Neuraminidase deficiency: case report and review of the phenotype

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SUMMARY A 12 year old boy with neuraminidase deficiency (sialidosis, mucolipidosis I) is described. His clinical features included coarse facies, cherry red spot, ataxia, myoclonus, and dysotosis multiplex. The level of neuraminidase activity in cultured fibroblasts was very low and intermediate levels were observed in both parents. The clinical disorders associated with neuraminidase deficiency are reviewed.

In 1968 two reports were published describing children who showed features of both a mucopolysaccharidosis and a sphingolipidosis. Initially described as a lipomucopolysaccharidosis, this entity was later classified as mucolipidosis I when the term ‘mucolipidosis’ was introduced as a common designation for a number of progressive disorders clinically related to both the mucopolysaccharidoses and the sphingolipidoses.

Subsequent studies revealed that patients with mucolipidosis I showed excessive intracellular accumulation and urinary excretion of sialic acid containing molecules in association with a neuraminidase (=sialidase) deficiency. The demonstration that other patients with a somewhat different clinical course also showed a deficiency of neuraminidase activity prompted the publication of a comprehensive review and classification of the different forms of neuraminidase deficiency, also known as sialidosis. This classification incorporated several different entities, including mucolipidosis I, Goldberg’s syndrome, and the cherry red spot-myoclonus syndrome.

We now report the findings in a 12 year old boy, who appears to be the first patient of Indian origin in whom sialidosis has been documented. We also review the clinical features of published cases of neuraminidase deficiency and hope that this brief overview will be of value for those confused by existing terminology.

Case report

The proband, a male aged 12 years, is the second child of healthy unrelated Indian parents. His older brother is healthy and there is no other relevant family history. He was born at term with birth weight 2.1 kg. He was first investigated at 18 months of age because of short stature and delayed milestones. He first walked at 20 months and began...
talking at two years. At three years of age he was noted to have coarse facial features and a diagnosis of a mucopolysaccharidosis was considered, although there was no hepatosplenomegaly or excess mucopolysacchariduria. Formal developmental assessment at that time revealed an IQ of approximately 75.

He was reassessed at the age of nine years because of poor school performance and failing vision. A coarse 'Hurleroid' facies was noted, a skin biopsy taken, and appropriate biochemical investigations initiated (results below). Using the Wechsler Intelligence Test for Children his full scale IQ was assessed at 67.

His first grand mal convulsion occurred at the age of 11 years and since then he has had frequent myoclonic jerks, particularly at night. Repeat IQ assessment at 11 years of age indicated mild deterioration in intellectual skills with a full scale IQ of 55.

On examination at the age of 12 years his height (118.5 cm), weight (20.5 kg), and head circumference (48 cm) all fell well below the 3rd centile. His facies was coarse with prominent lips, large tongue, and gingival hypertrophy (figs 1 and 2). There was limitation of abduction at the shoulders and of external rotation at the hips with mild limitation of extension at elbows and knees. Movements at other joints were normal. The liver and spleen were not enlarged. Neurological findings included ataxia with an intention tremor, mild generalised hypotonia, ankle clonus, extensor plantar responses, and fine vertical nystagmus.

Visual acuity was 6/60 in each eye with a low myopic correction. Both corneas exhibited very faint opacification of the superficial stroma. Other ocular findings included extensive dot lens opacities clustered around the lens nucleus, bilateral optic atrophy, and cherry red spots (fig 3). Visual field testing showed a central scotoma bilaterally. Ocular

FIG 2  AP and lateral views of the patient at 12 years.
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For identification of individual GAGs, Alcian Blue precipitated GAGs were separated by two dimensional electrophoresis on cellulose acetate and visualised with Alcian Blue. Oligosaccharides were separated by thin layer chromatography on commercial silica gel plates and visualised with orcinol.

Urine (50 μl) was added to ethanol (200 μl), centrifuged, and the supernatant evaporated to dryness. The resulting residue was dissolved in 20 μl methanol:water (1:1), applied to the TLC plate, and developed twice to 10 cm in n-butanol:acetic acid:water (2:1:1).

Skin fibroblasts

Fibroblasts were cultured as previously described except that the culture medium was Ham's F10 containing 12% fetal calf serum. Cells were harvested two days after confluence using trypsin (0.25% w/v).

Enzyme assays

The fibroblasts were hand homogenised in water and the neuraminidase assayed within two hours of homogenisation according to the method of Lake et al. 12 β-galactosidase was assayed as described previously, except that the incubation temperature

Biochemical investigations

METHODS

Urine

Random urine specimens were preserved with merthiolate (BDH Thiomersal, 1 in 10 000 w/v) and stored at −20°C before analysis.

Glycosaminoglycans (GAGs) were measured on two separate occasions, at the ages of nine and 12 years, using Alcian Blue 8GX. For identification of individual GAGs, Alcian Blue precipitated GAGs were separated by two dimensional electrophoresis on cellulose acetate and visualised with Alcian Blue.

