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CASE REPORT

Proteus syndrome revealing itself after the treatment of a bilateral subdural haematoma

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Abstract
Introduction Hypertrophy of the calvarium has different aetiologies, among them the rare Proteus syndrome.
Case report We report here the case of a young girl initially treated for relapsing right then left large chronic subdural haematoma, who progressively developed craniofacial hypertrophy consistent with the diagnosis of Proteus syndrome. Calvarium hypertrophy was shaved and remodelled combining midface advancement, essentially for cosmetic purposes. During the first calvarium remodelling, important bleeding of the bone required large volume of blood replacement. Haemostasis workup revealed platelets aggregation anomalies. Bleeding issues during subsequent surgeries were controlled with tranexamic acid and desmopressin acetate.
Discussion Other manifestations of Proteus syndrome, such as a right hypertrophy of the face with hypoplasia of its middle third, a pigmented epidermal nevus and asymmetric limbs and scoliosis, appeared progressively over time. Blood and fibroblast phosphatase and tensin homolog mutation was not found.
Conclusion Literature review of operated patients with Proteus syndrome did not reveal an association with platelets anomalies. A complete haemostasis workup following this unexpected haemorrhagic complication is recommended for this rare pathology.

Keywords Calvarium · Hypertrophy · Proteus syndrome

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Introduction

Proteus syndrome is a very rare condition, first described by Cohen [11], and mostly diagnosed during the first decade of life. It is thought that Joseph Merrick also known as the "Elephant Man", who lived in the late nineteenth century, had the Proteus syndrome [20]. It is characterised by progressive, segmental overgrowth of various tissues, most commonly affecting the skin, skeleton, adipose and central nervous system.

The case of a child with macrocrania and subdural haematomas as the initial presentation is discussed. The haemostasis workup revealed platelets aggregation anomalies.

Case report

A 10-year-old child born from a Swiss father and Filipino mother is reported. Pregnancy and delivery were uneventful. At the age of 6 months, she suffered from a minor head trauma, after falling from the changing table. At the age of 1 year, she was referred for progressive macrocrania at the neurosurgical outpatient clinic. At this time, head circumference was 53 cm (above the 97th percentile). Her neurological and developmental

examinations at this time were unremarkable. Silverman syndrome workup was negative.

Head CT and MRI showed a large right chronic subdural haematoma (Fig. 1a), which was treated with a right subduro-peritoneal shunt. A control CT scan 5 months later revealed a chronic subdural haematoma on the opposite side (Fig. 1b), which was also drained and shunted. A follow-up CT scan 2 months after this last operation showed that the haematomas were totally resolved.

The patient progressively developed over 1 year a growing firm and non-mobile frontal prominence which was cosmetically disfiguring. The CT scan (Fig. 2a) showed a bony thickness localised on the frontal bone, with intact inner and outer table. There was no evidence of intracranial extension or any compression of the brain. Retrospective review of the initial CTs showed that the thickness of the frontal bone was already abnormal and had increased with time (Fig. 1a, b).

