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Case Report

Revisiting the Association of Central Precocious Puberty with Neurovisceral Diseases owing to a Girl with Niemann-Pick Disease Type C

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Abstract
Niemann-Pick type C disease (NP-C) is a rare neurovisceral disorder caused by mutations in the NPC1 or NPC2 genes. Clinical symptoms of NP-C can appear at any age. Here we report a case of a girl diagnosed with NP-C who subsequently developed central precocious puberty (CPP). To our knowledge, this association has not been described in the literature till now. An 8 year old girl was referred to the pediatric metabolism outpatient clinic due to poor school performance, behavioral changes and periventricular white matter signal changes observed on cranial magnetic resonance imaging (MRI). The physical examination revealed vertical supranuclear gaze palsy (VSGP) and splenomegaly. The patient was diagnosed NP-C through genetic analysis and was started miglustat treatment. The patient was also referred to the pediatric endocrinology outpatient clinic due to breast development (Tanner stage 3) and pubic hair (Tanner stage 3). Laboratory work up revealed normal basal serum LH (0. 2 U/L) and the LHRH test showed a LH value of 8.48 U/L and a peak LH/ FSH ratio of 2. 8 (>0.66). Pelvic ultrasonography revealed an uterine length of 45 mm and mean ovarian volume of 5. 5 mL, Leuprolide acetate was started and at the first year of follow-up the patient's height velocity was 0.4 SDS and Tanner's pubertal staging was 3. This case report highlights a potential association of NP-C with CPP and confirms the need for careful assessment of pubertal development in patients with white matter disease.
Keywords: Niemann-Pick disease type C, precocious puberty, inherited metabolic disease

What is already known on this topic?
NP-C disease is a lysosomal storage disorder with a broad clinical spectrum. Different phenotypes of the disease are seen as a result of the accumulation of free cholesterol and glycosphingolipids in tissues and other organs, particularly in the brain. Precocious puberty has rarely been observed as a clinical symptom of LSD.
What this study adds?
This is the first report of a patient with NP-C disease presenting with CPP. This association has not been described so far.

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Introduction
Niemann-Pick type C (NP-C) disease is a rare autosomal recessive neurovisceral lysosomal storage disorder caused by pathogenic mutations affecting both alleles of the *NPC1* or *NPC2* genes. Loss of function in NPC1 or NPC2 proteins leads to the accumulation of unesterified cholesterol and glycosphingolipids in late endosomes and lysosomes. This defect impairs intracellular lipid trafficking, leading to progressive lipid storage in affected tissues. At least 95% of cases result from *NPC1* mutations, while fewer than 5% are due to *NPC2* mutations [1,2]. NP-C has a broad clinical spectrum and may present at any age with visceral, neurological, and psychiatric manifestations. Neurological involvement is a major determinant of disease phenotype and progression [3]. When NP-C is clinically suspected, the diagnosis can be confirmed by biochemical biomarkers (oxysterols, Lyso-sphingomyelin [Lyso-SM], Lyso-SM-509, and bile acid derivatives) together with molecular genetic testing of the *NPC1* and *NPC2* genes, typically using next-generation sequencing (NGS). Although no curative therapy is currently available, disease management consists of supportive care, and miglustat is the only approved disease-modifying therapy for neurological manifestations [4].
Central precocious puberty (CPP) is defined as the onset of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys, due to premature activation of the hypothalamic–pituitary–gonadal (HPG) axis. The diagnosis is based on clinical findings supported by biochemical evaluation, particularly a pubertal response in the GnRH stimulation test [5–7]. Increasing evidence suggests that neurodegenerative and neurometabolic disorders affecting the brain may influence neuroendocrine pathways regulating puberty [8]. In this context, lysosomal storage disorders (LSD) have been occasionally associated with CPP, possibly through disruption of hypothalamic function and GnRH regulation.
Herein, we present a girl with NP-C who was diagnosed with CPP at initial assessment, highlighting the importance of careful evaluation of pubertal development in patients with neurometabolic disorders.
Case Presentation
An 8-year-old girl was referred to the pediatric metabolism clinic due to poor school performance, behavioral changes, and periventricular white matter abnormalities detected on cranial magnetic resonance imaging (MRI).
The patient was born at 38 weeks of gestation via spontaneous vaginal delivery with a birth weight of 3800 g following an uneventful pregnancy. Her growth and development were normal until the age of seven; however, progressive cognitive decline and behavioral changes

were subsequently noted, leading to the initiation of special education. She is the fourth child of consanguineous parents (first-degree cousins), with no known family history of genetic or metabolic disorders.

