Nance-Horan syndrome

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Creation Date: January 2002
Update: June 2003

Scientific Editor: Professor Didier Lacombe

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Abstract
Nance-Horan syndrome (NHS) is a hereditary disorder that is characterised by the association in male patients of congenital cataracts with microcornea, dental abnormalities and facial dysmorphism. These symptoms constitute the main clinical manifestations of NHS but 30% of cases are also mentally retarded. In heterozygous females NHS, symptoms are identical to those observed in affected males, although they are not as severe and do not include intellectual impairment. NHS is a rare disorder, whose incidence has not been fully evaluated, but the disease is probably underdiagnosed. NHS is a genetic condition of X-linked semi-dominant transmission and results preferentially from mutations occurring in male gametes. To date, the gene has not been identified but has been localized in Xp22.2 and the pathogenesis is unknown. The disease is diagnosed on the basis of the clinical symptoms described above. Heterozygote detection and prenatal diagnosis are possible by linkage analysis with polymorphic markers in informative families.

Key-words
X linked syndrome, congenital cataract, microcornea, facial dysmorphism, dental anomalies, locus Xp22.2

Disease name and synonyms
Nance-Horan syndrome, X-linked cataract with dental anomalies, cataract-dental syndrome

Excluded diseases
solated cataracts, X-linked microphthalmia, Lenz syndrome, Oculo-cerebro-renal (Lowe) syndrome.

Definition - Diagnostic criteria
Nance-Horan syndrome is characterized by the association in male patients of congenital cataracts with microcornea, dental anomalies and facial dysmorphism.

Differential diagnosis
McKusick's catalog on hereditary disorders distinguishes Nance-Horan syndrome (NHS)

(MIM No.: 302350) from two forms of isolated X-linked congenital cataract:
- X-linked congenital cataract with posterior sutural opacities in heterozygotes (MIM No.: 302200),
- X-linked congenital cataract with microcornea or slight microphthalmia (MIM No.: 302300).
However, it is not certain that this distinction is justified. This classification was based on old publications, and these two forms of X-linked cataract without dental anomalies were described before NHS was recognized as a distinct entity. Microcornea has also been reported in some patients within families affected with cataract from the first group and posterior lens opacities have also been described in NHS heterozygotes. It is probable that NHS was not recognized in some cases owing to the lack of dental examination, as was the case for two families reported by Waardenburg *et al.* in 1961 and by Krill *et al.* in 1969. It is therefore possible that these three groups correspond to a single condition, possibly with variable expression. the recent report by Francis *et al.* of a first locus for isolated X-linked cataract on Xp22, in a region overlapping the NHS genetic interval, strongly supported this hypothesis.

Incidence
Incidence has not been fully evaluated. NHS is a rare disorder but which is probably under-diagnosed. Fewer than 20 families have been reported in the literature.

Clinical description
In male patients
Ocular findings
The diagnosis is made early, generally in the first year of life, and most often at birth, particularly in cases where there is a known family history. The ocular problem consists of congenital cataract, present in 100% of cases (it is bilateral, usually severe, dense and most often total), associated with microcornea (96% cases), or even microphthalmia. In the majority of cases (93%) it is responsible for severe visual impairment evidenced by nystagmus (93%), sometimes associated with strabismus (43%), and surgery is generally required (89% cases). Post-operative complications are nevertheless frequent and severe and may necessitate enucleation: they include glaucoma (28%), which is generally poorly controlled by medical treatment, retinal detachment (sometimes iterative) (14%), corneal lesions (14%), and even eyeball atrophy (12%). Visual prognosis remains poor overall, even after surgery.

