CAZ CLINIC

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BIOLOGICAL INACTIVE LEPTINE IN A CASE OF EARLY-ONSET SEVERE OBESITY

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REZUMAT

LEPTINA BIOLOGIC INACTIVĂ ÎNTR-UN CAZ DE OBEZITATE SEVERĂ CU DEBUT PRECOCE

Cuvinte-cheie: obezitate la sugari, retard motor, metabolismul leptinei, sugar.

Introducere: Obezitatea la copii debutează în copilăria timpurie, crescând dramatic costurile calității vieții aferente obezității. Obezitatea severă cu debut precoce la sugari este o trăsătură specifică obezității monogenice.

Scopul acestui studiu a fost de a descrie tabloul clinic, testele de laborator și imagistice la o fetiță de nouă luni cu obezitate monogenică.

Material și metode: Prezentăm cazul clinic al unui sugar de sex feminin în vârstă de nouă luni cu obezitate extremă și întârzierea severă a dezvoltării motorii.

Rezultate și discuții: O fetiță de nouă luni a fost prezentată ***în*** ambulatoriu cu acuze pentru întârzierea dezvoltării motorii. Evaluarea curentă a creșterii a evidențiat indici ai greutății și raportului greutate/ lungime mai mari decât percentila 99 și scorul Z > 3 SD. Evaluarea în dinamică la două luni a prezentat un ΔSD +0.5. Testele de laborator și imagistică nu au evidențiat anomalii. Cu toate acestea, nivelul seric al leptinei la acest pacient s-a constatat a fi ridicat – 17,11 ng/ml (interval de referință normal pentru această vârstă 0,54-5,18 ng/ml). Rezultatele obținute indică faptul că nivelurile circulante ale hormonului, ce par a fi normale în raport cu indicele de masă corporală și masa de grăsime, nu exclud mutațiile cauzatoare de boli ale genei care codifică leptina și ar putea să obstrucționeze procesul unui diagnostic corect. De aceea, un diagnostic genetic mai precis este fundamental într-o astfel de situație clinică.

Concluzii: Se impune diferențierea clinică a afecțiunii nutriționale cronice, precum este obezitatea care își are originea în copilărie.

РЕЗЮМЕ

БИОЛОГИЧЕСКИЙ НЕАКТИВНЫЙ ЛЕПТИН В СЛУЧАЕ РАННЕГО ТЯЖЕЛОГО ОЖИРЕНИЯ

Ключевые слова: детское ожирение, задержка моторики, метаболизм лептина, младенцы.

Введение: Детское ожирение начинается в раннем детстве, что резко увеличивает затраты на ожирение в течение жизни. Тяжелое раннее начало ожирения у младенцев - частый признак моногенного ожирения.

Цель исследования: Целью этого исследования было описание клинических проявлений, лабораторных и визуализирующих тестов у 9-месячной девочки с моногенным ожирением.

Материал и методы: Мы сообщаем о клиническом случае девятимесячного ребенка с крайним ожирением и серьезной задержкой моторики. Результаты и обсуждения: В поликлинику поступила девочка 9 месяцев с жалобами на задержку двигательного развития. Текущая оценка роста показала, что вес и вес/рост превышают 99 процентилей, а показатель Z > 3 SD. Последующее наблюдение через 2 месяца представило ΔSD + 0,5. Лабораторные и визуальные тесты отклонений не выявили. Однако уровень лептина в сыворотке у нашей пациентки оказался высоким 17,11 нг/мл (нормальный диапазон значений для возраста 0,54-5,18 нг/мл). Учитывая наши результаты, уровни циркулирующего гормона, которые кажутся нормальными по отношению к индексу массы тела и массе жира, не исключают вызывающие заболевание мутации в гене, кодирующем лептин, и могут затруднить постановку правильного диагноза. Таким образом, более точная генетическая диагностика является фундаментальной в такой клинической ситуации.

Заключение: Клинически важно отличать хронические нарушения питания как ожирение, возникающей в младенчестве.