On physical examination, body weight was 27 kg (−0.9 SDS), height 128 cm (−1.4 SDS), and body mass index (BMI) 16.48 kg/m² (−0.2 SDS), all calculated according to Turkish national reference standards [9]. Pubertal assessment revealed Tanner stage 3 breast development and pubic hair. According to parental history, pubertal signs were first noticed at approximately 7 years of age. Neurological examination demonstrated vertical supranuclear gaze palsy (VSGP) and slowed speech. Splenomegaly was also present. Cranial MRI showed T2-weighted hyperintense signal changes, predominantly in the parieto-occipital periventricular white matter. Routine laboratory investigations, including complete blood count, biochemical analysis, and urinalysis, were within normal limits. Lysosphingolipid analysis revealed elevated Lyso-SM (20.2 nmol/L; reference range 0–19.12 nmol/L), Lyso-SM-509 (4925), and an increased Lyso-SM-509/Lyso-SM ratio (243), markedly elevated compared to values reported to reported control values, consistent with NP-C disease. Molecular genetic analysis was performed using a targeted next-generation sequencing (NGS) panel, which identified a homozygous c.363+6T>G variant in the *NPC2* (NM_006432.4) gene. The variant was re-evaluated according to the ACMG/AMP variant interpretation guidelines and classified as likely pathogenic, fulfilling the PP3_Strong, PM2_Supporting, and PP5_Supporting criteria**.** Segregation analysis confirmed heterozygosity in both parents. Miglustat therapy was initiated based on body surface area.

At initial presentation, advanced pubertal development (Tanner stage 3) was noted, and bone age was consistent with 11 years based on the Greulich and Pyle method [10]. Basal serum LH was 0.3 IU/L, and GnRH stimulation testing demonstrated a peak LH level of 8.5 IU/L. Serum 17-OHP (17- hydroxyprogesterone) (1.4 ng/mL; reference range <2 ng/mL) and DHEAS (dehydroepiandrosterone sulfate) (44 µg/dL; reference range >40 µg/dL) [11]. Pelvic ultrasonography findings were consistent with pubertal development, with a uterine length of 45 mm (reference: >35 mm), corpus- to-cervix ratio (≥1) in pubertal girls) and a mean ovarian volume of 5.5 mL (reference: >2 mL), supporting pubertal activation [12,13]. These findings were consistent with central precocious puberty.

The diagnosis of central precocious puberty (CPP) was supported by advanced pubertal staging (Tanner stage 3), significantly advanced bone age, and a pubertal response to the GnRH stimulation test. Although the tempo of pubertal progression could not be assessed longitudinally, treatment was initiated in view of the underlying neurological disease and parental preference to delay menarche. The patient's mid-parental height SDS was −1.4, and predicted adult height was −1.3 SDS, suggesting no marked compromise in height potential. Accordingly, leuprolide acetate (3.75 mg every 28 days) was started. No treatment-related adverse effects were observed during one year of follow-up. Pubertal progression remained stable. However, a decline in growth velocity was noted during the first year of GnRH analog therapy in this euthyroid patient, with a growth velocity of −2.8 SDS/year at the most recent evaluation. Recombinant growth hormone therapy was recommended; however, it could not be initiated due to financial constraints (14).

Discussion

To our knowledge, this is the first reported case of a girl with NP-C disease presenting with CPP at diagnosis. Central precocious puberty has been reported in patients with inherited metabolic disorders, particularly those with central nervous system involvement [15].

In NP-C disease, intracellular lipid accumulation is associated with neuronal dysfunction, microglial activation, and neuroinflammation [16]. Accumulation of gangliosides such as GM2 and GM3 has been implicated in widespread neurodegenerative changes within the central nervous system [16]. Since our patient's neurological symptoms began after the age of seven, she was classified as having the juvenile form of NP-C.

