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# SEVERE VISUAL IMPAIRMENT AND RETINAL CHANGES IN A BOY WITH A DELETION OF THE GENE FOR NANCE-HORAN SYNDROME

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## ABSTRACT

We present the ophthalmologic findings in a boy with a deletion of Xp22 comprising the gene for Nance-Horan syndrome. Different mechanisms underlying the visual impairment in Nance-Horan syndrome are discussed.

## RÉSUMÉ

Nous présentons les données ophtalmologiques d'un garçon atteint d'une délétion du chromosome Xp22, comprenant le gène du syndrome de Nance-Horan. Différents mécanismes pouvant être responsables pour la malvoyance dans le syndrome de Nance-Horan sont investigués.

## KEY WORDS

Nance-Horan syndrome, *NHS*, *CDKL5*, visual impairment, retina

## MOTS-CLÉS

Syndrome de Nance-Horan, *NHS*, *CDKL5*, malvoyance, rétine

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## INTRODUCTION

The Nance-Horan syndrome (NHS), or the cataract-dental syndrome [NHS, MIM 302350], is a rare X-linked disorder, characterized by dental and ocular anomalies more pronounced in males than in heterozygous females. Ocular manifestations in affected males include bilateral congenital cataracts, typically involving the foetal nucleus and posterior Y-suture with variable zonular extensions in the posterior cortex. Microcornea, microphthalmia and nystagmus have been reported in some pedigrees (2, 4, 5). Characteristic dysmorphic features include a long narrow face, prominent nose and nasal bridge, anteverted pinnae of the ears, short fourth metacarpal bones and multiple dental anomalies, including screwdriver-shaped teeth due to narrow gingival and incisal margins (2). Mild mental impairment is found in approximately 30% of affected males (1, 2). Heterozygous females manifest with similar but less severe features, including posterior Y-sutural cataracts, with little or no loss of vision, and characteristic dental abnormalities (1, 2). The gene for NHS was mapped to chromosome Xp22 in 1990 (2) and subsequently cloned in 2003 (1). Here we present the ophthalmologic findings including retinal changes in a boy with a deletion in Xp22 including the *NHS* gene. This is the first report of retinal changes in Nance-Horan syndrome.



*Fig 1 A:* Patient at age of 18 months: bilateral microcornea, prominent nose and nasal bridge, thin hair, full lips and eyebrows.

## CASE REPORT

The clinical findings within the first year and the molecular data were reported previously (5). In summary, this boy presented with congenital cataracts, tetralogy of Fallot, mild facial dysmorphism and progressive encephalopathy, characterised by drug-resistant myoclonic epilepsy. At birth, the eyes were small and had leukocoria. Subsequent ophthalmic examination confirmed bilateral microphthalmia with a microcornea of 8 mm and a dense corticonuclear cataract. Ultrasound examination demonstrated that the retina was adherent. Additional MRI of the orbit revealed no other anomalies. The cataract was operated at the age of 3 weeks by lens aspiration via the pars plana. Appropriate aphakic contact lenses as well as glasses were subsequently adapted. Postoperatively there was no change in visual function and visual contact remained absent. There was no fixation or pursuit, but there was reaction to light. Fundoscopy showed bilateral small optic discs with a central cupping of 0,3. The macula and the peripheral retina were normal. Re-examination at the age of 10 months showed a hypotonic boy, with poor head control and severe developmental delay. Tendon reflexes were normal. His height was normal, but weight and head circumference were just below the third percentile. He had thin hair, and full lips and eyebrows (Fig. 1). Several dental abnormalities were noted, including misalignment, diastema of the central incisors and discoloured teeth. Ophthalmic examination showed asymmetrical microphthalmia, more pronounced on



*Fig 1 B:* Bilateral microphthalmia.

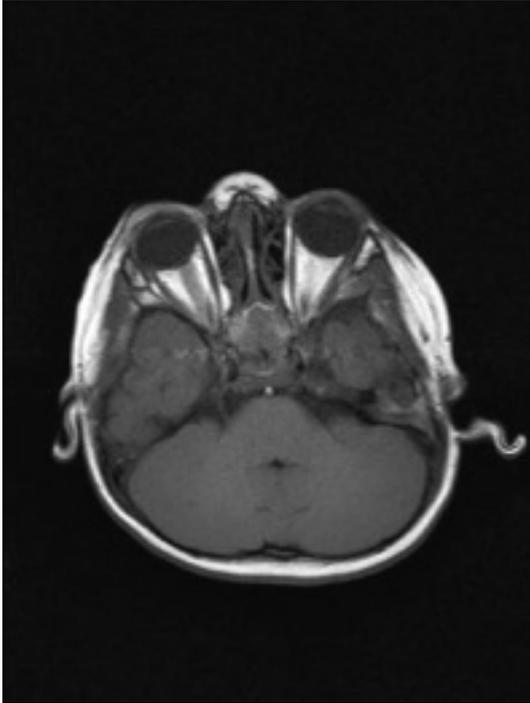


Fig 2: MRI at age of 22 months: bilateral asymmetrical microphthalmia. Axial length of the right eye was 17.9mm and the left eye 19.9mm.