SUMMARY

Key words: infant obesity, motor delay, leptin metabolism, infants

Background: Childhood obesity begins in early life, dramatically increasing lifespan costs of obesity. Severe early-onset obesity in infants is a common feature of monogenic obesity.

Aim: The aim of this study was to describe the clinical presentation, laboratory and imaging tests in a 9-months-old girl with monogenic obesity.

Material and methods: We report a clinical case of a 9-months-oldfemale infant presenting with extreme obesity and severe motor delay.

Results and discussion: A 9-months-old girlwas presented to the outpatient clinic complaining for a motor development delay. Current growth assessment revealed weight and weight/lenght higher than 99 percentile and Z score > 3 SD. Follow up after 2 months presented a ΔSD +0.5. Laboratory and imagistic tests didn`t reveal any abnormalities. However, the serum level of leptin in our patient appeared to be high 17.11 ng/ml (normal reference range for the age 0.54-5.18 ng/ml). Given our findings, circulating levels of the hormone that appear to be normal in relation to body-mass index and fat mass do not rule out disease-causing mutations in the gene encoding leptin and might obscure the correct diagnosis. Thus, a more precise genetic diagnostic is fundamental in such a clinical situation.

Conclusion: Distinguishing a chronic nutritional disorders as the obesity pattern thatoriginates during infancy is clinically important.

Background. Childhood obesity is a growing global health problem.Childhood obesity begins in early life, dramatically increasing lifespan costs of obesity. [1,7] Systematic reviewsreveal that rapid growth in infancy is associated withschool age and later obesity. [2]

Physicians often have difficulties to find guidance on managing the approximatively one third of their population who present formedical care regarding thevariety of medical problems due to obesity or because ofobesity itself. [1, 7]

Severe early-onset obesity in infants is considered one of the common feature of monogenic obesity. One of its cause could be various leptin biology dysregulation, such as: leptin deficiency or biologically inactive leptin. [4, 9]

Leptin plays an important role in regulating energy homeostasis, neuroendocrine and immune functions, and glucose, lipid and bone metabolism. [3, 5] During early infancy, leptin does not appearto play an anorexigenic role; leptin maintains an increasedappetite in infants to promote their survival during the period inwhich they lack feeding independence. [6] However, further research on molecular mediators of leptin resistance is needed for the development of targeted leptin sensitizing therapies for obesity and related metabolic diseases. [3, 4, 5]

Obese individuals exhibit high levels of leptin expression in adipose tissue and have elevated circulating leptin levels, and these high leptin levels fail to reduce excess adiposity, indicating leptin resistance.Mechanisms underlying leptin resistance may include disruption of leptin signaling in hypothalamic and other CNS neurons, impaired leptin transport across blood-brain barrier, hypothalamic inflammation, endoplasmic reticulum stress, and autophagy. [4, 5]

The commonest cause of monogenic obesity results from mutations in the leptin–melanocortin pathway encoding the MC4R receptor. However, these mutations account for less than 10% extreme obesity cases. [4, 9]

It is conceivable that serum leptin concentrations in breastfed infants are related to adipose tissue production during the firstmonths of life and to the leptin content

of human milk. However, reference values of leptin concentrations are missing for infants in the first months of life. [6]

Aim. The aim of this study was to describe the clinical presentationand imaging appearancein a 9-months-old girl with monogenic obesity.

Material and methods. We report a clinical case of a 9-months-old female infant presenting with extreme obesity and severe motor delay. The patient was admitted into the Neurology clinic from a tertiary level hospital providing pediatric services. We will emphasize its peculiarities in correlation with available literature data from PubMed/NCBI, based on analyzing published case presentations, synthesis and reviews on the following key-words: monogenic obesity, leptin resistance, leptin deficiency, infants.

breastfeeding up to 8-months-old. Since the age of 2-months-old, her mother noticed periodic subfebrility for no revealed reason. From the age of 3-months-old, our patient added about 1 kg in weight each month. Due to the developmental delay she was directed to the neurology unit for diagnosis and treatment. On clinical examination, the patient hardly holds her head, does not roll, does not sit, hardly fixes her eyes and follows objects. Also, she presented muscular hypertonus, hyperreflexia. Current growth assessment revealed the lenght of 71 cm (26th percentile, Z score +0.35 SD), weight 12.2 kg (>99th percentile, Z score +3.14 SD), Weight/Lenght higher than 99 percentile, Z score +3.32 SD, head circomference 45 cm (81st percentile, Z score +0.87 SD) (Figure 1).

