Arachnodactyly, aminoaciduria, congenital cataracts, cerebellar ataxia, and delayed developmental milestones

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SYNOPSIS Two male cousins are reported with arachnodactyly, selective aminoaciduria, congenital cataracts, cerebellar ataxia, and delayed developmental milestones, and a distant female relative with similar abnormalities. The syndrome is thought to be previously undescribed, though it has resemblances to Marinesco-Sjögren and Marfan’s syndromes.

A syndrome characterized by arachnodactyly, selective aminoaciduria, congenital cataracts, cerebellar ataxia, and delayed developmental milestones was observed in two young boys who were first cousins. In certain respects the presentation was similar to that of the Marinesco-Sjögren syndrome but with a few additional clinical and biochemical features. In certain other respects it was suggestive of Marfan’s syndrome. To our knowledge, such a combination of clinical and biochemical features has not been recorded hitherto.

CASE REPORTS

Two young male cousins, S., aged 18 years, and B. (MIN No. 6932/73), aged 12 years, were referred to us because of backwardness in intellect, cataracts since infancy, and unsteadiness in walking. Their relationship and the degree of consanguinity in their parents are brought out in the pedigree chart (Fig. 1).

CASE 1 (MIN No. 2549/68) S., the older of the cousins, was born full-term by natural delivery. His mother had not been seriously ill or exposed to radiation or known toxins during the pregnancy. He had been physically and mentally backward from early childhood. Speech was delayed till the third year, when he began to utter monosyllables. At the age of 2 years, he developed lenticular opacities in both eyes, which were ‘needled’ by an ophthalmologist. However, even after the vision had apparently improved, the expected gain in developmental milestones was not forthcoming. He remained ‘weak’ in the lower limbs and ‘clumsy’ in the upper limbs. He had not attended school.

On examination, he was a thinly built individual with a head circumference of 53 cm (21 in) (Figs 2, 3, and 4). He had a poor vocabulary but good comprehension. The volume of his voice was low and speech...
FIG. 2. The first cousins. Left: case 1; right: case 2, showing the squint in both and gynaecomastia in case 1.

FIG. 3. Cases 1 and 2. Lateral view showing dorsal kyphosis, flat chest, thin build, and the gynaecomastia in case 1.

FIG. 4. Cases 1 and 2. The thin build, Marfanoid features, and the normally developed external genitalia are shown.
syllables were split in a staccato way. Intelligence quotient tested on the Binet-Kamath scale gave a mental age of 5 years. The visual acuity was poor (1/60) in both eyes. An 'after-cataract' had developed in the right eye. The pupils were normal in size and reaction and the appearance of the left ocular fundus was normal. A concomitant squint was evident on relaxed forward gaze (Fig. 2). The intraocular tension was normal. The extraocular movements were full with coarse nystagmus on either horizontal gaze. The limbs were hypotonic with normal power in the upper limbs and MRC grade 4/5 power in both lower limbs. Finger–nose–finger and heel–knee incoordination were evident on both sides with mild truncal ataxia and intense gait ataxia, necessitating support while walking. The tendon jerks were quite brisk with flexor plantar response bilaterally. Sensory appreciation and sphincter control were intact.

The other characteristic features noticed in this young man were the thick bushy eyebrows and eyelashes (Fig. 2), flat feet (Fig. 6), mild upper dorsal kyphosis (Fig. 3), sabre tibiae, arachnodactyly (Fig. 7), high arched palate (Fig. 5), and bilateral gynaeco-
mastia (Fig. 3). His secondary sexual characters were well developed (Fig. 4). His height measured 152 cm, span 163 cm, and crown to symphysis pubis 73 cm. Liver and spleen were not enlarged.

CASE 2 (MIN No. 6932/73) B., the younger of the two cousins, was aged 12 years at the time of examination. He was also born by natural delivery after a full-term gestation. Until the age of 4 years, he was not able to sit up without support. He developed cataract at the age of 1½ years. Two years later, an ophthalmologist 'needled' the cataracts and some return of vision resulted. He was put to school only at the age of 10 years but discontinued two years later as he was unable to grasp the lessons taught. He continued to remain unsteady while walking and attempting to write.

On examination, he appeared to be more cheerful and cooperative than his elder cousin; it was possible to communicate with him by conversation. Speech was normal. Intelligence as tested by the Binet-Kamath method placed his mental age at the 8 year level. The visual acuity in the left eye was 6/18 and only hand movements could be perceived by the right eye. A prominent convergent squint was seen (Fig. 2). Extraocular movements were full with coarse nystagmus on looking to either side. In the right eye a dense after-cataract had developed which had occupied the entire pupillary aperture, while the left eye contained the capsular remnants of the previous needling procedure (Fig. 8).

