Oculofacial Alterations in NBAS-SOPH like Mutations: Case Report.

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ABSTRACT

Purpose: To describe the clinical features of a rare case of NBAS-SOPH-like mutations; to emphasize special aspects of the ocular and oro-facial regions.

Methods: Case report.

Case Description: We present a 5-year-old girl initially examined for her dysmorphic features, mental delay, strabismus, and high myopia. During the funduscopic examination, we observed optic atrophy with narrow thinned arterioles with the light brown reflex of the

central retina. A genetic assessment revealed NBAS-SOPH like mutation. An assessment by a team of orthodontists defined typical characteristics

Conclusions: NBAS mutations can also cause complex disease with a broad clinical spectrum ranging from isolated recurrent acute liver failure (RALF) to a multisystemic phenotype. Due to the heterogeneity of the expressions, a multispeciality approach to this situation is recommended.

INTRODUCTION

The NBAS (NeuroBlastoma-Amplified Sequence) mutation is an hereditary "short stature syndrome" characterized clinically and genetically by growth retardation with facial dysmorphism, ocular involvement and various bodily malformations [1]. Although many short stature genes have been identified, a unique and specific genetic assignment has not yet been achieved. Patients with NBAS-SOPH like mutation (Short stature, Optic nerve atrophy, and Pelger-Huet anomaly) have similar facial features with a pointed chin and mild proptosis, as well as loose skin, reduced subcutaneous fat and a progeroid appearance. Skeletal features such as slender bones, epiphyseal dysplasia with multiple phalangeal pseudo-epiphysis and cervical instability with myelopathy are often present [2], retinal dystrophy and optic atrophy have also been described [3, 4]. Some cases are reported in the scientific literature, focusing on ocular and facial features. We present another case presenting ocular peculiarities, also highlighting the indication of a multidisciplinary evaluation involving a pedo-orthodontist.

CASE DESCRIPTION

We present a 5-year-old girl, initially examined at the Ophthalmological clinic of the University of San Giuseppe, Milan, Italy, for signs of dysmorphia [Fig. 1], mental delay and strabismus.

Our patient had convergent strabismus with fixation preference in the right eye [Fig. 2]. On the evaluation of ocular motility, a pseudo-limitation of abduction in both eyes and nystagmus in the extreme positions was detected. The cycloplegic refraction was -10.50 D - 1.00 D × 030° for the right eye and -13.75 D - 0.00 D × 030° for the left eye. A subjective visual acuity assessment is not possible from the outset, taking into account the patient's age and mental delay. The anterior segment showed no significant alteration while the funduscopic examination showed optical atrophy with narrow thinned arterioles and a brownish appearance of the central retina, suggesting a defect in the nerve fiber layer with relevant myopic choroidosis [Fig. 3].

Therefore, severe pathologic myopia, optic sub-atrophy, and diffuse retinal depigmentation were the significant signs in our report sent to the Genetics Clinic, where a severe liver disease was revealed by a laboratory routine test. After a few months, an NBAS-SOPH like mutation was detected.

We also noted that growth retardation also affected tooth development, occlusion of the dental arch and mandible and that pedo-orthodontic assessment was requested through a comprehensive examination by the team of orthodontists of the orthodontic clinic of Biomedical Department, Surgical and dental sciences, University of Milan, Italy. A full review was not completed due to lack of cooperation. Nevertheless, we found, from an extraoral point of view, a pattern of normo-divergent growth with a class III skeletal tendency, due to maxillary retrognathism. A cephalometric radiograph is still pending to analyze the relationship of the anteroposterior jaw from an intraoral point of view, the patient had a normal development of the deciduous dentition. All twenty teeth were in the normal position of the mouth and no decay was detected during the examination. The patient has Class III dental malocclusion with 1mm overbite and no overjet. The opening of the mouth is within the normal range and no displacement is detected.

DISCUSSION

Among the short stature genes studied, we mention the CUL7 gene, which has been identified as responsible for the 3-M syndrome, which is a rare autosomal recessive disorder characterized by severe pre and postnatal growth retardation and facial dysmorphism but with a normal intelligence [5]. The Pelgere-Huët anomaly (PAH), characterized by an abnormal nuclear form in neutrophil granulocytes [4], is another similar type of “short stature” with normal intelligence and loss of vision. In recent studies, similar clinical features have been identified and have been associated with an identical missense mutation in the neuroblastoma amplified sequence (NBAS) gene [6]. NBAS is a component of the syntaxin complex18 and is involved in nonsense-mediated mRNA decay control. The NBAS deficiency was ranked among the first faults related to a major defect in retrograde transport. NBAS mutations can cause multisystemic disease involving the liver, eyes, immune system, connective tissue, and bones, caused by biallelic mutations of the associated gene. In these pathological families, multispeciality support is often useful for managing organ growth and maturation problems in the early years of life.

Mutations in the NBAS can also cause a complex disease with a broad clinical spectrum ranging from isolated recurrent acute liver failure (RALF) to a multisystemic phenotype [7]. The thermal susceptibility of syntaxin complex 18 is at the basis of fever dependence of ALF episodes. Parks & Lee recently described optic atrophy and achromatopsia in the NBAS mutation of two brothers [4] demonstrating the important role of the NBAS gene in retinal homeostasis. In Table 1, we have summarized the clinical features described in the few case reports present in the literature.

Clinical features in NBAS-SOPH	
Postnatal growth failure	Loose and senile skin with depressed turgor of tissue
Micromelia, brachydactyly	Bilateral optic nerve atrophy
Nonprogressive loss of visual acuity	Complete or incomplete achromatopsia
Hypolobulation of granulocyte nuclei	Brachycephalic skull with hypoplasia of the frontal and parietal tubers
Narrow forehead	Long senile face with small features
Small orbits	Bilateral exophthalmos
Hypoplastic cheekbones	Straight nose with prominent glabella
Long philtrum	Thin lips
High voice with harsh timber	Short neck
Hypermobility of small joints	Muscular hypotonia
Wide feet with a high arch	Facial asymmetry
Thick and/or bushy eyebrows	Epicanthus
Sandal gap	Wide big toes

Table 1. Clinical features described in NBAS-SOPH like syndrome [1, 8-10].

Reviewing all the clinical features provided by our patients, we readily recognize some of the described signs of mutations such as NBAS-SOPH: postnatal growth failure, non-progressive loss of visual acuity (unchanged on various follow-ups), narrow forehead,

small orbits, hypoplastic cheekbones, high voice with harsh timber, bilateral optic nerve atrophy, brachycephalic skull with hypoplasia of frontal and parietal tubercles, long senile face with small features, thin lips and facial asymmetry. An interesting aspect of our report is the characteristic oral changes that occur in people affected by this syndrome, relevant because of the early observation under conditions of low incidence. In view of the above, we believe that the multidisciplinary approach to patients is important because the characterization of oral malformations in these patients can provide an early indication of their support from a dental perspective.

In our case, a collaboration between medical teams specifically allowed for rapid management of oral facial growth patterns.

Declaration of conflicting interests

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