Report of a mucopolysaccharidosis occurring in Australian aborigines

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SUMMARY The first 2 reported cases of a mucopolysaccharidosis occurring in an Australian aboriginal family are presented. Though these children had the characteristic morphological features of the Hurler syndrome, enzyme assay of cultured fibroblasts showed normal levels of α-L-iduronidase and decreased activity of arylsulphatase B. Thus, they represented the Hurler syndrome clinically, while they had the enzyme defect of the Maroteaux-Lamy syndrome, and they may represent a new severe form of the Maroteaux-Lamy syndrome. The parents of these children were first cousins. Though the children were not full blood aborigines, examination of the pedigree indicates that the gene originated in the common aboriginal family.

The Hurler syndrome, or mucopolysaccharidosis (MPS) IH, is a well-recognised, but uncommon, recessively inherited abnormality. Children affected by it have a characteristic appearance and have a deficiency of the enzyme α-L-iduronidase. It causes progressive mental and physical deterioration in affected children and death usually occurs by the age of 10. Other mucopolysaccharidoses, such as the Maroteaux-Lamy syndrome (MPS VI), are even less common, but they also have their own characteristic morphological and biochemical features. These diseases share the common feature of excessive urinary mucopolysaccharide, increased levels of dermatan sulphate, heparan sulphate, or keratan sulphate being found. This paper documents 2 Australian aboriginal children who had the characteristic morphological features of the Hurler syndrome and biochemical evidence of a mucopolysaccharide disorder. Not only are they the first Australian aborigines to be described with a mucopolysaccharide disorder, but they represent a new form of MPS VI.

The clinical findings of these cases of MPS are presented with preliminary biochemical and enzyme assay findings. The origin of the gene mutation is discussed and the pedigree traced. The proband was identified during eye examinations performed by the National Trachoma and Eye Health Programme.

Report of family

The proband is a 5-year-old boy. He lives in the Neppabunna area of north-eastern South Australia. His parents are first cousins once removed, but belong to different sub-groups of the Gudnamutija tribe (Fig. 1). He was reported to have been a normal infant, but his parents noted that from the age of 1 year he had become mentally slow and his abdomen had swollen. Until the age of 2 he apparently had normal vision, but thereafter his sight deteriorated. His family reported that he often seemed to run into objects in his path. When seen, he had not yet started to speak and was unable to dress himself.

On examination, he was 90 cm tall (<3rd centile) and weighed 19 kg (50th centile). His head circumference was 56 cm (>98th centile) and he had scaphocephaly. He had a Hurler facies (Fig. 2) with a saddle nose, flared nasal tip, thickened lips, and a large tongue. His teeth were widely spaced and he had moderate naso-obstruction; he breathed through his mouth. His neck was short and thick, and he had a large pendulous abdomen and an umbilical hernia. His liver was firm and enlarged, extending 10 cm below the costal margin. The tip of an enlarged spleen was

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Fig. 1 Pedigree of aboriginal family containing mucopolysaccharide disorder. Consanguinity of parents of affected.

Fig. 2 Proband (V.34) showing many classical features of the Hurler syndrome.
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The division between Aururu and Matherie reflects 2 well-defined sub-tribal groups.

Palpable. There were no inguinal herniae or hydroceles. His ribs were splayed inferiorly and he had gynaecomastia. A loud systolic murmur maximal at the left sternal edge was present. His hands were broad with stubby fingers and some clawing of the 5th finger of each hand. There was restriction of joint mobility, especially of extension. He had genu valgum and pes planus. Fine lanugo covered most of his body, especially his face, and coarse hair covered his back.

Ocular examination showed mild bilateral trachoma, his corneae showing 1 mm of pannus. Fine scarring of the tarsal conjunctiva and small tarsal papillae were present. His corneae also had fine speckled opacities in the deeper layers which were more marked peripherally. The optic discs were large, pale, and swollen, while the retinal pigmentation was normal for his race. Though he responded to light, and could avoid objects, no accurate assessment of vision was possible because of his mental retardation. Though clinically he showed profound mental retardation, no formal investigation of his mental age was possible because of the field conditions. His hearing was normal.

Further questioning of the proband's parents revealed that an elder sister (V.31), who had recently died, had suffered from the same condition. Review of hospital records showed that she had first presented at the age of 18 months with gastroenteritis, and the diagnosis of the Hurler syndrome was made. She presented again at the age of 4 with a mild left-sided hemiparesis after a fall. At the age of 6, she showed clinical signs of hydrocephalus which was confirmed.