All four limbs were hypotonic and exhibited intention tremor. The tendon jerks were brisk with flexor plantar responses bilaterally. He was able to walk without support but was unsteady, swaying from side to side. The gait was broad based and tandem walking was impossible. There was no sensory deficit or lack of sphincter control.

On general examination, he was also of asthenic build (Fig. 4) with a dorsal kyphosis (Fig. 3), flat chest (Fig. 3), arachnodactyly (Fig. 7), flat feet (Fig. 6), high arched palate, thick eyebrows, and long eyelashes (Fig. 8). He had sparse pubic hair and a normally developed phallus and testes (Fig. 4). His height measured 142 cm, span 150 cm, and the crown to symphysis pubis 65 cm. Liver and spleen were not palpable.

LABORATORY INVESTIGATIONS The results of the routine laboratory investigations are listed in Table 1.

Urine screening tests for inborn errors of metabolism (Benedict's test, cyanide-nitroprusside test, CTAB test, ferric chloride test, and DNPH test) were normal. However, two-dimensional chromatographic study of the urinary amino acids on paper using butanol:acetic acid:water (40:7:5, v/v) and phenol:water (4:1, v/v) systems showed evidence for large quantities of glycine, tyrosine, leucine, and

![FIG. 8. Case 2. Dense after-cataract in the right eye and capsular remnants of 'needling procedure' in the left eye. The thick eyebrows and long eyelashes are also seen.](image)
histidine in the urine of both cases. (The method adopted for quantitation was that described by Varley, 1967). Analysis of the aminoacids in the patients' sera was also conducted. The serum and urine of a 12 year old boy (control) was analysed for the same aminoacids (Tables 2 and 3).

**Other investigations** In both cases, radiographs of the skull and chest were normal, while those of the hand proved the presence of arachnodactyly (Sinclair et al., 1960). Metacarpal index in case 1 was 9.4, and in case 2 it was 9.5 (normal range: 5-4 to 7-9). Buccal smear study in both of them proved to be chromatin negative with karyotype 22+ XY with no structural abnormalities of the chromosomes. In both cases the electroencephalograph and electrocardiogram were within normal limits. Electrophoretic patterns of serum lipoproteins were normal.

**TABLE 2**

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3†</th>
<th>Control‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystine</td>
<td>0.15</td>
<td>0.14</td>
<td>0.14</td>
<td>0.13</td>
</tr>
<tr>
<td>Glycine</td>
<td>0.85</td>
<td>0.90</td>
<td>0.72</td>
<td>0.12</td>
</tr>
<tr>
<td>Histidine</td>
<td>0.70</td>
<td>0.48</td>
<td>0.32</td>
<td>0.16</td>
</tr>
<tr>
<td>Leucine</td>
<td>0.40</td>
<td>0.17</td>
<td>0.30</td>
<td>0.02</td>
</tr>
<tr>
<td>Phenylalanine</td>
<td>0.04</td>
<td>0.03</td>
<td>0.04</td>
<td>0.06</td>
</tr>
<tr>
<td>Proline</td>
<td>0.06</td>
<td>0.06</td>
<td>0.05</td>
<td>0.06</td>
</tr>
<tr>
<td>Serine</td>
<td>0.05</td>
<td>0.06</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td>Threonine</td>
<td>0.12</td>
<td>0.11</td>
<td>0.11</td>
<td>0.11</td>
</tr>
<tr>
<td>Tryptophane</td>
<td>0.02</td>
<td>0.03</td>
<td>0.03</td>
<td>0.02</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>0.83</td>
<td>0.67</td>
<td>0.74</td>
<td>0.03</td>
</tr>
<tr>
<td>Valine</td>
<td>0.03</td>
<td>0.02</td>
<td>0.03</td>
<td>0.02</td>
</tr>
</tbody>
</table>

* Expressed as aminoacid/creatinine/24 hr.
† Case 3 refers to the 16 year old relative of the other two cases marked 'C' in the pedigree chart (Fig. 1).
‡ Control: unrelated boy aged 12 years.

