Proteus syndrome: report of a case with severe brain impairment and fatal course

R Rizzo, L Pavone, G Sorge, E Parano, M Baraitser

Abstract
A patient with Proteus syndrome is reported. He had hemihypertrophy, bilateral hypertrophy of the third fingers, skin anomalies, and varicosities, as well as mental retardation, seizures resistant to anticonvulsant treatment, and a very severe course with death at the age of 2 years.

Proteus syndrome is a recently delineated, congenital, hamartomatous syndrome. It is a severe condition with a wide spectrum of abnormalities, the main signs being unilateral gigantism and subcutaneous vascular tumours. We would like to emphasise the occasional severity of the brain involvement and the severe clinical course, which was rapidly fatal in our patient.

Case report
The child was the first born to non-consanguineous parents. The father was 44 years old and the mother was 38 at the time of the proband's birth, and both parents are Italian. The mother denied any drug use, radiation exposure, or infections during the pregnancy. Intrauterine ultrasonography was not performed and the mother felt normal fetal movements. Delivery was at term by caesarean section. Birth weight was 4450 g, length 58 cm, and head circumference 41.5 cm. On the third day of life he had hypoglycaemia with a value of 20 mg/100 ml. After glucose infusion the blood glucose reached normal levels. At the age of 20 days a CT scan showed cranial asymmetry, the right frontal and temporal bones being enlarged, and a larger right lateral ventricle with dilatation of the subarachnoid spaces and the interhemispheric fissures. The third and fourth ventricles were located on the median line but there was hypodensity of the periventricular white matter (fig 1). He came to the Pediatric Clinic of Catania University at the age of 4 months. On physical examination the baby's weight was 6600 g (50th centile), length 71 cm (>97th centile), and head circumference (OFC) 54 cm (>97th centile). His general condition was poor and generalised hypotonia was present. The patient showed several anomalies. There was dolichocephaly with large fontanelles and hemihypertrophy involving the entire right side, including the skull, ear, palate, nose, and neck (fig 2a). The right upper and lower limbs were larger and longer than the left. The right hemihypertrophy of the thorax and abdomen was less evident. There was hypodontia of the upper jaw and teeth were present only on the right side (fig 2b). Macrodactyly was evident bilaterally on the third finger of the hands.

Figure 1  CT scan at the age of 20 days. Cranial asymmetry, large right lateral ventricle, and dilatation of the subarachnoid spaces and the interhemispheric fissures.

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Received for publication 20 June 1989.
Revised version accepted for publication 22 January 1990.
Figure 2  (a) The patient at the age of 4 months showing hemihypertrophy of the right side. (b) Hypertrophy of the right eye and presence of teeth in the right upper jaw.

Figure 3  (a) Marked varicose vein on the left lateral side of the lower limb. (b) Linear epidermal naevus on inner side of the right lower limb. (c) Deep creases on plantar surface of the feet.
The second toe of the right foot was larger than the other toes. Prominent veins were present along the lateral side of the thorax bilaterally. The veins were particularly large and varicose at the level of the knees and along the lateral side of the lower limbs (fig 3a). Varices were also present on the ankle and on the right foot. There was skin involvement, with large, symmetrical, cutaneous haemangiomas located on several parts of the body: on the lateral side of the abdomen, distally on the lateral side of the lower limbs, and on the neck. An epidermal naevus was present on the right side of the face. The naevus had a linear aspect on the neck and on the right lower limbs extending from the knee to the ankle (fig 3b). The nails were dystrophic. There was hypertrophy of the sole of the right foot, which was soft to the touch. Deep creases on the plantar surface were also noticed (fig 3c). The heart, lungs, and all other organs were normal. The patient showed severe mental retardation.

He had an abnormal traction response and had no head control. He did not follow objects and showed poor reaction to the environment. At this age he began to have mixed epileptic seizures characterised by synchronised jerking movements of the arms and legs. The seizures were sometimes tonic-clonic and localised mainly in the left side of the body. The patient was unresponsive to ACTH, phenobarbital, and sodium valproate treatment. EEG showed a pattern of abnormally high, diffuse waves.

