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Clinical report

Proteus syndrome: Report of a case with *AKT1* mutation in a dental cyst

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ABSTRACT

Proteus syndrome (PS) is a sporadic and rare congenital disorder characterized by a patchy or mosaic postnatal overgrowth, sometimes involving the face. The onset of overgrowth typically occurs in infancy and can commonly involve skin, connective tissue, central nervous system, eyes and viscera. The progressive overgrowth causes severe complications, such as skeletal deformities, cystic lung disease, invasive lipomas, connective tissue hyperplasia, benign and malignant tumours and deep venous thrombosis with pulmonary embolism, which can cause premature death. This disorder is caused by somatic mosaicism for a specific activating *AKT1* mutation that would be lethal in a non-mosaic state. In this report, current knowledge of the aetiology, the diagnosis and the craniofacial manifestations of the disorder are reviewed. The short-term management of a 7-year-old patient with unusual oral manifestations is described. For the first time mutation of *AKT1* (c.49G > A) gene was detected both in cranial exostosis and in central odontogenic fibroma of the lower jaw.

Proteus syndrome (PS) is a sporadic disorder characterized by segmental or patchy overgrowth of multiple body tissues and cell lineages of all germ layers. Characteristic features include asymmetry overgrowth of body parts, connective tissue hyperplasia, hyperostosis associated with impaired mobility, hemangiomas, lipomas, tumours, dysregulated adipose tissue, central nervous system manifestations and vascular malformations [Biesecker et al., 1999; Cohen, 2005]. Deep venous thrombosis and pulmonary embolism are serious complications of PS and may contribute to the early mortality. This very rare disorder has an estimated incidence of 1 per 1 million [Biesecker and Sapp, 2012]. Affected infants have minimal or no manifestations at birth, but the disease rapidly progresses in childhood. Early surgical procedures are necessary to minimize the secondary deformity or the loss of mobility due to orthopaedic complications. Tissue overgrowth appears to stabilize after adolescence.

1. Introduction

The syndrome was first described in 1979 by Cohen and Hayden, who reported two cases [Cohen and Hayden, 1979]. In 1983, Wiedemann et al. described four children with similar findings and named the disorder Proteus syndrome, which refers to the mythical Greek god of the sea who was able to change his appearance to escape capture [Wiedemann et al., 1983]. In 1987, Happle et al. suggested a genetic cause and postulated that this disorder should result from somatic mosaicism, lethal in the non-mosaic state [Happle, 1987]. Referring to the highly variable phenotypes, mosaic distribution of lesions, sporadic occurrence, the reports of discordant monozygotic twins and the birth of unaffected children of affected parents, authors confirmed the hypothesis that PS is caused by a postzygotic mutation

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[Brockmann et al., 2008; Cohen, 1989, 1993, 2002; Happle, 1987]. The association of PS with mutations in the *PTEN* tumor suppressor gene was reported by Zhoue et al. [Zhou et al., 2001] and Smith et al. [Smith et al., 2002]. In 2011, Lindhurst et al. performed exome sequencing of DNA samples from affected and unaffected tissues of patients with PS and identified a recurrent somatic activating mutation in *AKT1* [Lindhurst et al., 2011; Wieland et al., 2013]. Of 29 patients with PS, 26 carried a heterozygous mutation in the oncogene *AKT1* (c.49G > A, which predicts a substitution of glutamic acid to lysine at amino acid 17 -p.Glu17Lys). This gene encodes a kinase, known to mediate cell proliferation and apoptosis. This mutation that activates AKT1 through phosphorylation, was already reported in various cancerous tissues and underlies the proliferative mechanism [Carpten et al., 2007]. Consistent with this, the up-regulation of AKT1 phosphorylation occurred in some tissues of patients with PS and could explain overgrowth and tumour susceptibility by activation of the phosphatidylinositol-3-Kinase/AKT (PI3K/AKT) pathway [Vivanco and Sawyers, 2002]. In addition to the recurrent activating *AKT1* mutation, other genetic alterations (chromosomal instability, CNV or SNV affecting tumor suppressor genes or other oncogenes) are probably required to promote cancer development. Molecular genetic testing for *AKT1* c.49G > A mutation in the affected tissues may confirm the diagnosis in individuals with clinical criteria and establish the diagnosis in individuals with ambiguous or mild clinical findings [Biesecker and Sapp, 2012].

2. Craniofacial and oral abnormalities

Cohen described a facial phenotype in the PS which can be associated with craniofacial distortion or abnormalities [Cohen, 1993]. Craniofacial disfigurement is progressive, less common than skeletal abnormalities of the limbs and spine and often due to focal overgrowth of membrane bones, which produced exostosis and/or overgrowth of condylar cartilage, which resulted in dentofacial deformity and malocclusion.

