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Galactosemia and timing of puberty: a case report of early diagnosed hypergonadotropic hypogonadism.

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Abstract

Galactosemia is an inborn error of galactose metabolism, characterized by the failure to metabolize galactose correctly due to enzyme deficiencies. Type I or classic galactosemia is the most severe form of galactosemia. The diagnosis is made by metabolic screening. Symptoms manifest from the first days of life and include feeding difficulties, vomiting, hypoglycemia, jaundice, and sepsis with E. coli. Long-term treatment consists of a strict galactose-free diet. However, patients may still develop endocrine complications, such as hypergonadotropic hypogonadism in females.

We report the case of a 9.5-year-old girl with classic galactosemia who was diagnosed with hypergonadotropic hypogonadism at an early age. The clinical follow-up until the start of puberty induction therapy is described. We highlight the importance of a timely diagnosis of hypogonadism to avoid a delay in the timing of puberty induction, which could lead to the potential complications.

Key-Words: Galactosemia, puberty, hypergonadotropic hypogonadism, primary ovarian insufficiency

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Introduction

Galactosemia encompasses a spectrum of disorders impacting galactose metabolism, each due to insufficient function of a specific enzyme within the pathway. There are four main types of galactosemia. Type I or classical galactosemia, caused by a deficiency of the enzyme galactose-1-phosphate uridyltransferase (GALT gene, chromosome 9p13, OMIM code 230400), is the most common and severe form in the Caucasian population (1).

The disease is inherited in an autosomal recessive form. Symptoms of the classic galactosemia, present early in life post ingestion of breast milk or formula, include feeding difficulties, vomiting, diarrhea, weight loss, hypoglycemia, jaundice with mixed-type hyperbilirubinemia, liver failure, and renal tubular damage with aminoaciduria. If not diagnosed early, these infants may develop sepsis from gram-negative bacteria (mainly E. coli). Late symptoms include pseudotumor cerebri and cataracts (2). Diagnosis is made by metabolic screening and confirmation by determining erythrocyte galactose-1-phosphate uridyltransferase activity and/or identifying pathogenic variants in the GALT gene (3,4). Treatment involves a lifelong strictly galactose-free diet (4). Despite adherence to a galactose-restricted diet, patients with galactosemia may develop long-term complications, such as cognitive deficits, verbal dyspraxia,

motor deficits, and endocrinological complications like delayed growth, reduced bone mineral density, and hypergonadotropic hypogonadism or delayed puberty in females (5).

We report the case of a 9.5-year-old girl with galactosemia who was diagnosed early with hypergonadotropic hypogonadism, detailing the diagnostic process and follow-up until pubertal induction. The aim of our report is to emphasize the need for endocrinological follow-up in patients with galactosemia, particularly females, due to the risk of associated endocrinopathies noted in guidelines. It is also important to note that an early diagnosis of hypergonadotropic hypogonadism allows the correct timing of the start of pubertal induction, with all the advantages this offers the patient.

Case Report

A 9.5-year-old girl was seen in the outpatient clinic for suspected precocious puberty. She was diagnosed with galactosemia at the age of 21 days, following neonatal metabolic screening and has been on a galactose-free diet since then. In 2018, endocrinological follow-up was discontinued after a diagnosis of isolated premature pubarche was made during an endocrinological evaluation at another centre. At the first visit in our center, stature and weight were within normal ranges for her age and sex (height -0,32 SDS and weight – 1,32 SDS). Bone age assessment was consistent with her chronological age (9 years according to Greulich and Pyle method). Examination revealed pubarche but no thelarche (B1 and PH2 according to Tanner). Blood tests showed high FSH levels (FSH 17.5 mcrUI/ml) with normal LH (LH 1.7 mcrUI/ml) and prepubertal estradiol levels (estradiol <5 pg/ml). Further investigations were initiated to exclude hypergonadotropic hypogonadism, due to the underlying galactosemia and hormone levels. Confirmatory blood tests showed low levels of estradiol (estradiol <5 pg/ml) and anti-Müllerian hormone (AMH 0.1 ng/ml), with a significant increase in FSH and LH on GnRH testing (peak FSH 87.6 mcrUI/ml and LH 84.6 mcrUI/ml) (Table 1).

Pelvic ultrasound described features of a prepubertal uterus and ovaries. With these results a diagnosis of hypergonadotropic hypogonadism, that is a common condition in female patients with galactosemia, was confirmed. The patient was monitored clinically and biochemically for sexual development and spontaneous puberty onset (Table 2). At 11.6 years, considering the absence of spontaneous puberty onset associated with a pubertal bone age, the FSH and estradiol values that confirmed the picture of hypergonadotropic hypogonadism, induction of puberty was initiated. Pubertal induction was started with low-dose transdermal estrogen (17 b-estradiol patches: 25 µg/day: 1/4 patch every 3.5 days). Following six months of therapy, thelarche was noted and the transdermal estrogen dosage was increased appropriately.

Table 1. Biochemical parameters at the diagnosis of hypergonadotropic hypogonadism.