Dental abnormalities
Dental abnormalities are present in 100% of cases and are of high diagnostic value. They are characteristic and specific of NHS, either by their type or by their aggregation in the same individual. Permanent and deciduous teeth are involved. Although typical and often marked, dental anomalies are easily overlooked. Their recognition requires careful physical and radiological dental examination.
- *Crown shape anomalies*
Characteristic anomalies are observed on the incisors, described as screwdriver-shaped or conical, sometimes with a medial notch or an irregular incisal edge, or also called Hutchinson's teeth. Less typically, the incisors may be pointed, small, narrow or cylindrical. The existence of cingulate cusps is characteristic. The canines are often enlarged, globular, sometimes dome-shaped or bud-shaped, or with a trilobate edge. Premolars and molars are rounded, globular and sometimes small. The common presence of central supernumerary cusps gives them a mulberry or lotus flower shape.
- *Number anomalies*
Number anomalies consist of supernumerary teeth, posterior teeth or incisors, which are often impacted. A characteristic finding is the mesiodens (median incisor located behind the normal upper incisors). Dental agenesis is possible (canines, premolars, molars). Impacted teeth are common, generally involving the supernumerary teeth, but they may also involve normal teeth (canines, molars).
- *Position and implantation anomalies*
A diastema is found in all cases. It is striking at the incisors, particularly the upper incisors. Malpositions or malimplantations (excluding common malpositions) consisting of germ translation or ectopic position, are possible.
- *Other anomalies*
Late persistence of deciduous teeth, or pulp chamber anomalies (taurodontism, wide pulp chambers, abnormally calcified pulps, pulp stones) are not specific to NHS but are observed with significantly higher frequency than in the general population.

Dysmorphic features
Facial dysmorphism is constant but sometimes subtle and difficult for an inexperienced examiner to recognize. It may include:
- a long, sometimes narrow, often rectangular face,
- marked, long sometimes vertical chin, and prognathism in all cases,
- a large nose, with a high, narrow nasal bridge,

- and large, often protruding, ears,

Mental retardation
Intellectual impairment is observed in about 30% cases. It is usually (80%) mild or moderate, homogeneous, without motor delay, but profound retardation is possible (20%) and is associated with autistic features.
Interfamilial phenotypic variability is observed but there is correlation in the severity of ocular, dental and dysmorphic features. Intellectual impairment also has marked inter- and intra-familial variability of expression but the existence and the degree of mental handicap are not associated with the severity of the other clinical findings.

In heterozygous female
Clinical manifestations are identical to those of affected males but they are attenuated and are often limited to infraclinical findings.
- **Ocular signs** are not always present but they are observed in more than 90% cases.
They consist of bilateral, but often asymmetrical, predominantly posterior lens opacities. Extensive or progressive opacities are observed in 18% of the cases. Microcornea is rare (6%) and microphthalmia has never been reported. Surgery is required in only a minority of cases (8%) with progressive lesions at an advanced age or with extensive congenital cataract. Post-operative complications do not usually occur and visual prognosis is good overall, vision generally being normal (>75% cases), or mildly decreased at an advanced age. Significantly low visual acuity is reported in only 3% of cases and strabismus in 2% of cases.
- **Dental anomalies** are present in all cases. They are identical to those observed in affected males but are generally less severe and less varied. They may be very subtle and are usually overlooked. In a few cases they are marked and require intensive orthodontic treatment.
- **Facial appearance** resembles that of affected males, but dysmorphic features are inconstant, often subtle and difficult for a non-trained examiner to recognize.
- There is no intellectual impairment in heterozygotes.
Expression of clinical signs in heterozygotes is not related to X chromosome inactivation.

Management including treatments
- Ocular abnormalities usually require surgery for cataract extraction although the results are poor. Complications (glaucoma, retinal detachment, ...) are treated medically or surgically depending on the type and severity. The ocular problem requires education appropriate for the degree of visual handicap and often necessitates education in special school for the visually impaired.
- Dental anomalies may require orthodontic treatment when there are supernumerary teeth or for aesthetic reasons.
- Intellectual impairment requires special education.

Etiology
NHS is a genetic condition of X-linked semi-dominant transmission, with high penetrance in heterozygotes. The pathogenesis is unknown. Epidemiological data suggest preferential occurrence of new mutations in male gametes. The gene has not been identified but is localized at Xp22.2 in a region of about 1 Mb. There is an animal model in the Mus musculus mouse, the mutant Xcat.

Biological diagnostic test
None

Genetic counseling
In the offspring of an affected male, all the daughters are heterozygotes and all the sons are unaffected. A heterozygous female has a 50% chance of transmitting the mutated gene: she has a 25% chance of having an affected son and a 25% chance of having a carrier daughter.
Heterozygote detection is based on the recognition of physical ocular and/or dental signs, which are generally infraclinical, and requires a directed ophthalmological examination and careful and complete clinical and radiological dental examination performed by an experienced examiner. Indirect molecular study based on the analysis of markers linked to the gene may be performed in familial cases, in comparison with the clinical data.

Prenatal diagnosis
It is possible by indirect molecular analysis in informative families.