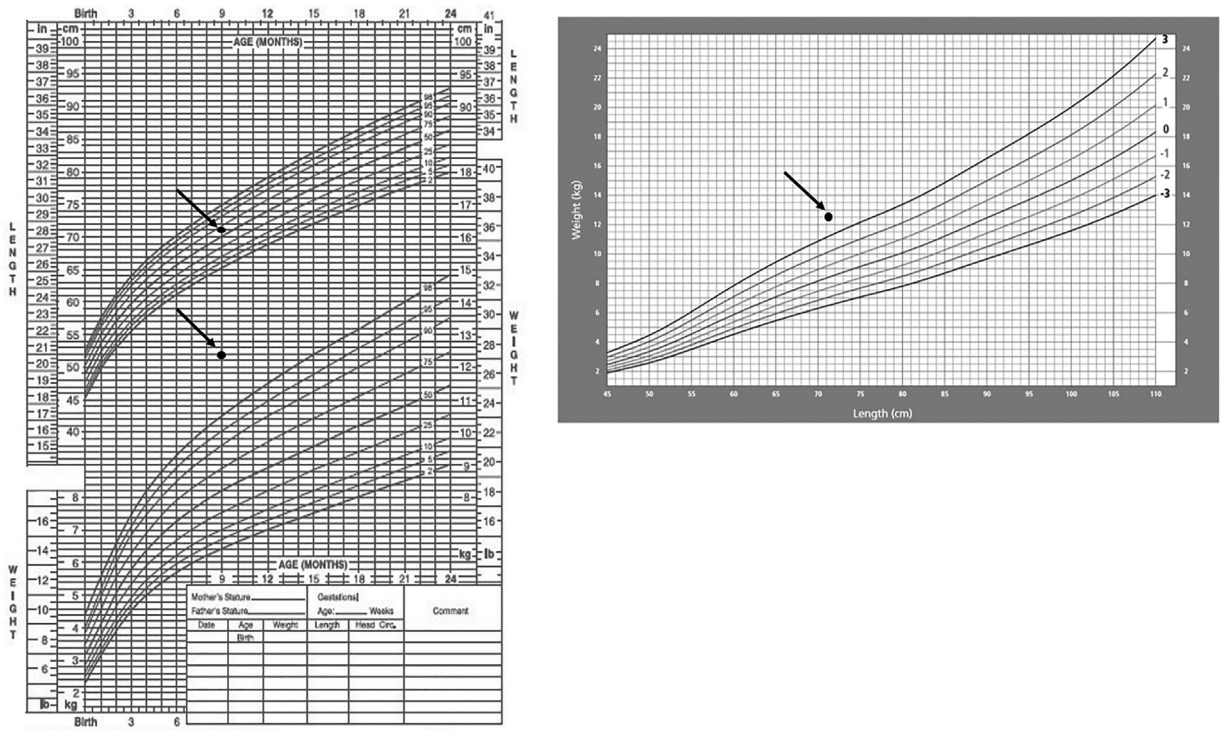


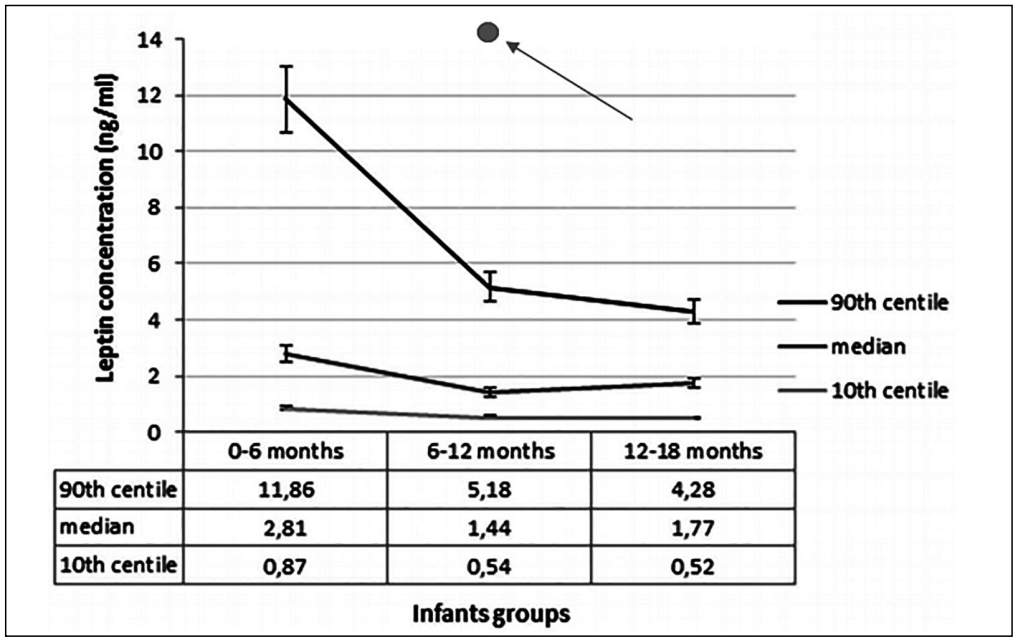
Fig. 1. ***Patients growth chart. On the left – current values at the age of 9-months-old. Upper – weight for length parameter in our case.***

Results and discussion. The patient is the first child, second pregnancy, of two healthy, normal-weight parents with unrevealed chronic conditions. The obstetrical anamnesis was complicated by a previous miscarriage in the first trimester. Further, the history was complicated by a 4-years duration of infertility. The current pregnancy was with associated risks, due to what it was under *Progesteronum* treatment. At birth, normal antropometric data were assessed (weight 3600g, height 52 cm, weight for height on the 25th percentile, -0,67 Z score). Our female patient was on exclusively

On laboratory examination, no abnormalities of the fasting glucose level, glycosylated hemoglobin (HbA1c) and lipid panel were not detected. Thyroid hormones level (TSH, fT4, T3) were within normal range for age, as well as prolactin level and insulin growth factor 1. As the patient was presenting severe early-onset obesity, we suspected a monogenic cause, as leptin dysregulation. The serum level of leptin in our patient appeared to be high - 17.11 ng/ml (normal reference range for the age of 0.54-5.18 ng/ml) (Figure 2).

On follow up, after 2 months, was detected a worsening of her nutritional status: her weight remained >99 percentile, Z score +3.20 SD, with a ΔSD +0.06. Regarding her weight/length indicator, it became +3.82 SD, ΔSD +0.5.

Imagistic studies, such as ultrasound examination



	0-6 months	6-12 months	12-18 months
90th centile	11,86	5,18	4,28
median	2,81	1,44	1,77
10th centile	0,87	0,54	0,52

Figure 2. ***Reference serum leptin concentrations in healthy infants: median and 10th-90th centile (Error Bars 10%) (Savino F., 2014) Red dot and array indicating our patients value at the baseline examination.***

of the thyroid and adrenal gland did not reveal any abnormalities. The eye exam and electroencephalography was normal as well. The brain CT suggest moderate-grade atrophic intracerebral changes, with the presence of multiple subcortical, cortical, periventricular calcifications distributed bilaterally diffusely and at the level of the basal nuclei (more likely in the CMV infection), moderate enlargement of the intra-extra-axial CSF spaces.

Genetic examination was conducted through karyo-typing. Any chromosomal disorders were not detected. Unfortunately, other genetic tests were not possible to be done at the moment.