Skin fibroblasts

Fibroblasts were cultured as previously described except that the culture medium was Ham's F10 containing 12% fetal calf serum. Cells were harvested two days after confluence using trypsin (0.25% w/v).

Enzyme assays

The fibroblasts were hand homogenised in water and the neuraminidase assayed within two hours of homogenisation according to the method of Lake et al. 12 β-galactosidase was assayed as described previously, except that the incubation temperature
was 37°C and the assay contained 0-1% human albumin. The protein content of the homogenate was determined by the method of Lowry et al. 14

RESULTS

Urine

Urinary GAG/creatinine ratios fell within the normal range (age related) on both occasions. Characterization of individual GAGs showed chondroitin sulphate as the major component, with heparan sulphate and very small amounts of dermatan and keratan sulphates also present.

Thin layer chromatography of urinary oligosaccharides showed a strongly staining band characteristic of mucolipidosis I. 15 This pattern differs from that seen in other mucolipidoses and GM1 gangliosidosis (fig 8).

Enzyme activities

The results of neuraminidase and β galactosidase activities are shown in table 1. Two separate subcultures were assayed for the patient and both parents. Neuraminidase activity in cultured fibroblasts was consistently very low in the proband and in the predicted heterozygous range in both parents.

Discussion

Clinical and biochemical details of dysmorphic patients with primary neuraminidase deficiency are summarised in table 2. At least five different clinical

FIG 5 Lateral view of the skull at 12 years.
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**FIG 7** Radiograph of the hands at 12 years.


**TABLE 1** Enzyme activities in two separate subcultures for patient and parents.

<table>
<thead>
<tr>
<th>Enzyme activities in cultured fibroblasts</th>
<th>Neuraminidase</th>
<th>ß galactosidase</th>
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</thead>
<tbody>
<tr>
<td>Patient</td>
<td>0.37</td>
<td>818</td>
</tr>
<tr>
<td></td>
<td>0.33</td>
<td>1336</td>
</tr>
<tr>
<td>Mother</td>
<td>3.1</td>
<td>1086</td>
</tr>
<tr>
<td></td>
<td>3.2</td>
<td>907</td>
</tr>
<tr>
<td>Father</td>
<td>5.8</td>
<td>935</td>
</tr>
<tr>
<td></td>
<td>3.9</td>
<td>946</td>
</tr>
<tr>
<td>Normal range (n=31)</td>
<td>6.32</td>
<td>360-1678</td>
</tr>
<tr>
<td>Mean±SD</td>
<td>12.1±4.6</td>
<td>605±245</td>
</tr>
</tbody>
</table>

nmol/h mg protein.

Entities can be recognised in which neuraminidase deficiency occurs. These are summarised below.

(1) Primary neuraminidase deficiency without dysmorphism.\(^7\)\(^{16-19}\) This condition represents the cherry red spot-myoclonus syndrome\(^7\) and was classified by Lowden and O'Brien\(^7\) as sialidosis type I. These patients usually present in the second decade with decreased visual acuity, myoclonus, or gait abnormalities. Vision and neurological function show slow deterioration. Intellect and appearance are normal and survival beyond 30 years is usual. Affected sibs of both sexes,\(^7\)\(^{16-19}\) parental consanguinity,\(^7\)\(^{18}\) and heterozygous levels of neuraminidase in parents\(^7\)\(^{17-19}\) indicate that inheritance is autosomal recessive.

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[Image of radiograph of hands]
(2) Primary neuraminidase deficiency with dysmorph-
ism, congenital form. 

Cases 1 to 9 in table 2. Of the
nine children listed in table 2, two died at birth and
one was still alive at the age of three months. The
mean age at death for the remaining six cases was 10
months. These children’s short lives were character-
ised by hepatosplenomegaly, corneal opacities,
dysostosis multiplex, and hydrops or ascites with
pericardial effusion. The description of affected sibs
suggests autosomal recessive inheritance. 

The classification of Lowden and O’Brien predated
the first description of this clinical entity in 1980. 

(3) Primary neuraminidase deficiency with dys-
morphism, childhood onset. 

Cases 10 to 21 in table 2. This group includes patients with
mucolipidosis I, the infantile form of type II
sialidosis, 

and Goldberg’s syndrome. 

(In the original report Goldberg’s patient had low β galac-
tosidase activity in skin, but subsequent studies showed normal β galactosidase activity in cultured
fibroblasts.)

Affected children present in early childhood with
mild developmental delay but it may be several
years before the diagnosis is suspected. Dispro-
portionate short stature with relatively long legs is
characteristic. By the age of 10 years these children
show a coarse facies and at around this time visual
and neurological problems develop. Radiographs
reveal dysostosis multiplex affecting the skull, ribs,
clavicles, pelvis, hands, and spine. Intellect is
usually only mildly impaired initially so that affected
children are able to attend normal school until
adolescence, when intellectual skills deteriorate.