CPP may occur in inherited metabolic disorders associated with the accumulation of toxic metabolites in the central nervous system. In these conditions, the HPG axis may be affected through various pathophysiological mechanisms. A total of 19 patients with inherited metabolic disorders associated with CPP have been reported in the literature, with LSDs representing the majority of cases. Up to now, 15 cases of CPP associated with LSDs have been described in the literature (Table 1). Proposed mechanisms include hypothalamic damage due to toxic metabolite accumulation, neuroinflammation, and disruption of inhibitory pathways regulating the HPG axis [17–27].

Based on these observations, it can be hypothesized that lipid accumulation and neuroinflammatory processes in NP-C may contribute to functional alterations in hypothalamic pathways. In our patient, no structural abnormalities of the hypothalamus or pituitary gland were observed on MRI. However, subtle or microscopic dysfunction cannot be excluded, and the possibility of a coincidental association should also be considered.

A limitation of routine NGS-based testing should be acknowledged. Targeted NGS panels interrogating coding regions and exon–intron boundaries are not designed to detect copy number variants (CNVs) or deep intronic variants. Therefore, additional molecular analyses may be considered in patients with a strong clinical suspicion of NP-C despite negative or inconclusive routine NGS results.

In conclusion, this case highlights a possible association between NP-C disease and CPP. Although direct involvement of hypothalamic GnRH neurons has not been demonstrated, it is plausible that disease-related processes, including lipid accumulation and neuroinflammation, may affect hypothalamic function and neuroendocrine regulation. Nevertheless, a causal relationship cannot be definitively established, and the possibility of a coincidental association should be considered. Clinicians should be aware of potential neuroendocrine involvement in patients with NP-C disease. Further clinical and mechanistic studies are needed to clarify the relationship between NP-C disease and central precocious puberty.

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Table 1. Chronological overview of clinical case reports of inherited metabolic diseases associated with precocious puberty

Study	N Patients/ Sex	Diagnosis	Clinical features of precocious puberty	Possible pathogenic mechanisms	Treatment
Tanaka et al. (21), 1985	1/ F	Tay-Sachs Disease	Breast enlargement was observed at the age of 4 years. At 5 years and 9 months, breast development corresponded to Tanner Stage III–IV, while pubic hair was at Tanner Stage III. Menstruation started at 6 years and 3 months. Advanced bone age, basal FSH and LH levels, and an exaggerated response to the LHRH test were observed	-Damage to LHRH-containing neurons due to GM2 ganglioside accumulation may stimulate gonadotropin release from the pituitary gland -Selective interruption of the inhibitory influences on the HPG axis	Not treated
Büyükgebiz et al. (17), 1994	1/ F	Phenylketonuria (PKU)	7.5 years, premature thelarche, advanced bone age (9 years), pubertal level LH response to LHRH stimulation test, normal pelvic ultrasound. Menstruation started at 9 years	High serum phenylalanine levels may cause early activation of the HPG axis due to their toxic metabolic effect	Cyproterone acetate, poor compliance
Tylki-szymanska et al. (23), 1995	3/M	Mucopolysaccharidosis Type IIIA (Sanfilippo IIIA)	Ages 5.9, 6.6 and 9.6, basal and GnRH stimulated LH and FSH at pubertal levels, high testosterone levels, large testicular volume, but no progress in growth rates and bone age	No details	Two patients were started on GnRH agonist and it was effective

Aysun et al. (27), 2000	1/F	Late infantile neuronal ceroid lipofuscinosis	6 years 7 months, breast development (Tanner stage III-IV) and pubic hair (Tanner stage III), advanced bone age, exaggerated response to the LHRH test	Selective destruction of inhibitory pathways in the hypothalamus, or chronic disruption of neurons containing LH-RH, or stimulation of gonadotropin release from the pituitary gland due to the accumulation of lipofuscin-like material	Not reported
Polgreen et al. (25), 2008	4 (1F, the genders of the other patients are not reported)	Mucopolysaccharidosis Type IH (MPS IH)	7.11 years, pubic hair Tanner stage III, 7.7 years LH-ICMA 2.0 mIU/l, estradiol 19 pg/ml. In 2 patients, biochemical findings were consistent with precocious puberty, but there were no clinical signs of puberty	Effects associated with HSCT or associated to MPS IH	Not reported

