CORNELIA DE LANGE SYNDROME - RARE MUTATION OF SMC1A GENE

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ABSTRACT Introduction: Cornelia de Lange syndrome is a genetic disorder with variable and multisystemic expression marked by physical, cognitive and behavioural characteristics. The prevalence is underdiagnosed but is estimated between 1:10,000-30,000 live births. Mutations in the NIPBL gene are responsible for 60-70% of cases. Description of case: Premature female newborn delivered at 34 weeks of gestation was admitted to neonatal intensive care unit with feeding difficulties. Family history was unremarkable. Fetal ultrasounds revealed third-trimester oligohydramnios and growth restriction: fetal Karyotype 46, XX. transfontanellar, abdominal and kidney ultrasounds were normal. Echocardiogram showed patent oval foramen. During the first months of life, she had insufficient weight gain associated with facial features (synophrys, winged ears, hypertrichosis, small eyelid slits) and adducted thumbs. A presumptive diagnosis of Cornelia de Lange syndrome was made. A genetic study revealed mutation on the SMC1A gene, missense variant c.2365A>C(p.Ile789Leuc) in heterozygosity, associated with a mild phenotype. Conclusion: This case reports a rare mutation on the SMC1A gene (MIM #300040), causing Cornelia de Lange syndrome. We intend to reinforce the importance of a high level of clinical suspicion for the diagnosis of this syndrome.

KEYWORDS Cornelia de Lange syndrome, SMC1A gene, failure to thrive, facial dysmorphism, intellectual deficit

Introduction

Cornelia de Lange Syndrome (CdLS) is a multisystemic disorder with variable expression marked by intellectual deficit, characteristic facial dysmorphism, severe fetal growth restriction, upper-limb reduction, among numerous other signs and symptoms[1,4]. However, mototype have less severe growth and cognitive delay, do not have upper limb reduction, despite maintaining the characteristic facial features of CdLS[1,3]. The prevalence is estimated between 1:10,000-30,000 live births[3], and it is slightly more frequent in females (1.3:1), but no differences were found in the race[4]. In addition to clinical findings, diagnosis is based on identifying a mutation in one of the following genes: NIPBL, SMC1A, SMC3, RAD21, BRD4, HDAC8 and ANKRD11[3]. The major gene involved, the NIPBL gene, is mutated in approximately 60-70% of patients[1,3].

Typical or classic CdLS is more easily identified from birth[1,3]. The diagnostic suspicion can increase in the presence of the following craniofacial appearance (more than 95% of cases): microcephaly, synophrys, highly arched eyebrows, anteverted nares, high and arched palate with clefts (30%), small widely spaced teeth, micrognathia (80%), mandibular spurs (42%), and short neck[1,2,4]. Growth delay is present in more than 95% of cases, weight at birth is commonly in the 5th percentile, and there are specific ranges for height, weight and head circumference[1,3]. Growth delay depends on genetic mutation involved and is less affected in patients with SMC1A compared with the NIPBL variants[1,3]. The diagnosis of symmetric intrauterine growth restriction is common[1,3]. Intellectual disability and limb abnormalities are equally frequent in more than 95% but less affected in mild CdLS[1,3]. Hirsutism in 80% of cases[1]. Other characteristics: cardiac defects (25%), renal malformations (10%); gastroesophageal reflux disease, constipation and dysphagia[3,5,6]. Recurrent respiratory infections are also frequent[1,3]. Sometimes immunological anomalies occur, and
thrombocytopenia is common but are mostly non-progressive and asymptomatic[1,3]. Regarding ophthalmic characteristics - 50% ptosis, 60% myopia, 14-17% nystagmus[1,3], frequent synophrys, blepharitis, epiphora, hypertrichosis of the eyebrows and eyelashes and nasolacrimal duct obstruction[9]. Conductive and sensorineural hearing loss is noted in 85-90%[1,3].