2.1. Craniofacial symptoms

The most common cranial signs include hyperostosis, cranial hemihyperplasia (resulting from hemimegalencephaly), craniosynostosis, unilateral condylar hyperplasia and cerebriform connective tissue nevus [Adolphs et al., 2004; Cohen, 1993, 2002, 2005]. The deformities observed in the nasal bridge and hyperostosis of the external auditory canal are observed at low frequency [Jamis-Dow et al., 2004]. A facial phenotype has been described previously and is characterized by dolichocephaly, long face, minor downslanting of palpebral fissures, mild ptosis, low nasal bridge, wide or anteverted nares and open mouth at rest.

2.2. Oral symptoms

In 2002, Bektor et al. detailed craniofacial and oral findings associated with PS [Becktor et al., 2002]. Oral characteristics of the PS include abnormal development of dentition, gingival hypertrophy, high arched palate, crowding, malocclusion, multiple frenulae, hypertrophied tonsils or tongue and enamel hyperplasia.

2.3. Dento-maxillofacial imaging

In 2005, Korbmacher et al. [Korbmacher et al., 2005] described the clinical and imaging findings: precocious dental age on the affected side and cystic transformation of a dental follicule …

3. Case report

The patient was a 7-year-old girl born to unrelated healthy parents. At 22nd weeks' gestation, ultrasound and magnetic resonance imaging demonstrated ventriculomegaly leading to amniocentesis for foetal karyotyping. No chromosomal abnormality was detected. Normal vaginal delivery was at 40 weeks' gestation, with an Apgar score 10/10, weight 3340 g (50th centile), height 46 cm (2nd centile) and head circumference 37 cm (97th centile). Psychomotor development was normal until 2 years of age (first walking at 18 months). Around one year of age, her mother noted a small bump on the scalp. At three years of age, she was referred to a neuropaediatrician at the Children's Hospital of Toulouse (France) for poor language skills. Physical examination showed a weight of 14,5 kg (60th centile), height of 91 cm (25th centile) and head circumference of 50 cm (90th centile). A bump of 8 cm diameter was found on the left parietal region of his scalp corresponding on the radiograph of the skull to a local thickening of the cranial vault. She had also an epidermal nevus at the base of the neck (Fig. 1). None other disproportionate or asymmetric overgrowth was found in the body. Existence of mild learning difficulties was confirmed by the neuropaediatrician. At age 4 years, a progressive increase of local hyperostosis of the skull was observed (Fig. 2) and confirmed by a magnetic resonance imaging. Surgical removal of this exostosis was decided and DNA was extracted from the bone fragments. First, a sequencing of the *PTEN* gene was performed and no mutation was detected neither in DNA from blood nor in DNA from the exostosis. In the meantime, Lindhurst et al. demonstrated the role of the oncogene *AKT1* in PS [Lindhurst et al., 2011]. Finally, the somatic activating mutation c.49G > A (p.Glu17Lys) of *AKT1* was found in an allelic ratio of 35% in the DNA extracted from the exostosis and this mutation was not detected in blood. Annual evaluations were performed and no recurrence, no asymmetry, no overgrowth was noted during a 2 years follow-up. At the last paediatric follow-up, aged of 6.5 years, the patient presented a mild recurrence of the local skull hyperostosis needing no surgery. Ophthalmologic examination revealed a small thickening of the outside layer of the cornea of the left eye. She had no physical anomaly, no intellectual disability and reading was acquired. However, some orofacial praxis were defective leading to orthophonic guidance.

The patient was referred for check up at the dental service of the Toulouse University Hospital at 7 years old. Main abnormal dental

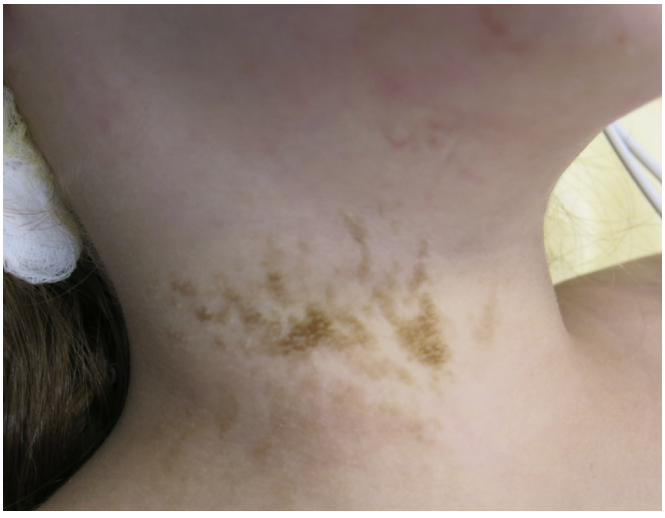

Fig. 1. Epidermal nevus at the base of the neck.