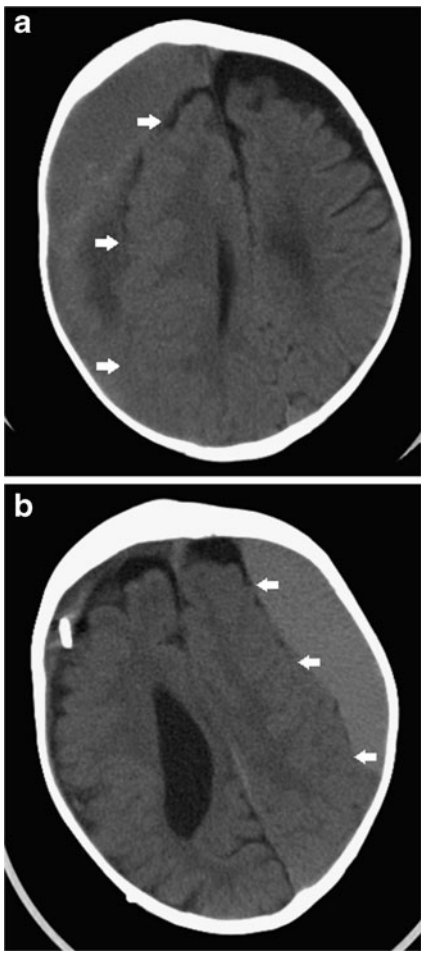

Fig. 1 **a** CT scan showing the initial right isodense chronic subdural haematoma, delimited by *white arrows*. **b** CT scan showing the contralateral subdural haematoma, delimited by *white arrows*. Note the thickness of the frontal bone

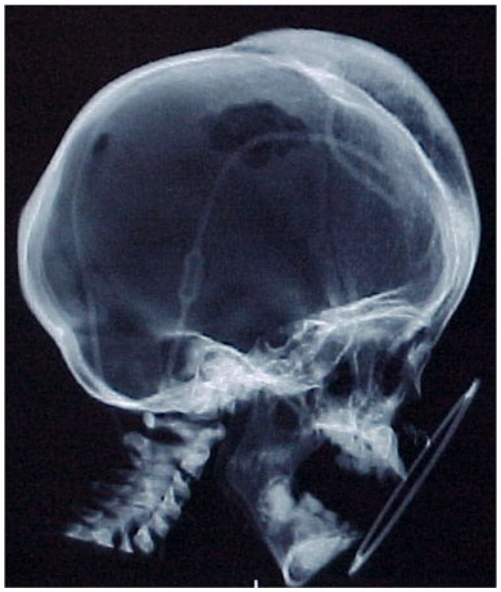

Fig. 2 Lateral X-ray illustrating the frontal bossing

The hypertrophied bone was shaved and remodelled with a high-speed burr, when she was 3 years old, allowing an acceptable forehead. At the same time, the subduro-peritoneal shunts were removed with the exception of the intracranial part of the catheters that were adherent to the brain. Shaving of the frontal bone was complicated by a massive bleeding, requiring a blood transfusion and the administration of tranexamic acid.

Haemostasis workup disclosed platelets dysfunction with absence of aggregation after stimulation with epinephrine.

Genetic workup including blood and skin karyotypes, as well as phosphatase and tensin homolog (PTEN) mutation search in these two tissues, did not show any abnormality.

Histology of the removed bone showed a reactive aspect of cancellous bone without evidence of fibrous dysplasia or neoplasia. The patient recovered well after surgery and remained neurologically normal. At 1-year follow-up, there was no recurrent skull deformity.

The girl was also followed at the neuro-ophthalmologic outpatient clinic for a right eye strabismus which was present since birth. A right optic atrophy was also discovered at diagnosis without any evidence of intracranial hypertension. A lipodermoid of the right conjunctiva was excised at the age of 3 years.

Overtime, the patient's phenotype changed. The right hypertrophy of the face progressed with a broad nasal root and a midfacial hypoplasia. Orthodontic examination disclosed a chaotic implantation of the teeth, especially on the left side, associated with a convex philtrum, a prominent inferior lip and maxillary retrusion (Fig. 3a–c). A pigmented epidermal naevus of the neck was diagnosed and a small "café au lait" spot was described over the right flank (Fig. 3d). The left hand had a trident aspect with a valgus

