A presumptive new variant of Norrie's disease

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SUMMARY
The present report describes a Brazilian Negro sibship with six males affected by a presumptive new variant of Norrie’s disease, an X-linked congenital oculo-acoustical-cerebral degeneration. In addition to the typical stigmata of the disease, all the patients were microcephalic and two of them had cryptorchidism. Possible non-genetic aetiology was investigated with negative results. Xg blood group studies were informative and the lod scores are given, together with those for two previously reported families with Norrie’s disease.

Norrie’s disease is a sex-linked recessive disorder causing retinal degeneration. Mental retardation appears in one-third of the cases and sensory hearing loss is present with equal frequency. The onset of bilateral blindness occurs at birth or during the first few months of life. The gene has complete penetrance, but its expressivity is highly variable, especially with respect to mental retardation and hearing loss (Warburg, 1971, 1975). Genetic linkage data (Warburg et al., 1965; Nance et al., 1969) are compatible with loose linkage between the loci of Norrie’s disease (Nd) and glucose-6-phosphate dehydrogenase deficiency (G6PD), but no measurable linkage between Xg and Nd loci. The family presented here is the only one to date where microcephaly, cryptorchidism, and measurable Xg linkage are associated with the classical signs of Norrie’s disease. These are also the first cases of Norrie’s disease reported in South America.

Subjects and methods
The patients belonged to a Brazilian Negro family. All the affected individuals were male and belonged to the same sibship (Fig. 1), their ages varying from...
3 to 15 years. The parents (non-consanguineous) and their children were submitted to clinical examination, including ophthalmological and otological studies. Two affected boys, who could not respond to audiometric tests because of poor mental condition, were submitted to electrocochleography. Cephalic circumferences were measured and compared with the normal means for the patient's age.

In order to check the non-genetic factors causing microcephaly or blindness, x-ray examination of the skull, IgM fluorescent antibody tests for toxoplasmosis, and a search for cytomegalovirus intra-nuclear inclusion bodies were performed. Levels of serum testosterone were measured by radio-immunoassay in two of the affected boys (III.4 and III.5), since these patients showed clinical signs of hypogonadism.

Psychological tests (WISC and Ghwaki-Kohs Tactile Block Design) were used for evaluating the intellectual level of the patients.

Linkage of the Nd locus with G6PD and Xq loci was investigated. The study of G6PD was made by spectrophotometric assay (Saldanha et al., 1969). Xq blood groups were determined in London by Dr Ruth Sanger and the staff of the MRC Blood Group Unit.

Case reports

The clinical diagnosis of Norrie's disease was based on severe ocular affection, mental retardation, and hearing loss. X-linked congenital retinoschisis and X-linked microphthalmia associated with mental retardation were excluded. Laboratory tests for congenital toxoplasmosis and cytomegalovirus infections were negative. X-ray examination of the skull revealed diminished cranial diameters and failed to show intracranial calcifications. These data enabled us to discard non-genetic aetiological factors.

Ophthalmological findings, summarised in Table 1, show various grades of ocular morphology disorganisation. The descriptions refer to the more affected eye, but the differences between right and left eyes were small in all the cases. The least affected patient (III.5) could perceive light, had clear cornea and lens, and normal anterior vitreous.

![Patient III.2. The photographs show typical phthisis bulbi and microcephaly.](image)

Table 1  Ophthalmological findings

<table>
<thead>
<tr>
<th></th>
<th>Patients III.2</th>
<th>III.3</th>
<th>III.4</th>
<th>III.5</th>
<th>III.8</th>
<th>III.9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
</tr>
<tr>
<td>Cornea</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
<td>Amaurosis</td>
</tr>
<tr>
<td>Anterior chamber</td>
<td>Shallow Atrophic, opacification</td>
<td>Shallow Atrophic, opacification</td>
<td>Shallow Atrophic, opacification</td>
<td>Deep Sluggish reaction</td>
<td>Shallow Atrophic, opacification</td>
<td>Deep Posterior synechiae, hypotrophic</td>
</tr>
<tr>
<td>Iris</td>
<td>Shallow atrophic, ectropion uveae, osteo-amyloidosis, keratopathy</td>
<td>Shallow atrophic, ectropion uveae, osteo-amyloidosis, keratopathy</td>
<td>Shallow atrophic, ectropion uveae, osteo-amyloidosis, keratopathy</td>
<td>Deep Sluggish reaction</td>
<td>Shallow atrophic, ectropion uveae, osteo-amyloidosis, keratopathy</td>
<td>Deep Posterior synechiae, hypotrophic</td>
</tr>
<tr>
<td>Lens</td>
<td>Examination not possible</td>
<td>Examination not possible</td>
<td>Examination not possible</td>
<td>Examination not possible</td>
<td>Examination not possible</td>
<td>Examination not possible</td>
</tr>
<tr>
<td>Vitreous and retina</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
</tr>
<tr>
<td>Ocular tension</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
<td>Phthisis bulbi</td>
</tr>
<tr>
<td>White mass at posterior vitreous</td>
<td>Hypotension</td>
<td>Hypotension</td>
<td>Hypotension</td>
<td>Hypotension</td>
<td>Hypotension</td>
<td>Hypotension</td>
</tr>
</tbody>
</table>
The posterior vitreous was invaded by a vascularised mass which made the retina inaccessible to examination. Intraocular tension was 5 mmHg. The most severely affected patient (III.2, Fig. 2) presented severe ocular morphology disorganisation, amaurosis, ocular atrophy, band keratopathy, atrophy of the iris, shallow anterior chamber, deep-set eyes, and presence of intraocular calcifications (shown by x-ray examination).

