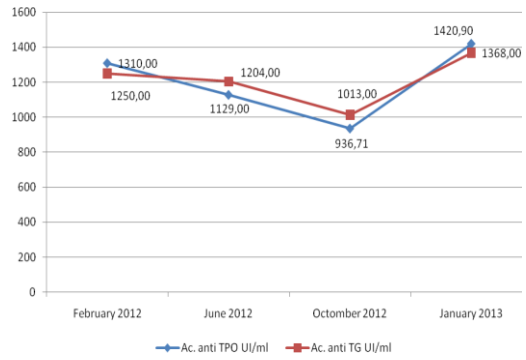

Figure no2. Evolution of the thyroid antibodies

Chronological age=12 years and 11 months	Real weight=47kg	Real height=157 cm
Age-for-height=13 years and 3 months	Weight-for-height=50 kg	Height-for-age= 155.74 ± 6.60 cm
	BMI=19.10kg/m^2 (50th -75th percentiles)	Z score= + 0.19

Tabel no 2: Anthropometric measurement in January 2013

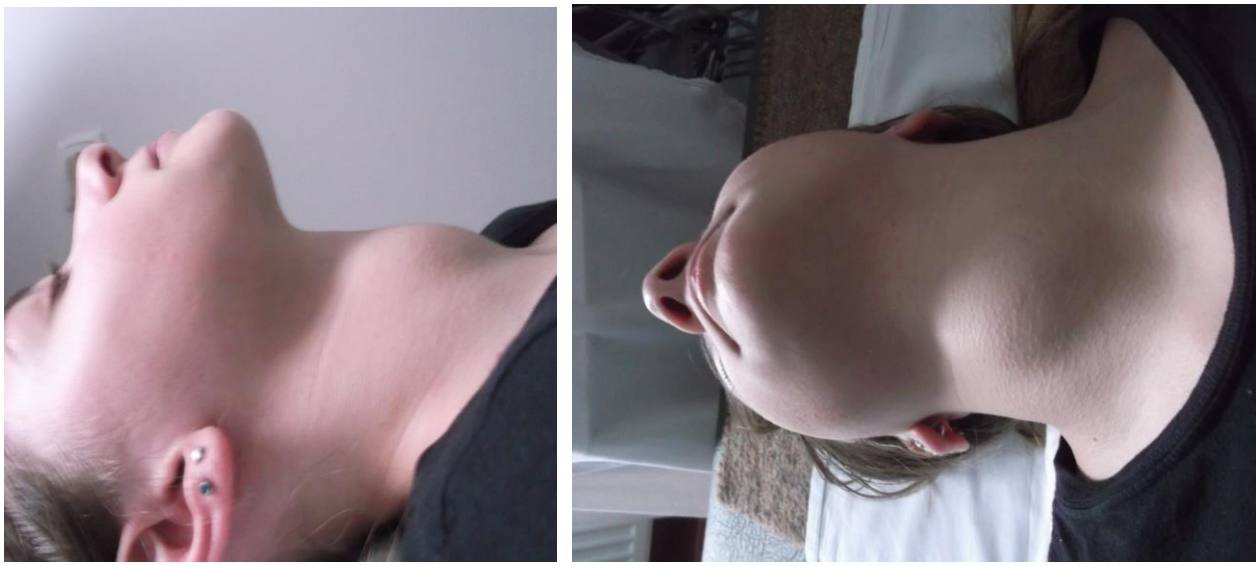

Figure 3 Clinical aspects of the increased goiter

Her laboratory assessment revealed normal blood counts, electrolytes, lipid profile and liver and kidney function. Her serum thyroid-stimulating hormone (TSH) level was elevated at 6.80μg/dl (normal range 2.9 to 4.2 μg/dl) and her free thyroxine level was suppressed at 0.82 pg/ml (normal range, 0.90 to 6.8 pg/dl). The FT3 level was within normal range. An anti-thyroid peroxidase antibody (anti TPO) was elevated at 1228.9 UI/ml (normal, <5.6 UI/ml), and the serum anti-thyroglobulin antibody (anti TG) was increased at 1260 UI/ml (normal, <34 UI/ml).

The cardiologic consult revealed the present of tachycardia and a minor form of right bundle- branch block. No association with another autoimmune disease was encountered.