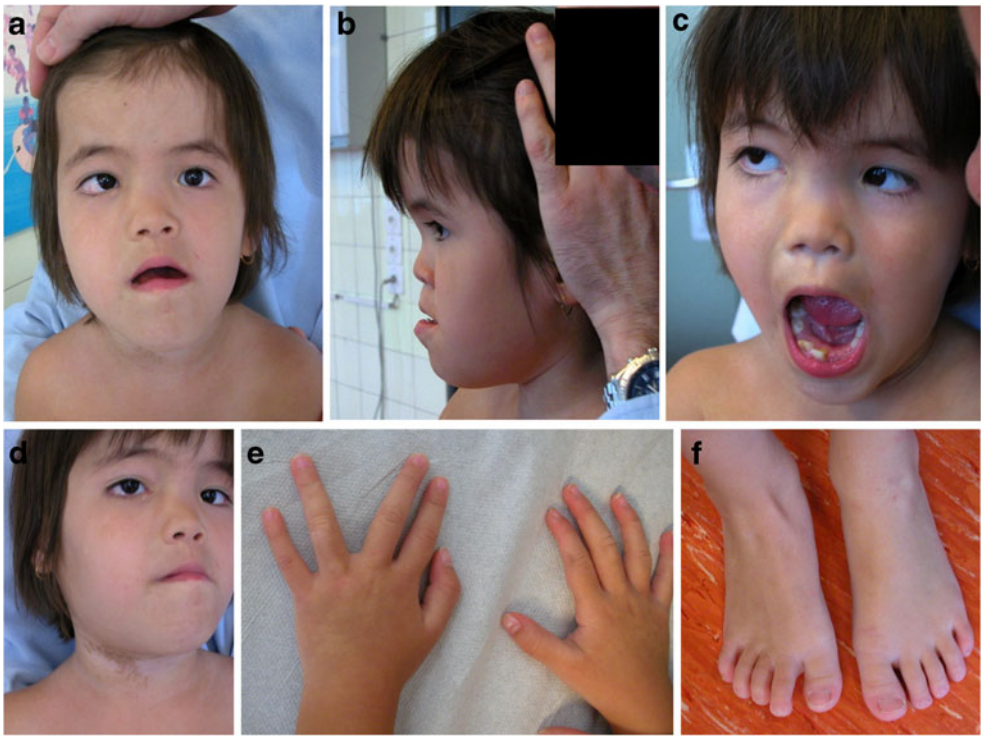

Fig. 3 **a**–**c** Pictures taking at the age of 5 showing a right hypertrophy of the face with a broad nasal root, mandibular prognathisme and a chaotic implantation of the teeth. **d**–**f** Pictures showing a pigmented naevus of the neck, left hand deformation and left foot hypertrophy

of the thumb and a separation between the third and fourth fingers (Fig. 3e). A 5-cm length difference between the legs and a progressive scoliosis were also noted.

Formal neuropsychological testing at the age of 4 years revealed a neurological development delay of 1 year, which necessitated special education.

Unfortunately, the frontal prominence progressively reappeared, with concomitant development of a progressive maxillary retrusion. At the age of 9 years, a LeFort III osteotomy was performed, and internal distractors were applied. The frontal bone was again shaved at the age of 10 years, together with the removal of the distracters. To prevent a recurrent haemorrhage, the patient was prepared by administering desmopressin acetate (0.3 μg/kg) and tranexamic acid preoperatively (10 mg/kg and 2 mg/kg/h) during the surgery. The surgery was uneventful.

Discussion

Proteus syndrome is a very rare congenital overgrowth condition with a prevalence lower than one in 1,000,000. According to Legendre et al., only 205 cases have been published in the world's literature, among them only 97 satisfy the recently published diagnosis criteria of Proteus syndrome [19]. The phenotypic expression of this disorder is highly variable and affect patients in a mosaic manner [6], including osseous, vascular and skin modifications.

A workshop on Proteus syndrome was held in March 1998, at the National Institutes of Health (Bethesda, USA), and participants developed recommendations for diagnostic criteria, and the presented case meets these criteria [6].

Craniofacial hyperostosis is observed in patients with Proteus syndrome in approximately 30 % of all cases [24, 26]. At the time of onset, hyperostosis is known to be variable, but most of the manifestations occur during the first year of life [1].

Limb deformities are a common feature of this syndrome; these can vary from macrodactyly of a single digit to true asymmetric gigantism of digits or toes [2].

Common vascular anomalies are lymphatic malformations, haemangiomas and varicosities. Connective tissue naevi, epidermal naevi, pigmented naevi, subcutaneous hamartomatous tumours and plantar skin hyperplasia are commonly reported [7, 24, 27]. Patients with a greater number of skin abnormalities tend to have a greater number of extracutaneous abnormalities [23].