	Laboratory data	Reference values
Basal FSH (mIU/mL)	48.5	< 11.1 mIU/ml
Peak FSH (mIU/mL)	87.6	< 11.1 mIU/ml
Basal LH (mIU/mL)	62.2	< 11.9 mIU/ml
Peak LH (mIU/mL)	84.6	< 11.9 mIU/ml
Estradiol (pg/mL)	<5	12.4 -233 pg/mL
AMH (ng/mL)	0.1	0.0 – 2.4 ng/mL
TSH (uUI/mL)	1.1	0.27 -4.2 uUI/mL
FT4 (pmol/L)	16.9	12 – 22 pmol/L
ACTH (pg/mL)	23.9	7.2 – 63.3 pg/mL
Cortisol (ug/dL)	12.8	7.3 – 32.3 ug/dL

Table 2. Biochemical parameters during the follow-up.

Age of patient	FSH (mIU/ml)	LH (mIU/ml)	estradiol (pg/mL)	AMH (ng/ml)
9.5 years old	**17.5**	**1.7**	**<5**	
9.7 years old	**48.7**	**62.2**	**<5**	**0.1**
10.7 years old	**93.2**	**26.2**	**<5**	**0.1**
11.2 years old	**89.7**	**24.5**	**<5**	**0.9**

Discussion

The knowledge of the endocrinological complications of galactosemia in females allowed us to suspect and then confirm hypergonadotropic hypogonadism.

In fact, the girl presented to our centre with a suspicion of precocious puberty, with hormonal tests that at the first visit could have been consistent with puberty onset. Therefore, since ovarian insufficiency in galactosemic patients can present at different ages and in a chameleon-like manner, we would like to emphasise the importance of the medical history in the evaluation of this suspected diagnosis, as well as the need for careful follow-up over time.

Hypergonadotropic hypogonadism represents a significant long-term complication of galactosemia in women, despite an early diagnosis and the strict adherence of affected individuals to a galactose-restricted diet. This condition is observed in approximately 80-90% of female subjects with classical galactosemia who are born alive (5). The spectrum of clinical manifestations is heterogeneous: primary amenorrhea without development of secondary pubertal characteristics; primary amenorrhea with normal development of secondary sexual characteristics; secondary amenorrhea with normal development of secondary sexual

characteristics; menstrual irregularities to early adult menopause (6). The earliest medical records of a potential association between galactosemia and hypergonadotropic hypogonadism date back to 1979. The exact pathophysiological pathways causing premature ovarian insufficiency in women with galactosemia are still unknown, despite substantial investigation. The fundamental explanation is thought to be an internal build-up of galactose metabolites, primarily galactose-1-phosphate, which causes early cell death and an early decrease in ovarian reserve. (7,8).

International Guidelines on the management of classic galactosemia recommend endocrinological follow-up for these patients. Screening for hypergonadotropic hypogonadism should be conducted in all girls with galactosemia who have not exhibited secondary sexual characteristics by age 12, or who have not had menarche by age 14, or in the case of menstrual irregularities. Furthermore, the recommendations suggest that female with galactosemia that have undergone puberty and have regular ongoing menstrual periods be monitored annually for signs or symptoms of premature ovarian insufficiency. It is recommended that measurements of FSH and estradiol be employed in the context of both diagnosis and follow-up (4).

Screening for hypogonadism is crucial in this patient population, given the pivotal role of sex hormones in individual development. Sex steroids are essential in controlling the development of secondary sexual characteristics and the regular growth of the uterus. In addition, they are essential for the psychological and social development of the individual. During puberty and later stages of life, they ensure the attainment of appropriate peak bone mass and optimal muscle trophism (9). A long-term complication in individuals with classic galactosemia is a reduction in peak bone mass, a condition that would be exacerbated by a lack of sex hormones.

The timely diagnosis of our patient enabled us to initiate pubertal induction at a time that perfectly matched the physiological onset of puberty. This ensured the above-mentioned beneficial metabolic and psychological impacts. To start puberal induction as early as possible and to improve the outcome of young patients, it is desirable that this early diagnosis be made in all types of hypogonadism.

Regarding the optimal age for the start of pubertal induction, the current European guidelines emphasize the importance of individualizing the timing of pubertal induction, taking into account not only the chronological age but also the girl's psychosocial maturity. In most cases, the optimal age for the commencement of pubertal induction is 11 years in girls who have not yet initiated puberty, who exhibit no signs of puberty and who have undergone diagnostic tests to confirm the presence of hypogonadism (9). Regarding the therapeutic management of these young patients, the preferred treatment option is initiation of therapy with transdermal 17-beta-estradiol, commencing with low doses and subsequent gradual increase until the introduction of a cyclic progestogen to induce the menstruation (10).

In conclusion, regarding the topic of fertility, a small number of young people with galactosemia have had spontaneous pregnancy documented in the literature, since the phenotypical expression of this disease

could be different. According to the current standards, fertility preservation techniques could be offered in a small number of prepubertal girls with galactosemia after an appropriate ethical evaluation and in a research setting. Finally, it should be noted that fertility preservation may not be successful (9;10).

Conclusions

Hypergonadotropic hypogonadism is a common long-term complication in women with galactosemia. Clinical assessment and FSH and estradiol levels should guide diagnosis and follow-up until the age of pubertal induction. Early diagnosis of hypogonadism is crucial for timely initiation of pubertal induction therapy to prevent further long-term complications in these patients.

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Informed consent: was obtained by the parents.

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