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ORIGINAL PAPER

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Early recognition of basal cell naevus syndrome

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Abstract The basal cell naevus syndrome is an autosomal dominant syndrome characterised by major manifestations such as basal cell carcinomas, jaw cysts, palmar or plantar pits, and intracranial calcifications. Early recognition is important in order to reduce morbidity due to cutaneous and cerebral malignancy and oromaxillofacial deformation and destruction, although diagnosis in infancy is rare. We describe three unrelated children with basal cell naevus syndrome who appeared to be the first patient in each family. *Conclusion:* Our observations lead us to recommend looking for other manifestations of this disease in patients who present with cardiac fibroma, cleft lip/palate, polydactyly or macrocephaly. Bifid, fused or splayed ribs should be considered a major criterion of great help in establishing a diagnosis, particularly in young children.

Keywords Bifid ribs · Ectopic calcification · Gorlin syndrome · Macrocephaly · Polydactyly

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Abbreviation BCNS: basal cell naevus syndrome

Introduction

The basal cell naevus syndrome (BCNS), also known as Gorlin Syndrome (OMIM 109400) is an autosomal dominant syndrome comprising basal cell carcinomas, odontogenic keratocysts, dyskeratotic pitting of the palms and soles, and intracranial calcification [5,10]. Most of these features become apparent at juvenile and adolescent age, although children with the syndrome may first present with a wide range of congenital anomalies and/or dysmorphic features. Various diagnostic criteria have been used to diagnose BCNS [4, 9,11], including major and minor clinical and radiological manifestations of the disease. The diagnosis can often be confirmed by mutation analysis (e.g. detection of germline mutations in the *PTCH* gene) [7,8]. The diagnosis of BCNS can easily be overlooked in young patients especially if there is no family history. We describe three young patients presenting with features of BCNS, in whom the suspected clinical diagnosis was later established by molecular analysis. Our patients also illustrate the importance of using the diagnostic criteria proposed by Kimonis et al. [9] in a paediatric population, since confirming the diagnosis at an early age may reduce the severity of complications including cutaneous and cerebral malignancy and oromaxillofacial deformation and destruction due to jaw cysts [2, 4,6]. Early recognition of the syndrome is also important in view of providing genetic counselling.

Case reports

Case 1

The patient, a girl, is the first child of healthy, non-related parents. The mother developed a polyhydramnion

between the 20th and 26th week of pregnancy. The baby was born prematurely at 28 weeks with a birth weight of 1120 g (P50), a birth length of 40 cm (P97) and an OFC of 27.5 cm (P90). She had a cleft lip and palate on the left side and a postaxial polydactyly on her left hand. Additional investigations revealed absence of the right kidney, agenesis of the callosal body with colpocephaly, a patent ductus Botalli and diffuse transient nuclear cataract in the eyes with a persistent membrana pupillaris.

Chromosome analyses revealed a normal female 46, XX karyotype. During the 1st year of life, she developed macrocephaly with frontal bossing and hypertelorism. An epidermoid cyst was surgically removed from her nasal bridge at the age of 9 months and confirmed by histological investigations. Subcutaneous calcifications were palpable in the skin of her scalp. X-ray films of her skull, the vertebral column and ribs at first revealed no abnormalities. BCNS was suspected due to the combined congenital anomalies and phenotypical appearance (Fig. 1); however, physical examination of the parents and X-ray films of their jaws revealed no abnormalities.

At the age of 4 years her skull circumference was 5 cm above the P97. She had learning difficulties. Her chest was asymmetric with a minimal scoliosis. Additional X-ray films revealed a minimal splayed right fourth rib, with vertebral fusion defects of vertebrae Th1-Th4. The diagnosis of BCNS was confirmed by DNA analysis 1 year later. A frame shift mutation in the *PTCH* gene was detected in exon 2, codon 97 (AAC to AAAC). This mutation was not found in the parents.

Case 2

The patient is a boy, the second child of healthy, non-related parents. He has a healthy sister. He was born at 40 weeks gestation to a 28-year-old mother and a 36-year-old father and had a birth weight of 4470 g (>97th percentile). Macrocephaly was noted at the age of 6 weeks (OFC 43.2 cm, >97th percentile). During the first months of life, he had feeding problems due to laryngomalacia. Ophthalmological examination revealed an ectopic pupil of the left eye and the right eye was highly myopic. Motor development was retarded and explained by his large head and poor vision. An MRI scan of the brain showed large ventricles. A cardiological examination at age 13 months revealed mild valvular pulmonary stenosis and a large tumour in the right cardiac ventricle, which disappeared spontaneously at the age of 2 years.