Fig. 3 (V.31) Affected older sister.
by air encephalography. This was managed conservatively. She also had scaphocephaly, a Hurler facies (Fig. 3), kyphosis, an umbilical hernia, hepatosplenomegaly, and hazy corneae. Radiological examination showed the classical changes of dysostosis multiplex usually associated with the Hurler syndrome. Reilly bodies were found in her circulating lymphocytes. She was finally admitted to hospital at the age of 10 with pneumonia and otitis media. She developed meningitis and septicaemia and died.

At necropsy, the brain showed the features of hydrocephalus. The meninges were thickened and oedematous. There was a heavy infiltrate of foamy macrophages and polymorphs. Neurones showing hypoxic and ballooned storage changes were seen. The neuroglial network was loose and oedematous. Excessive lipofuscin was seen, as was an occasional Zebra body. The pituitary showed numerous vacuolated acidophils.

The heart showed focal myofibrillary fat change and valvular and perivalvular endocardial fibrosis. There were numerous histiocytes in the collagenous valve tissue.

The liver showed excessive portal fibrous tissue, Kupffer cell hyperplasia, and slight centrilobular fatty change. Slight PAS positive material was found after digest clearing, and toluidine blue metachromatric material was found in frozen sections.

The spleen was depleted of white pulp and had foamy storage histiocytes. In the kidney, there was mild tubular fatty change, focal calcification, and protein casts. The suprarenal gland showed severe lipid depletion. There was severe atrophy of the thymus. Growth arrest had occurred at the costochondral junctions. The lungs showed the changes of bronchopneumonia.

The proband's younger sister (V.35), aged 18 months, was regarded by the family as a normal infant. Her height was 77 cm (25th centile). She had a broad saddle nose with nasal obstruction (Fig. 4), but her mouth, tongue, and dentition were normal for age. Her hands and feet were normal, and her joints freely mobile. The ribs were splayed and there was a soft systolic murmur at the left sternal edge. Her abdomen was protuberant and 6 cm of firm liver was palpable. The tip of the spleen could also be felt. She had recently developed an umbilical hernia. No ocular stigmata of MPS were apparent, though she did have trachoma with follicles in the upper tarsal conjunctiva. Vision and hearing were normal.

A female first cousin once removed (IV.15), aged 38, showed a number of abnormalities. She had been regarded by her family as slow and 'funny' since the age of 9. She was 147 cm tall and was obese, weighing 76 kg. She had a broad saddle nose, hypertelorism, epicanthic folds, a large mouth with irregularly spaced teeth, and a large tongue (Fig. 5). She suffered from nasal obstruction and sinusitis.

Her neck was short and thick and her hands were small, with shortening of the metacarpals and flexion deformity of the 5th fingers. Joint mobility was slightly reduced, being more obvious in her wrists. She had severe restriction of right shoulder movement with crepitus, and restricted movement in her left knee and ankle. She had genu valgum. The left leg was deformed with large exostoses at each end of the tibia and fibula. Her feet were broad with webbing of the second and third toes, and an overriding fourth toe on each foot.

The abdomen was pendulous. She had an umbilical hernia, but no inguinal herniae were present. There was a right lower paramedian scar following hysterec-
tomy 5 years previously for chronic cervicitis and endometrial polyps. The liver was firm and palpable 10 cm below the costal margin. The tip of her spleen was also palpable. Her lower ribs were splayed and she had poor chest expansion. A loud systolic murmur at the left sternal edge and a third heart sound were audible. She had fine lanugo, especially on the face and back. She showed moderate mental retardation and her hearing was normal.

Ocular examination showed a mixed astigmatism which, when corrected, resulted in an acuity of 6/
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The pedigree for the family (Fig. 1) was constructed from information supplied by the relatives and where possible was confirmed by local and mission records of births, deaths, and marriages. Included are 262 people.

Apart from the 4 cases presented, another 57 members of the family were examined, none of whom showed any stigmata of an MPS disorder, though a 9-year-old male cousin (V.33) was deaf and dumb. Two great-uncles (III.2, III.3) were said to have been mentally retarded and to have died at the ages of 60 and 62 without marrying or having children. Those questioned reported no other family members with significant physical or mental abnormalities. Two stillbirths (V.23, V.24) and 4 deaths in infancy (IV.11, IV.13, IV.63 from diphtheria, and IV.71 from whooping cough) were noted.

**BIOCHEMICAL INVESTIGATIONS**

Urine and skin biopsies were taken from members of the affected family. Peripheral blood leucocytes were also obtained from the proband. Early morning urine collections were screened for the presence of mucopolysaccharides (Table 1).

