

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

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17 **ABSTRACT**

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

20 *Methods: Case report.*

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

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

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

30 INTRODUCTION

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

44 CASE DESCRIPTION

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

48 Our patient had convergent strabismus with fixation preference in the right eye [Fig. 2]. On
49 the evaluation of ocular motility, a pseudo-limitation of abduction in both eyes and
50 nystagmus in the extreme positions was detected. The cycloplegic refraction was -10.50 D
51 - 1.00 D × 030° for the right eye and -13.75 D - 0.00 D × 030° for the left eye. A subjective
52 visual acuity assessment is not possible from the outset, taking into account the patient's
53 age and mental delay. The anterior segment showed no significant alteration while the
54 funduscopy examination showed optical atrophy with narrow thinned arterioles and a
55 brownish appearance of the central retina, suggesting a defect in the nerve fiber layer with
56 relevant myopic choroidosis [Fig. 3].

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

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

73 DISCUSSION

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

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

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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

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

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

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

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

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