The patient was diagnosed with autoimmune thyroiditis with hypothyroidism and goiter. Therefore, given the combination of her laboratory parameters and clinical signs, the decision was made to initiate thyroid hormone replacement therapy at a dose of 25 μg/day with Euthyrox administered in the morning, at least 20 min before eating or ingestion anything. This dose normalized the serum TSH and free thyroxine values. The patient was clinical and biological (TSH, FT3, FT4, anti TPO and anti TG) evaluated every 3-4 months. She has remained euthyroid on a stable dose of Euthyrox for over 6 months without recurrences, normal growth and sexual development.

During her last visits in our department, it impresses the elevations of the values of her thyroid hormones and antibodies as described in the figures below (Figure no.1, Figure no.2). This fact was followed by the increasing of the dose of the substitution hormone (from 25 μg/day up to 50μg/day).

In January 2013, she came to the hospital for the periodical evaluation. Her anthropometric measures (table no. 2) were according to the tables and percentiles for age and sex and the clinical examination was normal except the fact that she was still dysphonic with cough and her goiter was increased (Figure no 3).

The ENTT examination (indirect laryngoscopy) revealed the presence of free space glottis with vocal cords slightly thickened and congested but mobile with phonation and respiration. This was suggestive for a severe episode of laryngitis.

All the thyroid parameters were modified. TSH level was increased at 9.97μg/dl (normal range 0.53 to 3.59 μg/dl) and all thyroid hormones were free suppressed: FT3 at 5.47 pg/ml (normal range, 35 to 77 pg/dl) and FT4 at 12.15 ng/dl (normal range, 12-20.6 ng/dl). The anti-thyroid peroxidase antibody was elevated at 1420.9 UI/ml (normal, <5.6 UI/ml) while the serum anti-thyroglobulin antibody (anti TG) was normal. The thyroid ultrasound showed an increased volume of thyroid gland and identified multiples hypoechogenities in both thyroid lobes.

In order to exclude the presence of malignant nodes and to elucidate the cause of goiter enlarger, MRI examination and thyroid scintigraphy were performed. The magnetic resonance (Figure 5,6) imagistic examination described the presence of thyroid gland increased in size overall with the right thyroid lobe = 2.3/1.9/6.3 cm, the left thyroid lobe = 2/1.6/5.7 while the pyramidal lobe = 0.7/1.3/2 cm, isthmus=1 cm, gadophil and homogeneous tissue, without focal lesions. Several nodular formations (one nodule posterior to the carotid artery, 1 cm dimension, in the right part and 3 nodules localized between the trachea and the common carotid artery, maxim 8 mm dimension in the left part) were identified lower to the thyroid lobes and paratracheal. They were visible in T1, T2 isosignal, homogeneous and gadophil.

A thyroid scintigraphy (figure 7) was performed after she stopped the hormone substitution and described a decreased function of thyroid and a diffuse capture.

The results of these imagistic evaluations described a thyroid gland with increased size and decreased function, characteristic to the Hashimoto's thyroiditis. The nodular formations described at MRI were considered as cervical lymphadenopathy secondary to the laryngitis.

The cause of this goiter enlargement and thyroid hormone abnormalities was the poor compliance to the hormone substitution. The adolescent admitted the fact she took her treatment every day around 12 o'clock

Discussions and conclusions

The case presented nicely illustrates a typical case of an autoimmune thyroiditis with goiter and hypothyroidism due to glandular dysfunction in a teenager. Optimal quantities of thyroid hormone substituted are critical to neurodevelopment and growth in a child diagnosed with autoimmune thyroiditis. Once biochemical euthyroidism has been achieved, TSH can be monitored every 4–6 months in the growing child and yearly up to the attainment of final height. Also, growth and sexual development in these patients should be followed systematically as in any pediatric patient, because they may be deranged. Similar to other endocrine causes of growth failure, linear growth is compromised to a greater degree than weight gain, and the bone age is delayed . In the case presented, the teenager had a normal height gain (from 147 cm up to 157 cm), with a growth velocity of approximately 5 cm/year.

Typically, hypothyroidism induces pubertal delay. Medical literature had reported cases of pseudoprecocious puberty induced by hypothyroidism and manifested as testicular enlargement in boys, breast development, and/or vaginal bleeding in girls . Clinically, it may vary from true precocity by the absence of accelerated bone maturation and linear growth. Our teenager girl had a normal sexual development with menarche installation at 12 years and 3 months.

One problem frequent identified, especially in the adolescents is the poor compliance to the hormone substitution. This is an important cause of treatment failure. FT4 should be measured when it is suspected. A serum TSH greater than twice normal, with a concomitant normal FT4 level, suggests intermittent omission of the medication. It should be administered at least 20 min before eating or ingestion of any medication. The girl presented considered that it was not so important the period of day when Euthyrox was administered. Also she was passing through a difficult period in her life, which marked her because her parents divorced.