the right eye, and aphakia (Fig. 2). The iris was blue, with a reduced number of crypts, but no transillumination was noted. The pupil was round, well centred and reacted to light stimuli. Pupil dilatation was difficult to obtain, although there were no postoperative synechiae. Little plaques of chorioretinal atrophy with alterations of the retinal pigment epithelium were noted in the mid-periphery of the fundus of both eyes. Nystagmus was absent and the intraocular pressure was normal. Flash visual evoked potentials (VEP) obtained at the age of 10 weeks and at 5 months showed a response. An electroretinogram performed under anaesthesia at the age of 10 months showed a reduction in the overall retinal function with a more pronounced deficit of the rods (rod-cone dystrophy). A second ERG confirmed these results six months later (Fig. 3). Chromosome X-array Comparative Genomic Hybridisation-analysis was performed at the age of 10 months and showed a 2,8Mb microdeletion at Xp22, encompassing multiple genes (5). The deletion is absent in the mother, indicating that it

occurred *de novo* in the child. The deleted region includes, among others, the cyclic-dependent-kinase-like 5 gene (*STK9/CDKL5*) and the entire *NHS* gene. He died at the age of 25 months due to a gastrointestinal complication after surgery for gastrostomy.

## DISCUSSION

We present the ophthalmologic findings in a boy with a deletion of Xp22 comprising the *NHS* gene, resulting in microphthalmia, microcornea, corticonuclear cataract, and absent visual contact even at the age of 22 months. He also has retinal pigment alterations. Changes in electrophysiology were more important than would be expected based on the presence of microphthalmia alone. To the best of our knowledge, retinal changes or retinal dysfunction have not been reported earlier in Nance-Horan syndrome. However, retinal pigment epithelium alterations were reported in the charts of another patient with NHS followed in our department. However his ERG during infancy was normal. It is noteworthy that Lewis et al. noted that visual acuity was reduced in patients with Nance-Horan syndrome, regardless of the age of surgical intervention, the absence of nystagmus at time of surgery early in life, the surgical technique, or the method of postoperative visual rehabilitation (2). However, the mechanisms underlying the reduced visual acuity were not discussed. Potential reasons for the severe visual impairment in our patient include deprivation amblyopia. However, this is very unlikely since the cataract was operated early and optical revalidation was uneventful. In addition, nystagmus was not observed in the months following the surgery. Secondly, some NHS-patients are blind due to secondary glaucoma. Nearly half of affected males have developed glaucoma one to several decades following cataract surgery. The structural or mechanical alterations that may cause this glaucoma, typically resistant to medical and occasionally to surgical management, are still unclear (2). The patient reported here had a normal intraocular pressure and the optic discs had a normal excavation. An advanced glaucomatous optic neuropathy was therefore excluded as a potential cause of severe visual impairment. A third possible explanation is the deletion of the complete *NHS* gene