On clinical examination microophathy was found in all the patients (Table 2). Bilateral cryptorchidism with a palpable inguinal testis was present in cases III.4 and III.5. Pubic and axillary hair was completely absent in these patients. Serum testosterone levels were 42.9 ng/100 ml (1.49 nmol/l) in case III.4 and 45.8 ng/100 ml (1.59 nmol/l) in case III.5, both values being below normal for the patient's age (Tanner, 1975).

Audiometric tests revealed normal hearing thresholds for cases III.2, 3, 5, and 9. Electrocochleography was performed in cases III.4 and III.8. Lesions in the cochlea, at the external ciliary cells, resulting in severe hearing impairment were found in case III.4. A peripheral disorder of the auditory organ, causing complete hearing loss, was detected in case III.8.

The psychological tests performed in cases III.2 and III.3 revealed IQs of 45 and 65, respectively. Case III.9 was not old enough to be tested and the other patients (III.4, 5, and 8) were obviously mentally retarded.

Table 2  Head circumferences of patients

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age (y and m)</th>
<th>Head circumference* (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>III.2</td>
<td>15-6</td>
<td>61.3</td>
</tr>
<tr>
<td>III.3</td>
<td>14-3</td>
<td>50.9</td>
</tr>
<tr>
<td>III.4</td>
<td>13-2</td>
<td>48.5</td>
</tr>
<tr>
<td>III.5</td>
<td>12-1</td>
<td>46.9</td>
</tr>
<tr>
<td>III.8</td>
<td>5-2</td>
<td>44.3</td>
</tr>
<tr>
<td>III.9</td>
<td>3-4</td>
<td>45-3</td>
</tr>
</tbody>
</table>

* all values more than 2 SD below the normal mean for age (according to data from Nellhaus, 1968).

Table 3  Lod scores for Norrie's disease and Xg

<table>
<thead>
<tr>
<th>Recombination fraction (%)</th>
<th>0.05</th>
<th>0.1</th>
<th>0.15</th>
<th>0.2</th>
<th>0.25</th>
<th>0.3</th>
<th>0.35</th>
<th>0.4</th>
<th>0.45</th>
</tr>
</thead>
<tbody>
<tr>
<td>Present study</td>
<td>-0.902</td>
<td>-0.414</td>
<td>-0.183</td>
<td>-0.062</td>
<td>-0.001</td>
<td>0.23</td>
<td>0.25</td>
<td>0.015</td>
<td>0.004</td>
</tr>
<tr>
<td>Warburg et al. (1965)</td>
<td>-3.691</td>
<td>-2.324</td>
<td>-1.557</td>
<td>-1.069</td>
<td>-0.722</td>
<td>-0.467</td>
<td>-0.281</td>
<td>-0.146</td>
<td>-0.056</td>
</tr>
<tr>
<td>Nance et al. (1969)</td>
<td>-4.465</td>
<td>-2.789</td>
<td>-1.870</td>
<td>-1.267</td>
<td>-0.841</td>
<td>-0.532</td>
<td>-0.308</td>
<td>-0.151</td>
<td>-0.050</td>
</tr>
<tr>
<td>Total sum of lod scores</td>
<td>-9.058</td>
<td>-5.527</td>
<td>-3.610</td>
<td>-2.398</td>
<td>-1.564</td>
<td>-0.976</td>
<td>-0.564</td>
<td>-0.282</td>
<td>-0.102</td>
</tr>
<tr>
<td>Relative probability for our data</td>
<td>0.125</td>
<td>0.385</td>
<td>0.656</td>
<td>0.867</td>
<td>0.998</td>
<td>1.054</td>
<td>1.059</td>
<td>1.035</td>
<td>1.009</td>
</tr>
<tr>
<td>Relative probability for pooled data</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.004</td>
<td>0.027</td>
<td>0.106</td>
<td>0.273</td>
<td>0.522</td>
<td>0.791</td>
</tr>
</tbody>
</table>

Linkage analysis

Only the genes for Xg blood group factor and Norrie's disease were segregating informatively (no G6PD variant or deficiency was identified). The data were analysed by the application of the lod scores of Morton (1955) as presented in the tables of Maynard-Smith et al. (1961). The lod scores are given in Table 3, together with the antilogs of their sums, which represent the relative probabilities of the recombination fraction 0. We also pooled our results with the previous data of Warburg et al. (1965) and Nance et al. (1969).

Discussion

The pedigree data favour the X-linked recessive mode of inheritance, since only males are affected. The probability of chance occurrence under the hypothesis of autosomal recessive inheritance is only 1/64. Moreover, all the clinical signs described for the classical form of Norrie's disease, which undoubtedly depends on an X-linked gene, are present in our cases: mental retardation, hearing loss, and typical ophthalmological stigmata.

Hara et al. (1969) found hypogonadism in a Negro kindred with Norrie's disease. Of the 6 patients in our pedigree, 2 had both clinical and hormonal features of hypogonadism. It is, therefore, probable that such findings are non-obligatory components of the disease, though this is not mentioned in any of the families reviewed by Warburg (1975).

Microcephaly is described here for the first time in association with Norrie's disease. Its presence in the 6 patients suggests that we are dealing with a new variant of Norrie's disease. In order to establish this, it is recommended that a search for microcephaly be made both in new and in already reported cases of Norrie's disease.

The genetic relationship between the two forms of Norrie's disease could result from the following situations: (1) the two forms depend on different
alleles; (2) they depend on different loci on the X-chromosome; (3) they result from the action of a modifier on the Nd gene.

If it could be shown that the genes causing the two forms of the disease are located at different distances from an X-linked marker, then they could be assigned to different loci. Only more linkage data in familial cases of Norrie's disease with associated microcephaly will show whether two loci are involved.

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References


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