Discussions. We describe a case of early-onset, extreme obesity caused by a biologically inactive leptin that was present at high levels in the circulation.The clear clinical phenotype of our patient, led us to the hypothesis that the serum leptin probably is not functional and therefore is unable to mediate a satiety signal in the central nervous system.Taking in count our laboratory findings, circulating levels of the hormone that appear to be normal in relation to weight/length index and fat mass do not rule out disease-causing mutations in the gene encoding leptin and determine difficulties in the correct diagnosis work-up. Thus, a more precise genetic diagnostic is fundamental in such a clinical situation.

Severe early-onset obesity (SEOO) is associated with a high risk of persistence of obesity into adulthood. In contrast to later-onset obesity SEOO is more likely to be caused by genetic factors, by both monogenic mutations as well as syndromes associated with early rapid weight gain. [9] Epigenetics is thoughtto play a large role in the precipitous rise in obesity overthe past 30 years. [1]

Genetic causes of obesity should be considered in childrenwith severe obesity before the age of 5 years. [1] The most common form of monogenic obesity is due to mutations in the melanocortin-4 receptor (MC4R) gene. Mutations in genes involved in leptin pathway (leptin gene, leptin receptor gene) are very rare and only a couple of patients have been described so far inEuropean populations. [3,9] Seven additional mutations have been reported. [8]

Leptin has been proposed to be responsible for some of thebeneficial effects of breastfeeding and is thought to be involved inpreventing infants to obesity. Leptinconcentrations in breast milk positively correlate with maternalcirculating leptin levels, BMI, and adiposity. [6]

It has been suggested that leptin deficiency or leptin receptor defects, inherited in an autosomal recessive pattern, could be found in up to 3% of patients with SEOO. In 2015, it was first described that there are also patients in whom leptin is measurable in high concentrations in the blood, but it is biologically inactive. In these individuals mutated leptin is not able to bind to its receptor. [9]

Current clinical recommendations advise that leptin serum concentrations be measured in children who have rapid weight gain in the first months of life, to identify patients with congenital leptin deficiency. [8] Reference intervals are essential for the interpretation of clinicallaboratory tests and for the care of patients with signs or a familyhistory of endocrine disorders or metabolic diseases. [6]

Leptin levels have been shown to be consistentlyhigher in females than in males later in life. Probably, these differences are related to differences inbody composition or hormone levels in males and females. [6]

The differential diagnosis of children with obesity startswith an assessment of linear growth.Weight assessment of a child with obesity is accomplishedby considering both the age of the child and the severity of theobesity. For infants up to the age of 2, BMI is not assessed.Instead, the infants' weight percentile is compared to lengthpercentile. [1] A child < 2 years of age should be diagnosed as obese if the sex-specific weight for recumbent length is >95th percentile on theWorld Health Organization (WHO) charts. [7]

Managing a child with obesity is age dependent. The prevention of pediatric obesity by promotinghealthful diet, activity, and environment should be a primary goal, as achieving effective, long-lastingresults with lifestyle modification once obesity occurs is difficult. [7] In the first 6months of life, exclusive breast feeding is the nutrition of choice. Complementary foods should ideally be delayed until 6 monthsof age. Infants withobesity should not be given any sugar sweetened beverages, norany fast food or desserts. Infants should notbe watching TV or any screen of any kind for the first two yearsof life. Normal infants may need to sleep up to 18 h a day, andshould sleep at least 12 h a day. Infants should be allowed to beas active as possible, either on the floor or in a playpen and theparents should be encouraged to have as much direct interactionwith them as possible. [1]

Conclusion. Obesity is a chronic disease which when originating in childhoodcan lead to medical and psychological complications andpremature comorbidity and mortality. Distinguishing a chronic nutritional disorders as the obesity pattern thatoriginates during infancy is clinically important. Further studies are needed to better understand the mechanisms underlying leptin resistance in common forms of obesity, and how these could be targeted specifically to treat obesity, diabetes and related metabolic diseases.

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