Brain anomalies are uncommon in this syndrome [12]. Intellectual impairment and seizures are also rare, being observed in 20 and 13 % of patients, respectively. Among those patients with intellectual impairment, 88 % have cranial abnormalities. Hemimegalencephaly and concomitant dilatation of the ipsilateral ventricle may be seen [14, 22]. Some authors report an asymmetry of the central nervous system at both cerebral and brainstem levels, comparing brainstem-, somato-sensorial and visual auditory-evoked potentials [22]. Dandine et al. reported a case of Proteus syndrome associated with a severe intracranial hypertension which resolved after fronto-parietal craniectomy [12].

There are many differential diagnoses for the Proteus syndrome. The two disorders most commonly confusing are

Klippel–Trenaunay–Weber syndrome and hemihyperplasia/lipomatosis syndrome [2, 6]. Klippel–Trenaunay–Weber syndrome is a vascular malformation involving lower or upper limbs and/or trunk and is always combined with capillary, venous and lymphatic malformations; the pigmentary lesions are evident at birth or in early life. This syndrome is usually more severe at birth than Proteus syndrome [2, 7, 17, 21]. Hemihyperplasia/lipomatosis syndrome is not associated with connective tissue naevi, exostoses, linear naevi and deep vascular malformations as seen in Proteus syndrome [17].

Encephalocraniocutaneous syndrome is generally localised to the craniofacial areas and may be a localised form of Proteus syndrome [2, 21]. In Maffucci syndrome, the vascular anomalies are venous and occur with enchondromas not found in Proteus syndrome [2, 17, 23].

Osteopetrosis is a heterogeneous group of rare inherited disorders of the skeleton, caused by failure of osteoclast development or function. The major neurological symptoms are due to the restriction of skull foramina growth. There is a varying amount of calvarial and skull base thickening that occurs [15].

The PTEN tumour suppressor gene is a central negative regulator of the PI3K/AKT signalling cascade that influences multiple cellular functions including cell growth, survival, proliferation and migration in a context-dependant manner [9]. Proteus syndrome has recently been shown to be caused by a somatic activating mutation in AKT1 [13, 20]. The association of Proteus syndrome with germ line mutations of PTEN suppressor gene had previously been reported by some authors [25, 28] but could not be confirmed by others [3, 6].

A literature review did not report any bleeding problem in the Proteus syndrome. Hypercoagulopathy is noted in one case reported by Dandine et al., as their patient presented a pulmonary embolism and a left transverse sinus thrombosis [12]. In the present case, a platelet aggregation test showed an impaired responsiveness to epinephrine with normal coagulogram. Even if a depressed responsiveness to epinephrine in platelets from healthy subject has been reported, this condition can explain the initial subdural haematomas and the massive bleeding during the surgery [8, 16]. Another explanation could be a disseminated intravascular coagulopathy during surgery, but this does not explain the initial haematomas. The administration of tranexamic acid may be a useful adjunct in the medical treatment of high-risk patients with Klippel–Trenaunay–Weber syndrome and other vascular naevi complicated by coagulopathy [18].

As the Proteus syndrome is progressive in character, the craniofacial distortion typically increases with age. There is no specific treatment. Simple corrective procedures might be performed in early life. As the overgrowth in Proteus syndrome is relentless, major osteotomies should be performed after completion of skeletal growth and might be repeated in order to stabilise the symmetrical appearance of the craniofacial skeleton [1, 4–6, 10, 23]. In localised forms, one can consider a total replacement of the calvarium by heterologous plasty.

Conclusion

To our knowledge, this is the first reported case of Proteus syndrome with platelets anomalies. Further cases should be collected for a better understanding of this association. In all cases, a multidisciplinary approach is required, anaesthesiologist team have to be aware for increased bleeding risk and a complete haemostasis workup should be performed before any surgery.

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