Sequential thin layer chromatography (Humbel and Chamoles, 1972) was also performed on the urine obtained from the proband. Dermatan sulphate and heparan sulphate were present in large quantities and chondroitin-4-sulphate was markedly raised. Semi-quantitative estimation of the visualised glycosaminoglycans indicated that derman sulphate was the major component.

Enzyme assays were performed on cells grown in tissue culture (Table 2). The assay for α-L-iduronidase was based on the breakdown of iduronosyl (4H) anhydromannitol sulphate to (4H) anhydromannitol sulphate (Hopwood and Muller, 1977; Hopwood, 1978). Arylsulphatase B was separated electrophoretically from arylsulphatase A (Rattazzi et al.,

**Table 1 Results of mucopolysaccharide screening of early morning urine samples of proband and his family**

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (y)</th>
<th>Creatinine* (mg/100ml)</th>
<th>Acid albumin turbidity</th>
<th>Azure A</th>
<th>Cetylpridinium chloride turbidity (mg/l)</th>
<th>(mg/g creatinine)</th>
<th>Normal range (mg/g creatinine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father IV.12</td>
<td>33</td>
<td>116</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>24</td>
<td>Less than 110</td>
</tr>
<tr>
<td>Mother IV.69</td>
<td>32</td>
<td>131</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>55</td>
<td>Less than 110</td>
</tr>
<tr>
<td>Sib V.30</td>
<td>12</td>
<td>137</td>
<td>-</td>
<td>-</td>
<td>92</td>
<td>67</td>
<td>Less than 150</td>
</tr>
<tr>
<td>Case 2 V.31</td>
<td>10</td>
<td>31</td>
<td>++</td>
<td>+</td>
<td>217</td>
<td>700</td>
<td>Less than 140</td>
</tr>
<tr>
<td>Sib V.32</td>
<td>8</td>
<td>85</td>
<td>-</td>
<td>-</td>
<td>92</td>
<td>108</td>
<td>Less than 160</td>
</tr>
<tr>
<td>Sib V.33</td>
<td>4</td>
<td>155</td>
<td>-</td>
<td>-</td>
<td>176</td>
<td>114</td>
<td>Less than 180</td>
</tr>
<tr>
<td>Proband V.34</td>
<td>5</td>
<td>76</td>
<td>++</td>
<td>+</td>
<td>540</td>
<td>710</td>
<td>Less than 175</td>
</tr>
<tr>
<td>Sib V.35</td>
<td>1½</td>
<td>10</td>
<td>-</td>
<td>-</td>
<td>28</td>
<td>280</td>
<td>Less than 400</td>
</tr>
<tr>
<td>Second cousin IV.13</td>
<td>38</td>
<td>177</td>
<td>-</td>
<td>-</td>
<td>98</td>
<td>55</td>
<td>Less than 110</td>
</tr>
<tr>
<td>Second cousin (2nd specimen)</td>
<td>3</td>
<td>13</td>
<td>-</td>
<td>-</td>
<td>02</td>
<td>67</td>
<td>Less than 110</td>
</tr>
</tbody>
</table>

*For conversion to SI units, 1 mg/100 ml ≈ 88.4 µmol/l.
Table 2  \( \alpha-L \)-iduronidase and arylsulphatase B activity in members of the affected family, normal controls, and people with either the Hurler or Maroteaux-Lamy syndromes

<table>
<thead>
<tr>
<th>Cultured skin fibroblasts</th>
<th>( \alpha-L )-iduronidase (pmol/min per mg)</th>
<th>Arylsulphatase B (% A &amp; B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father IV.12</td>
<td>239,293</td>
<td>---</td>
</tr>
<tr>
<td>Mother IV.69</td>
<td>132,147</td>
<td>79</td>
</tr>
<tr>
<td>Proband V.34</td>
<td>190,229</td>
<td>12, 14</td>
</tr>
<tr>
<td>Case 2 V.31</td>
<td>184,281</td>
<td>22, 26, 29</td>
</tr>
<tr>
<td>Sib V.35</td>
<td>197,222</td>
<td>---</td>
</tr>
<tr>
<td>Second cousin IV.31</td>
<td>162,155</td>
<td>66</td>
</tr>
<tr>
<td>Normal range</td>
<td>87-679 (n = 25)</td>
<td>38-84 (n = 12)</td>
</tr>
<tr>
<td>Hurler range</td>
<td>0.6-4.4 (n = 6)</td>
<td>---</td>
</tr>
<tr>
<td>Maroteaux-Lamy range</td>
<td>---</td>
<td>11.29 (n = 3)</td>
</tr>
<tr>
<td>Peripheral blood leucocytes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proband V.34</td>
<td>100</td>
<td>0</td>
</tr>
<tr>
<td>Normal range</td>
<td>27-134 (n = 24)</td>
<td>12-88 (n = 11)</td>
</tr>
<tr>
<td>Hurler range</td>
<td>3-5-6 (n = 3)</td>
<td>---</td>
</tr>
<tr>
<td>Maroteaux-Lamy range</td>
<td>---</td>
<td>0 (n = 3)</td>
</tr>
</tbody>
</table>

1973). Some modifications were used to improve separation and to quantify arylsulphatase B activity as a percentage of arylsulphatase A and B.