SMC1A encodes structural maintenance chromosomes protein 1A, a core component of the cohesin complex. Variants in this gene are identified in 5% of CdLS cases, designated missense mutations or small-frame deletions in SMC1A and are evenly spread over the gene[3,11-14]. Most children exhibit the non-classic phenotype[1,3,11,12]. There are reported cases of mosaic more frequently associated with the NIPBL variant, rarely with the SMC1A variant[1,3,11-13]. Morbidity and mortality increase due to existing major malformations[1].

Case report
Six years-old female child, caucasian race with healthy non-consanguineous parents and unremarkable family history. Fetal ultrasounds revealed third-trimester oligohydramnios and intrauterine growth restriction. Fetal karyotype was normal with female chromosomal complement. She was born at 34th-week gestation, appropriate for gestational age, excepting microcephaly (P3-10) and was admitted to neonatal intensive care unit with feeding disabilities and global hypertonicity. transfontanellar, abdominal and kidney ultrasounds were normal. Echocardiogram showed patent oval foramen/interauricular communication and electrocardiogram was normal. During ambulatory monitoring, it was evident typical facial features (unibrow, winged ears, hypertichosis, small eyelid slits – figure 1), adducted thumbs and pubic and back thin hair and insufficient weight gain with microcephaly. She had a global development disability in the hearing and speaking area, eye-hand coordination and realization area. Constipation and gastroesophageal reflux disease were also present. The hormonal study was normal. Brain MRI showed global enlargement of circulation e spaces of liquor in the subarachnoid space. The regular hearing evaluations were normal. The NIPBL molecular study was negative, so a multigene panel included known genes associated with CdLS phenotype, NIPBL, SMC1A, SMC3, HDAC8, RAD21, was performed that confirmed CdLS - mutation on the SMC1A gene (MIM #300040), missense variant c2365A>C(p.Ile789Leuc) heterozygotic. De novo variant after testing parents, which was normal. She maintains multidisciplinary follow-up to neonatology, cardiology, otorhinolaryngology, ophthalmology and rehabilitation appointments.

Discussion
Cornelia de Lange Syndrome is rare in children, the classic form of the disease being more easily identified by its typical facial features and severe cognitive delay, and the milder phenotypes may be underdiagnosed[1,3]. Typical manifestations for diagnosis include physical and cognitive characteristics[1,4]. Diagnosis is both clinical and genetic[1,3,4], being identified as a genetic cause in 95-97% of cases[1]. The severity of symptoms varies, but the association with ophthalmic pathology and hearing loss is common (90% of cases)[9,10]. In SMC1A (MIM #300040) related-CdLS, the clinical manifestations are lighter compared to individuals with NIPBL variants: growth is less affected, facial signs are less exuberant, there are no major anomalies in the limbs, they have a higher level of cognitive and adaptive functioning and self-injurious behaviour is less frequent[1,3,11-13]. As for the differential diagnosis of these SMC1A variants, they may present a phenotype similar to Rett syndrome[13]. The treatment must be multidisciplinary and according to the attainment of the disease, with the support of physiotherapy, speech and occupational therapy being important[1,3]. Growth hormone (GH) secretion has been reported to be normal, and to date, there is no scientific evidence to suggest treatment with recombinant human GH in patients with CdLS[14]. The recommended follow-up in infancy and early childhood is annual[1,3], being mandatory evaluation by ophthalmology and otorhinolaryngology (with auditory brainstem response and otoacoustic emissions test, in the presence of sensorineural hearing loss)[10]. Adolescents and adulthood it is suggested every 3-5 years[3]. Prognosis depends on multiorgan achievement[1,3].

The authors want to reinforce the importance of clinical suspicion to diagnose a syndrome in patients with typical body features and the need to look for other mutations in other genes when the suspicion is strong. The genetic syndromes manifest themselves with many clinical presentations, and the prognostic depends on the gene mutations and precocious intervention. This case showed a new variant on the SMC1A gene, connected to a less severe phenotype.

Abbreviations
CdLS - Cornelia de Lange Syndrome
GH - Growth hormone

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Conflict of interest
There are no conflicts of interest to declare by any of the authors of this study.

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