Unsolved questions and comments
It is still unknown whether the interfamilial phenotypic variability of NHS and the putative existence of isolated X-linked congenital cataracts are the result of allelic mutations in a single gene or whether NHS is a contiguous gene syndrome. Similarly, the nosologic relationships with X-linked microphthalmias and Lenz syndrome (colobomatous microphthalmia with various visceral and skeletal malformations) are not clear at the moment.

References

Bergen A.A., Ten Brink J., Schuurman E.J.M., Bleeker-Wagemakers E.M. Nance-Horan syndrome: linkage analysis in a family from the Netherlands. Genomics, 1994, 21: 238-240.

Bixler D., Higgins M., Hartsfield J. The Nance-Horan syndrome: a rare X-linked ocular-dental trait with expression in heterozygous females. Clin.Genet., 1984, 26: 30-35.

Francis P.J., Berry V., Hardcastle A.J., Maher E.R., Moore A.T., Bhattacharya S.S. Alocus for isolated cataract on human Xp; J. Med. Genet., 2002, 39: 105-9.

Horan M.B., Billson F.A. X-linked cataract and hutchinsonian teeth. Aust. Pædiat. J., 1974, 10: 98-102.

Krill A.E., Woodbury G., Bowman J.E. X-chromosomal-linked sutural cataracts. Am. J. Ophthalmol., 1969, 68: 867-872.

Lewis R.A. Mapping the gene for X-linked cataracts and microcornea with facial, dental, and skeletal features to Xp22: an appraisal of the Nance-Horan syndrome. Trans. Am. Ophthalmol. Soc., 1989, 87: 658-728.

Nance W.E., Warburg M., Bixler D., Helveston E.M. Congenital X-linked cataract, dental anomalies and brachymetacarpalia. Birth Defects Orig. Art. Ser., 1974, X(4): 285-291.

Seow W.K., Brown J.P., Romaniuk K. The Nance-Horan syndrome of dental anomalies, congenital cataracts, microphthalmia, and anteverted pinna: case report. Pediatric dentistry, 1985, 7: 307-311.

Stambolian D., Lewis R.A., Buetow K., Bond A., Nussbaum R. Nance-Horan syndrome: localization within the region Xp21.1-Xp22.3 by linkage analysis. Am. J. Hum. Genet., 1990, 47:13-19.

Toutain A., Ayrault A-D., Moraine Cl. Mental retardation in Nance-Horan syndrome : clinical and neuropsychological assessment in four families. Am. J. Med. Genet., 1997, 71 : 305-314.

Toutain A., Ronce N., Dessay B., Robb L., Francannet C., Le Merrer M., Briard M-L., Kaplan J., Moraine Cl. Nance-Horan syndrome: linkage analysis in 4 families refines localization in Xp22.31-p22.13 region. Hum. Genet.,1997, 99:256-261.

Toutain A., Dessay B., Ronce N., Ferrante M.I., Tranchemontagne J., Newbury-Ecob R., Wallgren-Pettersen C., Burn J., Kaplan J., Russo S., Walpole I., Hartsfield J.K.,Oyen N., Nemeth A., Bitoun P., Trump D., Moraine C., Franco B. Refinement of NHS locus on chromosome Xp22.13 and analysis of five candidates genes. Aur. J. Hum. Genet., 2002, 10:516-20.

Van Dorp D.B., Delleman J.W. A family with X-chromosomal recessive congenital cataract, micropthalmia, a peculiar form of the ear and dental anomalies. J. Pediat. Ophthal. Strabismus., 1979, 16: 166-171.

Walpole I.R., Hockey A., Nicoll A. The Nance-Horan syndrome. J. Med. Genet., 1990, 27: 632-634.

Walpole S.M., Ronce N., Grayson C., Dessay B., Yates J.R.W., Trump D., Toutain A. Exclusion of RAI2 as the causative gene for Nance-Horan syndrome. Hum. Genet., 1999, 104 : 410-411.

Zhu D., Alcorn D.M., Antonarakis S.E., Levin L.S., Huang P.C., Mitchell T.N., Warren A.C., Maumenee I.H. Assignment of the Nance-Horan syndrome to the distal short arm of the X chromosome. Hum. Genet., 1990,86: 54-58.

Zhu D., Li Y., Traboulsi E., Mitchell T., Maumenee I. Refined mapping of the Nance-Horan syndrome to a 2 cM region on Xp22.2. Am. J. Hum. Genet., 1998, 63 (suppl) :A317.