Routine laboratory investigations, including a haemogram, CBC, BUN, glucose, protein, lactic and pyruvic acids, screening for aminoacidopathies, ammonaemia, and urine analysis, were normal. A skeletal survey showed no abnormalities and the bone age was normal, as was a G banded karyotype (46,XY). Fundus examination showed increased right intraocular pressure and buphthalmos. Doppler studies of the cerebro-afferent vessels showed no alteration in size or course and in the lower limbs showed no alteration of the arterial blood or communication between the varicose veins and arterial vessels. The left saphenous vein was absent. The ultrasound scan showed no enlargement of internal organs. Histological examination of the skin of the right leg was compatible with a linear epidermal naevus.

The baby was followed as an outpatient. He continued to show epileptic crises which were sub-entrants and mainly of tonic-clonic type. An EEG performed at the age of 10 months was asymmetrical and showed a pattern of spike waves localised mainly in the left occipital area. The child died at 12 months during an epileptic seizure.

Discussion
To date, 26 cases of Proteus syndrome have been reported, including the present case. The clinical features are summarised in the table and it can be seen that the syndrome shows great phenotypic variability.5,6

Severe brain involvement, apart from hemihypertrophy, seems to be unusual and intellectual development has been reported as normal in most cases. Mental retardation has been reported in eight patients with Proteus syndrome and seizures in four. Our patient showed significant brain involvement. A CT scan was performed at 20 days, which showed severe asymmetry of the cerebral hemispheres with the right side larger than the left. The child had severe mental retardation with epileptic seizures resistant to treatment. The seizures were a mixture of infantile spasms and tonic-clonic fits and occurred daily. The interictal EEG initially showed a pattern of diffuse waves but then it became notably asymmetrical and spikes in the occipital area became evident. Brain involvement was extremely marked and the clinical course of our patient was particularly severe, similar only to that described by Mayatepek et al.4 We think that the developmental delay and epileptic attacks have resulted from a variety of intracranial pathological conditions, including hemimegalencephaly, or structural abnormalities of neural tissue, or both.

Some diseases, such as neurofibromatosis, Maffucci's syndrome, Klippel–Trenaunay–Weber syndrome, and encephalocraniocutaneous lipomatosis (ECCL),7 share some characteristics in common with Proteus syndrome. There are also some common anomalies with the linear epidermal naevus syndrome and with malformation syndromes associated with hemimegalencephaly.

It has been suggested that Proteus syndrome might

<table>
<thead>
<tr>
<th>Manifestations of Proteus syndrome.</th>
<th>Previous cases</th>
<th>Our case</th>
</tr>
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<tbody>
<tr>
<td>Growth</td>
<td></td>
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</tr>
<tr>
<td>Asymmetry</td>
<td>26/26</td>
<td>+</td>
</tr>
<tr>
<td>Macroactyly</td>
<td>22/26</td>
<td>+</td>
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<tr>
<td>Skin</td>
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<td></td>
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<tr>
<td>Epidermal naevus</td>
<td>15/26</td>
<td>+</td>
</tr>
<tr>
<td>Thickening of skin and subcutaneous tissue</td>
<td>18/26</td>
<td>+</td>
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<tr>
<td>Subcutaneous masses</td>
<td>21/26</td>
<td>-</td>
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<tr>
<td>Skeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bony prominences of skull</td>
<td>12/26</td>
<td>+</td>
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<tr>
<td>Scoliosis, kyphosis</td>
<td>23/26</td>
<td>+</td>
</tr>
<tr>
<td>Angulation defects of knee</td>
<td>11/26</td>
<td>-</td>
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<tr>
<td>Eye</td>
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<tr>
<td>Strabismus</td>
<td>7/26</td>
<td>-</td>
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<tr>
<td>Myopia</td>
<td>3/26</td>
<td>-</td>
</tr>
<tr>
<td>Enlarged eye</td>
<td>4/26</td>
<td>+</td>
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<tr>
<td>Other</td>
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<td></td>
</tr>
<tr>
<td>Mental retardation</td>
<td>8/26</td>
<td>+</td>
</tr>
<tr>
<td>Seizures</td>
<td>4/26</td>
<td>+</td>
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<tr>
<td>Muscle atrophy</td>
<td>9/26</td>
<td>-</td>
</tr>
<tr>
<td>Pelvic lipomatosis</td>
<td>10/26</td>
<td>-</td>
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</table>
result from a somatic mutation, lethal in the non-mosaic state. Receptors of the tissue growth factors or the local production or regulation of tissue growth factors may be involved, causing overgrowth of cellular elements in skin, bone, and other connective tissue.

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J Med Genet 1990 27: 399-402
doi: 10.1136/jmg.27.6.399

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