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 corneae 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.](http://jmg.bmj.com/first-published-as-10.1136/jmg.24.5.283-on-1-May-1987. Downloaded from http://jmg.bmj.com/)
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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 confluency 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. 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.

Oligosaccharides were separated by thin layer chromatography on commercial silica gel plates and visualised with orcinol.
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.\textsuperscript{14}

RESULTS

Urine

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

Thin layer chromatography of urinary oligosaccharides showed a strongly staining band characteristic of mucolipidosis I.\textsuperscript{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
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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></th>
<th>Enzyme activities in cultured fibroblasts</th>
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<tr>
<td></td>
<td>Neuraminidase β galactosidase</td>
<td></td>
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<tr>
<td><strong>Patient</strong></td>
<td>0-17</td>
<td>8818</td>
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<tr>
<td></td>
<td>0-33</td>
<td>1336</td>
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<td><strong>Mother</strong></td>
<td>3-1</td>
<td>1056</td>
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<td></td>
<td>3-2</td>
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<td><strong>Father</strong></td>
<td>3-9</td>
<td>955</td>
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<td></td>
<td>3-9</td>
<td>946</td>
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<tr>
<td><strong>Normal range (n=31)</strong></td>
<td>6-32</td>
<td>360-1678</td>
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<tr>
<td><strong>Mean±SD</strong></td>
<td>12±4</td>
<td>695±245</td>
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nmol/h mg protein.

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

(1) Primary neuraminidase deficiency without dysmorphism. This condition represents the cherry red spot-myoclonus syndrome and was classified by Lowden and O'Brien as sialidosis type 1. 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, and heterozygous levels of neuraminidase in parents indicate that inheritance is autosomal recessive.
Primary neuraminidase deficiency with dysmorphism, 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 characterised 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’Brien17 predates the first description of this clinical entity in 1980.20, 21

(3) Primary neuraminidase deficiency with dysmorphism, childhood onset. 2 4 6 23 25-29 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.6 (In the original report Goldberg’s patient had low β-galactosidase 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. Disproportionate 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.4 6 28 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.27 This child had severe renal involvement and may have had a different form of neuraminidase deficiency.30 However, renal involvement has also been noted in other forms of neuraminidase deficiency,21 31 and may simply be a 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 heterogeneity. 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 hepatosplenomegaly. Long term study of other patients is necessary to clarify whether further subdivision is justified.

(4) Combined neuraminidase/β-galactosidase deficiency, infantile onset.31-34 This relatively rare condition presents either at birth with hydrops or ascites,32 33 or in infancy with coarse facies, hepatosplenomegaly, and skeletal changes.31 34 In a recent classification of the sialidoses, Spranger35 subdivided patients in this group into early and late infantile onset. Andria et al34 suggested the term ‘galactosialidosis’ for combined neuraminidase/β-galactosidase 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...
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<table>
<thead>
<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><strong>Liver</strong></td>
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intellect at the age of eight years.

(5) Combined neuraminidase/β galactosidase deficiency, juvenile onset. 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 al. demonstrated complementation between cells cultured from patients from groups 1 and 4, 3 and 4. In early and groups 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. D’Azzo et al. 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 types and should in principle be possible for all forms of neuraminidase deficiency. 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 studies 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**