Table 1. Continued

Study	N Patients/ Sex	Diagnosis	Clinical features of precocious puberty	Possible pathogenic mechanisms	Treatment
Concolino et al. (24), 2008	2/M	Mucopolysaccharidosis Type IIIA (Sanfilippo IIIA)	Ages 7.6 and 7.7, increase in testicular volume (6 ml), serum basal LH, FSH levels, and GnRH stimulation test results at pubertal levels	Heparan sulfate accumulation affects fibroblast growth factor morphogenesis and hypothalamic pathways Impaired glia-neuron interaction	GnRH agonisti, effective
Lucaccioni et al. (18), 2014	1/F	Phenylketonuria (PKU)	2.2 years, breast development, pubic hair growth, vaginal discharge, advanced bone age (4.62 years) LH response at pubertal levels to LHRH stimulation test, Pelvic ultrasound, enlarged uterus (length 4.75 cm); fundus-cervical ratio 1.17, endometrial thickness 5.7 mm. Ovaries are of normal size but there is a large follicle	Plasma phenylalanine levels are within the recommended range, so it is coincidental	GnRH agonist (Triptorelin), effective
Acar et al. (22), 2018	2/F	Tay-Sachs Disease	Age, 6 years 10 months and 5 years 10 months, breast development (Tanner stage II-III), pubic hair growth (Tanner stage II), advanced bone age, pubertal development on pelvic ultrasound, high LH and estradiol levels	Increased gonadotropin secretion due to chronic destruction of GnRH neurons associated with GM2 ganglioside accumulation	GnRH agonist
Belli et al. (26), 2018	1/F	Metachromatic leukodystrophy (MLD)	4.7 years bilateral thelarche. At 4.8 years, progression of pubertal development, pelvic ultrasound showing increase in uterine diameter, LH response at pubertal level to GnRH stimulation test	Dysfunction in the HPG axis due to the accumulation of sulfatides	GnRH agonisti, effective
Bizjak et al. (19), 2020	1/F	3-Methylglutaconic aciduria type 1 (3-MGA-1)	5.5 years breast development, advanced bone age, increased growth rate, LH response at pubertal level to GnRH stimulation test	The accumulation of toxic substances causes microscopic damage to the hypothalamus	GnRH agonist, effective

Table 1. Continued

Study	N Patients/ Sex	Diagnosis	Clinical features of precocious puberty	Possible pathogenic mechanisms	Treatment

Saito et al. (15), 2021	1/M	Neuronal ceroid lipofuscinosis type 8	8.3 years, pubic hair Tanner stage III, 6 ml testicular volüme, advanced bone age, serum basal LH, FSH levels, and GnRH stimulation test results at pubertal levels	-The accumulation of autofluorescent storage material in lysosomes (pathological evaluation was not done) - Coincidental	GnRH agonist, not reported
Zhu et al. (20), 2024	1/M	X-linked adrenoleukodystrophy (X- ALD)	6.8 years 5-6 ml testicular volume, onset of pubic hair, advanced bon age, LH levels at pubertal levels in response to GnRH test	Causes disruption in the HPG axis of ALDP, which is also found in the hypothalamus	Not treated, due to slow pubertal progression
Present study	1/F	Niemann Pick type C disease (NP-C)	8 years, bilateral thelarche (Tanner stage III), pubic hair growth (Tanner stage III), pelvic ultrasound uterine length 45 mm, mean ovarian volume of 5. 5 mL pubertal response to LHRH stimulation test	-Damage to LHRH-containing neurons due to GM2 and GM3 ganglioside possible accumulation may stimulate gonadotropin release from the pituitary gland -Selective interruption of the inhibitory influences on the HPG axis -Coincidental	GnRH agonist, effective

FSH: Follicle-stimulating hormone GnRH: Gonadotropin- releasing hormone HPG: hypothalamic-pituitary-gonadal HSCT: Hematopoietic stem cell transplantation
ICMA: Immunochemilumimetric assay LH: Luteinizing hormone