Three patients have died at the ages of 21, 22, and
22 years. During the late stages of their illness
they became severely disabled, being chairbound,
incontinent, and unable to cater for their own
basic needs. The other death in this group occurred
at the age of five years. This child had severe renal
involvement and may have had a different form of
neuraminidase deficiency. 

However, renal involvement has also been noted in other forms of
neuraminidase deficiency, and may simply be an
manifestation of generalised visceral storage.

Confusion has arisen because patients have been
described at different stages in the natural history of
this illness, raising the possibility of further hetero-
genity. For example, review of the cases in table 2
indicates that they could be divided into two groups
based on the presence or absence of hepato-
splenomegaly. Long term study of other patients is
necessary to clarify whether further subdivision is justified.

(4) Combined neuraminidase/β galactosidase defi-
ciency, infantile onset. 

This relatively rare
condition presents either at birth with hydrops or
ascites or in infancy with coarse facies, hepa-
splenomegaly, and skeletal changes. 

In a recent
classification of the sialidoses, Spranger subdivided
patients in this group into early and late infantile
onset. Andria et al. suggested the term ‘galacto-
sialidosis’ for combined neuraminidase/β galacto-
sidase deficiency and concluded that the infantile
group could be subdivided into mild and severe. The
prognosis in mildly affected patients appears good:
the oldest patient described had normal growth and

### Table 2 Published cases of neuraminidase deficiency with dysmorphism.

<table>
<thead>
<tr>
<th>Case No</th>
<th>Reference</th>
<th>Consanguinity</th>
<th>Sex</th>
<th>Age at death</th>
<th>Short stature</th>
<th>IQ or mental state</th>
<th>Hydrops or ascites</th>
<th>Course facies</th>
<th>Dysostosis multiplex</th>
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<td></td>
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<td>4 20</td>
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<td>2M 2F</td>
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<tr>
<td>5</td>
<td>21</td>
<td>-</td>
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<td>23 (case 2)</td>
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<td>75 12</td>
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<td>18 28</td>
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<td>1:3/12 1:9/12</td>
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<td>21 29</td>
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<td>12</td>
<td>+</td>
<td>67 9</td>
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<table>
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<tr>
<th>Enlarged</th>
<th>Myoclonus Ataxia</th>
<th>Cherry Lens red spot opacities</th>
<th>Corneal opacities</th>
<th>Neuraminidase in fibroblasts</th>
<th>β galactosidase in fibroblasts</th>
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<td>Spleen</td>
<td>Patient</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>↓↓↓</td>
</tr>
</tbody>
</table>


intellect at the age of eight years.

(5) Combined neuraminidase/β galactosidase deficiency, juvenile onset.30-33 These patients usually present in their early teens with gait disturbance, myoclonus, and failing vision. They are of moderately short stature and have coarse facial features. Skeletal changes are most apparent in the lumbar vertebrae. Angiokeratoma occur commonly. Features which distinguish this entity from primary neuraminidase deficiency with dysmorphism and childhood onset (type 3 in this classification) are its later age of onset, longer survival, relatively normal intellect, milder skeletal changes, ethnic distribution (almost entirely Japanese), and associated β galactosidase deficiency.

Confirmation that these disorders represent discrete entities comes from complementation studies. Hoogeveen et al43 demonstrated complementation between cells cultured from patients from groups 1 and 4, 3 and 4, 1 and 5, and 3 and 5. Complementation did not occur using cells from patients from groups 1 and 3, or 4 and 5. These observations have been confirmed by others.31,32 D’Azzo et al35 speculated that the basic defect in combined neuraminidase/β galactosidase deficiency lies in a glycoprotein normally required to protect these two enzymes against intralysosomal degradation. This contrasts with the defect in mucolipidosis types II and III in which there is believed to be a lack of recognition markers for targeting enzymes to lysosomes, so that activities of all lysosomal enzymes are low in cultured fibroblasts but raised in serum.

Thus, in summary, neuraminidase deficiency may present as at least five different disease entities. Affected sibs, parental consanguinity, and heterozygous levels in parents indicate that all of these entities show autosomal recessive inheritance. Prenatal diagnosis has been recorded for several types20,32 and should in principle be possible for all forms of neuraminidase deficiency.44 It is hoped that this short review will enhance recognition of neuraminidase deficiency and enlighten those who, like the authors, find the nomenclature confusing.

The authors are grateful to Dr R K Turner for providing details of the developmental assessments and to Mrs Susan Kenney for typing the manuscript.

Note added in proof

Recent studies45 have revealed differences in the biosynthesis of the defective ‘protective protein’ between the early infantile, late infantile, and juvenile forms of combined neuraminidase/β galactosidase deficiency.

References

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