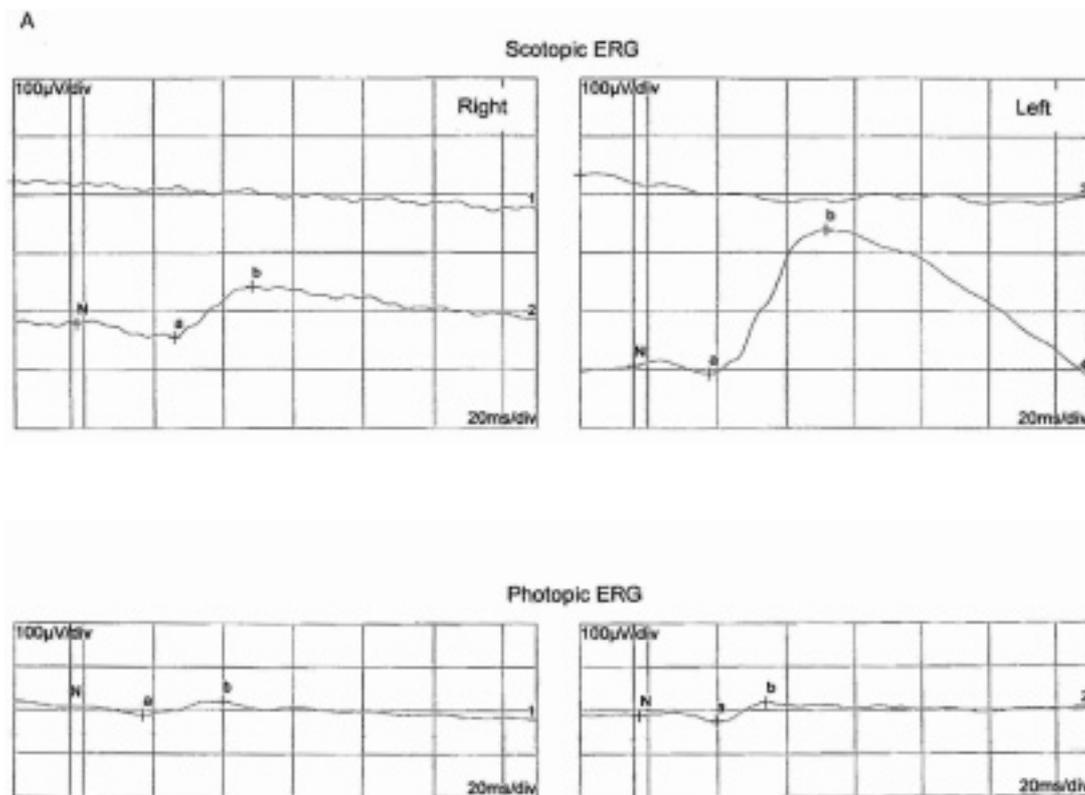


Fig 3 A: Scotopic and photopic electroretinogram of our patient. The scotopic ERG of both eyes is absent (curve 1 & 3: response only rods, 2 & 4: maximal combined response). The photopic ERG of the right eye is 25% of normal and left eye is 50% of normal.

in our patient. Mutations in *NHS* reported so far are nonsense mutations leading to truncation of the protein (3). Therefore, the total absence of the *NHS*-protein in the retina might explain the poor retinal function and the pigment epithelial changes. The *NHS* gene is a large gene that has an important regulatory role in the development of ocular, craniofacial and neural tissues. It is highly conserved across vertebrate species, supporting its vital role in the overall development. The *NHS* protein is expressed in the midbrain, lens, tooth and retina (1). However, the possible influence of the deletion of one or more of the 15 other genes in the deleted interval should also be considered (5). However, none of these genes have

been associated with ocular abnormalities, and more specifically, no known genes for X-linked retinitis pigmentosa are located in the deleted region. The deletion of the *CDKL5* gene, responsible for the atypical Rett-syndrome, characterized by early-onset seizures, leads to the severe developmental delay and progressive encephalopathy seen in our patient. Thus far, only one boy with a *CDKL5*-mutation has been described (6). He presented with severe therapy-resistant seizures, profound mental retardation, spastic quadriplegia, and cortical blindness. It is therefore impossible to exclude cerebral visual impairment (cortical blindness) caused by a deletion of *CDKL5*, even in the absence of any brain abnormality on MRI.

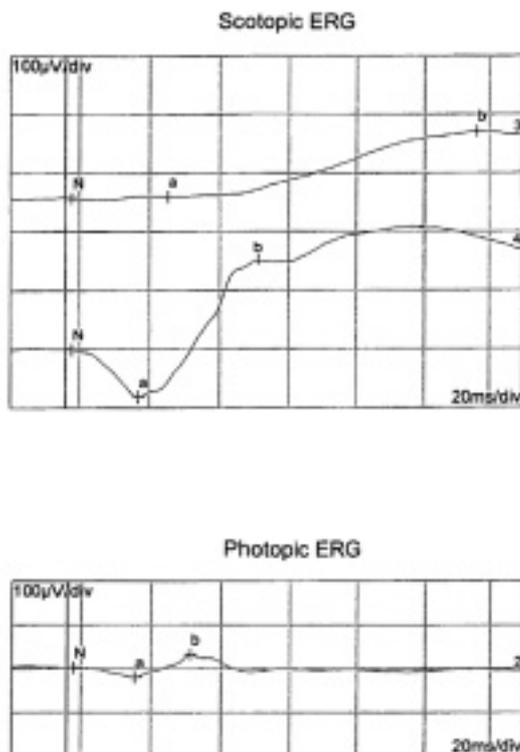


Fig 3 B: Normal scotopic and photopic electroretinogram of similar aged patient.

## CONCLUSION

Visual impairment in patients with Nance-Horan can be explained by different mechanisms. Until now, it has been attributed to deprivation amblyopia (secondary to cataract) or advanced glaucomatous neuropathy. In the case presented here, there could be a retinal degenerative component. In addition, a cerebral visual impairment secondary to the deletion of *CDKL5* may contribute to the severity of the visual problems. Further research on Nance-Horan syndrome is required in order to better understand the function of the NHS protein in the retina, and to see whether genotype-phenotype correlations can be established. It is also mandatory that all NHS patients have detailed clinical ophthalmologic examinations, including funduscopy.

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