**TABLE 3**

<table>
<thead>
<tr>
<th>Amino Acid</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Control*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycine</td>
<td>2.1</td>
<td>1.4</td>
<td>1.8</td>
</tr>
<tr>
<td>Histidine</td>
<td>1.4</td>
<td>1.7</td>
<td>1.4</td>
</tr>
<tr>
<td>Leucine</td>
<td>2.4</td>
<td>2.1</td>
<td>2.5</td>
</tr>
<tr>
<td>Tyrosine</td>
<td>1.2</td>
<td>1.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.90</td>
<td>0.74</td>
<td>0.66</td>
</tr>
</tbody>
</table>

* Control: boy aged 12 years.

**Other family studies** A distantly related 16 year old girl (case C in Fig. 1) also has bilateral after-cataracts, thin build, arachnodactyly, and Marfan-like features. Only urine was available for testing but showed the same selective aminoaciduria as the probands (Table 2). Unfortunately, the living sibling of case 1 is not available for study.

**DISCUSSION**

Both cases satisfied the criteria for the Marinesco-Sjögren syndrome (Marinesco et al., 1931; Sjögren, 1950)—namely, oligophrenia, cerebellar ataxia, and congenital cataracts. Some of the other findings in our cases were also recorded by other authors: flat feet were observed by Richards (1950); brisk tendon jerks and equivocal plantar responses were recorded by Dureux et al. (1958) and Sjögren (1950); scoliosis and kyphoscoliosis by Garland and Moorhouse (1953); and ocular squint by Alter et al. (1962). Many other clinical features additional to the basic Marinesco-Sjögren syndrome are on record. These include prominent ears (Doğulu and Mutlu, 1957); pes cavus (Dureux et al., 1958); genu valgum, deformed fingers, and short stature (MacGillivray, 1957); anomalies of sex organs (Freycon and Freycon, 1965); dental anomalies, hypopituitarism, and retinitis pigmentosa (Carriero and Di Gennaro, 1965); myopathic features (Alter and Kennedy, 1968), etc.

Accepting our cases as basically examples of the Marinesco-Sjögren syndrome, there are some additional observations: (1) arachnodactyly with high arched palate and other skeletal abnormalities reminiscent of Marfan's syndrome, and (2) presence of selective aminoaciduria (glycine, leucine, histidine, and tyrosine). These findings could be considered coincidental, but, in view of their consistent presence in more than one sib, appear less likely to be so.

In Marfan's syndrome, which our cases resembled morphologically, the presence of specific aminoacidurias, cerebellar features, and lenticular opacities have not been recorded. Again, the negative cyanide-nitroprusside urine test excluded homocystinuria, which sometimes presents clinically as a Marfan-like syndrome (Dunn et al., 1966).

Aminoaciduria, cataracts, and oligophrenia
constitute the oculocerebrorenal syndrome of Lowe (Lowe et al., 1952). Cerebellar dysfunction, nystagmus, intention tremor (McCance et al., 1960), and rachitic features have also been recorded in this clinical entity. However, the absence of the following characteristic features of this syndrome does not favour the diagnosis of Lowe syndrome in our cases: (1) hypotonia and areflexia (Chutorian and Rowland, 1966); (2) renal tubular acidosis (Sagal et al., 1970); (3) aminoaciduria, involving most of the common amino-acids (Schoen and Young, 1959).

The occurrence of aminoaciduria in cases of the Marinesco-Sjögren syndrome is unknown. However, involvement of the kidney has been recorded in literature. Crome et al. (1963) described a syndrome resembling a combination of the Marinesco-Sjögren and Lowe’s syndromes presenting with congenital cataracts, renal tubular necrosis, and encephalopathy in two sisters. Similarly D’Angelo and Ahlheid (1968) discovered deposits of a lipoid substance in the lungs, kidney, liver, and spleen at necropsy in a case of Marinesco-Sjögren syndrome. But selective aminoaciduria was not described in either of these reports.

Histidine, leucine, and tyrosine share a common transport mechanism with other amino acids like phenylalanine, valine, threonine, etc. In the present study, the excretion of phenylalanine, threonine, serine, cystine, proline, valine, and tryptophane was well within normal limits, indicating a selective defect in the renal tubular transport mechanism. This defect seems also to affect the transport of glycine, which usually shares a common transport mechanism with proline and hydroxyproline. The explanation for this selective transport defect resulting in the excretion of this combination of amino acids remains obscure.

It is suggested that this syndrome, characterized by arachnodactyly, selective aminoaciduria, congenital cataracts, cerebellar ataxia, and delayed developmental milestones which was observed in a few members of a family, is a genetically determined disorder probably transmitted in the autosomal recessive manner. The condition could well be an instance of a hitherto undescribed disease with features common to Marfan’s and the Marinesco-Sjögren syndrome.

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