These tests showed the presence of mucopolysaccharides in the urine of the 2 affected children (V.34 and V.31). Mucopolysaccharides were not raised in the urine of other family members. The enzyme studies showed normal \( \alpha-L \)-iduronidase levels and low arylsulphatase B levels in the affected children. Both enzymes were normal in the others. These findings give a biochemical diagnosis of Maroteaux-Lamy type mucopolysaccharidosis (MPS type VI).

Tests for mucopolysaccharide disorders were normal in the second cousin (IV.13) (Table 1). Assays showed that the activity of the following enzymes in her fibroblast cultures were normal: hexosaminidase A and B, \( \beta \)-galactosidase, \( \alpha \)-galactosidase, \( \alpha \)-mannosidase, \( \alpha \)-glucosidase, \( \beta \)-glucosidase, and \( \beta \)-glucuronidase.

Discussion

The mucopolysaccharidoses are well recognised and well documented disorders of mucopolysaccharide storage. They are transmitted recessively, with the exception of the Hunter syndrome (MPS II A and B), which is transmitted as an X-linked disorder. The clinical features, genetics, and biochemical defects have been comprehensively reviewed by McKusick (1972). MPS, such as the Hurler syndrome, have been noted in many different races, but until now none has been reported as occurring in the Australian aborigine.

The exact nature of the defect of MPS storage in the cases presented here is not yet known, though the presence of heparan sulphate, dermatan sulphate, and raised levels of chondroitin-4-sulphate in the urine confirms that such a disorder exists.

The results of enzyme analysis suggest the diagnosis of MPS VI, though heparan sulphate is not usually found in the urine in this condition. It is, however, present in MPS IH.

Children with MPS VI differ from those presented in several important clinical features. Most significantly, they have normal intelligence and in some cases even better than normal. The cases presented here showed severe mental retardation. Those affected with MPS VI are usually taller and have a longer life span. Morphologically, these cases showed more of the classical features of MPS IH rather than those of MPS VI. In particular, they had the coarse faces and features of the Hurler syndrome. The radiological features were also suggestive of MPS IH, though less severely affected MPS VI patients the changes may be indistinguishable from MPS IH.

MPS VI is known to occur in 2 forms; a mild form, VIB, which clinically resembles MPS IS, and a more severe form, VIA (McKusick, 1972). If the children presented here are of an MPS VI type then they represent an even more severe form of MPS VI than previously reported.

A deficiency of arylsulphatase B is also found in the metachromatic leucodystrophy variant with multiple arylsulphatase deficiencies. Mucopolysacchariduria may also be present. However, the clinical appearance of this condition is quite different.

The children were not full blood aborigines. The mother of these children (IV.69) had 15/16 aboriginal blood. She had a European maternal great-great grandfather (I.7). The father (IV.12) had 7/8 aboriginal blood, since his maternal great-grandfather was Indian (II.1). These children, therefore, had 29/32 aboriginal blood. It is suggested that the gene originated in the common full blood aboriginal family, as the parents are first cousins once removed. Though the 2 families intermarried on 6 occasions, only one family has affected children.

The young child (V.35) showed the difficulty in recognising an MPS disorder in aborigines. The Australian aborigine tends to have a broad saddle nose and a large mouth. Protuberant abdomens and hepatomegaly are common as a result of poor nutrition. Despite these racial and environmental effects, the proband had a classical ‘Hurler’ appearance, and was easily recognised as being different from his sibs.

The 38-year-old female second cousin (IV.13) showed a number of clinical characteristics of an MPS disorder, though none of the biochemical characteristics were found. Other tissue storage diseases were also excluded biochemically. The multiple exostoses she had may represent this common dominant trait, but no other family member was found with multiple...
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exostoses. The exact nature of her disability is not yet known.

The 2 children presented in this report clinically had a mucopolysaccharidosis which was confirmed by the presence of increased amounts of mucopolysaccharide in their urine. The clinical features are almost identical to those of the Hurler syndrome, but normal α-L-iduronidase activity and decreased arylsulphatase B activity were found in cultured fibroblasts, suggesting the Maroteaux-Lamy syndrome. Further enzyme studies may pinpoint their metabolic deficiency.

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References

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