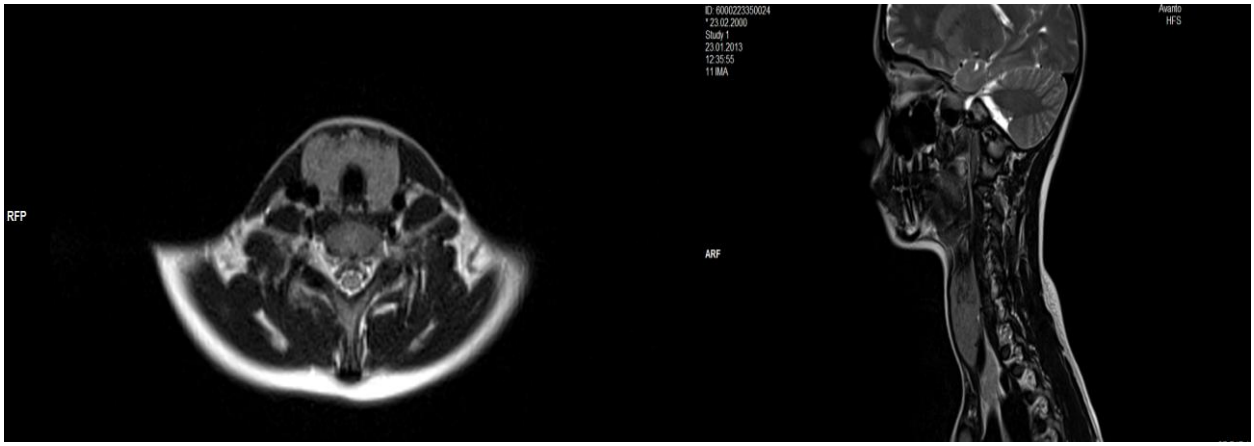

Figure 5, 6 Thyroid MRI image

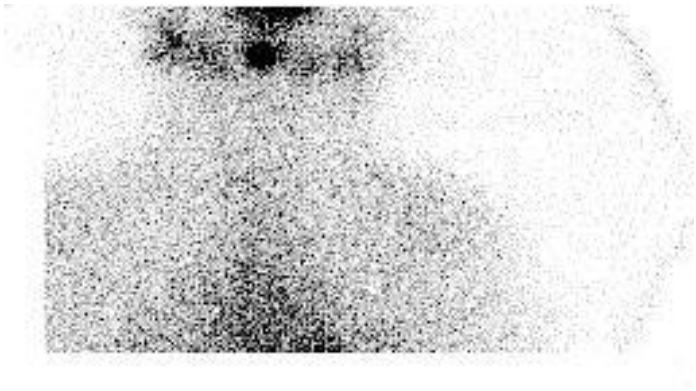

Figure 7 Thyroid scintigraphy aspect

Parents of children with autoimmune thyroiditis should be advised that the hypothyroidism is likely to be permanent and monitoring of thyroid function for all patients should be lifelong although they are adolescents. This is a difficult period when they want to be independent, they believe they know everything, they think they are able to do without any help from the adults.

Also as a physician we have to keep in mind that there are a variety of conditions (phenylketonurie, cystic fibrosis, cirrhosis, and mucosal diseases of the small bowel, bypass and small bowel resection) or drugs (calcium and iron supplements, sucralfate, potassium binding resins, antacids drugs containing aluminium) may alter thyroid hormone requirements .

The hormone dose replacement should be adapted always according to the values of thyroid hormones. It is important to elucidate the cause of a sudden increased of the dose of therapy and sometimes imagistic investigations are required.

It is important to remember that thyroid nodules are more often malignant in adolescent than in adults. A recent study published analyzed the relationship between autoimmune thyroiditis, cancer, and thyroid nodules in a large case series of paediatric patients. Thyroid nodules were found in 115 of 365 patients with autoimmune thyroiditis (31.5%), more frequent presented as a solitary nodule (60.0%) palpable at clinical examination and confirmed by ultrasonography. On histologic examination after total thyroidectom, papillary carcinoma was detected with exhibiting lymph node metastasis. The prevalence of male sex among patients with cancer was greater than that among patients with autoimmune thyroiditis. When it is even a little suspicion of malignant cancer exist, imagistic evolutions should be performed.

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