He was referred to our genetic department at the age of 16 months. His height was 83 cm (90th percentile) and OFC 53 cm (+2 cm >97th percentile). Physical examination showed a large head with prominent frontal veins and low-set ears. He had an inner canthal distance of 3.5 cm (>97th percentile) and an outer canthal distance of 9.8 cm (>97th percentile), with a broad nasal bridge, upturned nose with anteverted nares, a thin upper lip and down-turned corners of the mouth. Both thumbs had immobile interphalangeal joints (Fig. 2). There was an initial suspicion of Gorlin syndrome, which led to additional tests, although radiology of the hands and spine showed no abnormalities. Bifid third and fourth ribs were noted on a chest X-ray film.

Fig. 1 Case 1 at age 14 months. Note frontal bossing and hypertelorism, surgically repaired cleft lip, and scar on nasal bridge

Fig. 2 Case 2 at age 4 years. Large head with low-set ears, broad nasal bridge, ectopic pupil in left eye. Note proximal position of immobile thumb

Chromosome analyses revealed a normal male 46X,Y karyotype.

Taking into account his facial appearance, the macrocephaly, immobile thumbs, cardiac tumour and skeletal abnormalities, and using the diagnostic criteria of Evans et al. [4] at that time, we considered the diagnosis of BCNS and recommended annual MRI imaging of the brain to screen for a medulloblastoma. Neither parent showed any clinical or radiological signs of BCNS. At the age of 4 years, DNA analysis of our patient confirmed the diagnosis by identifying a nonsense mutation in the *PTCH* gene (2619C > A). Neither parent carried this mutation.

Case 3

This boy was the second child born to non-related parents. He has a healthy brother. He was born at 40 weeks gestation with a birth weight of 4060 g (> 97th percentile). A right-sided inguinal hernia was surgically corrected at the age of 2 months. He had feeding problems due to severe gastro-oesophageal reflux and at age 5 months he was admitted to hospital for further evaluation of the feeding problems, macrocephaly (OFC 47.5 cm) and slight delay in motor development. Medication was prescribed for the gastro-oesophageal reflux. CT and MRI scans of the brain showed slightly enlarged ventricles. Neurological examination revealed slight hypotonia, especially of the legs, but metabolic studies were all normal. He had a normal male karyotype. During his 1st year of life, he had several periods of fever and, in addition, he had severe constipation. Extensive immunological and endocrinological investigations showed no abnormalities. At age 13 months his height was 72 cm (P3), weight 7800 g (< P3) and OFC 51 cm (5 cm > P97) (Fig. 3). His motor development was retarded—he only started walking at 3 years old—but his mental development was normal.

Repeated CT scans of his brain were performed. At age 4.5 years, small calcifications were noted on the tentorium cerebelli and falx and he also had a hallux varus and an overlapping fifth toe bilaterally. X-ray films showed a triangular shaped proximal phalanx of the first toe and an extra metatarsal bone between metatarsals 4 and 5 of the right foot. Despite repeated examinations by several medical specialists, no syndrome could be diagnosed.

At age 12 years, he had recurrent painful swelling in his left mandible. X-ray films revealed cysts in his left and right mandibles, and one cyst in the right maxilla, causing displacement of several teeth (Fig. 4). The cysts were surgically removed and diagnosed as odontogenic keratocysts by histopathological examination. BCNS was then considered for the first time and additional tests performed. X-ray films of the thorax showed one bifid rib whereas ophthalmological and dermatological examinations were normal. DNA studies revealed a frame shift mutation in the *PTCH* gene (3139delC), which was not detected in the parents.

Fig. 3 Case 3 at age 13 months. Besides the large head, he showed no other typical facial BCNS features. Note hypotonic posture

Discussion

At a young age, all our patients were admitted to hospital with a variety of symptoms, but at that time they did not show the major clinical and radiological manifestations of BCNS, e.g. odontogenic keratocysts, palmar and/or plantar pits, multiple basal cell carcinomas and intracranial calcifications [4,11]. These major features usually develop over time. Various clinical and radiological diagnostic criteria are used and the diagnosis of BCNS can be made when two of the five major manifestations, or one major and two minor items are present [4,11]. Minor manifestations include congenital skeletal anomalies, cardiac fibroma, medulloblastoma, cleft lip and/or palate and macrocephaly. However, Kimonis et al. [9] have added bifid/splayed/synostosed ribs as a major criterion; an important discriminating feature which can be detected at birth. These authors found rib anomalies in 42% of affected individuals in their review of clinical data on 105 patients with BCNS, whereas the frequency of bifid ribs in the general population is very low [9].

If we had applied the criteria of Kimonis et al. [9], an earlier diagnosis of BCNS could have been made in all our patients. In our first patient the syndrome was suspected because of her cleft lip and palate, and postaxial polydactyly (Table 1). Only after repeated radiological examinations was a rib anomaly detected and the

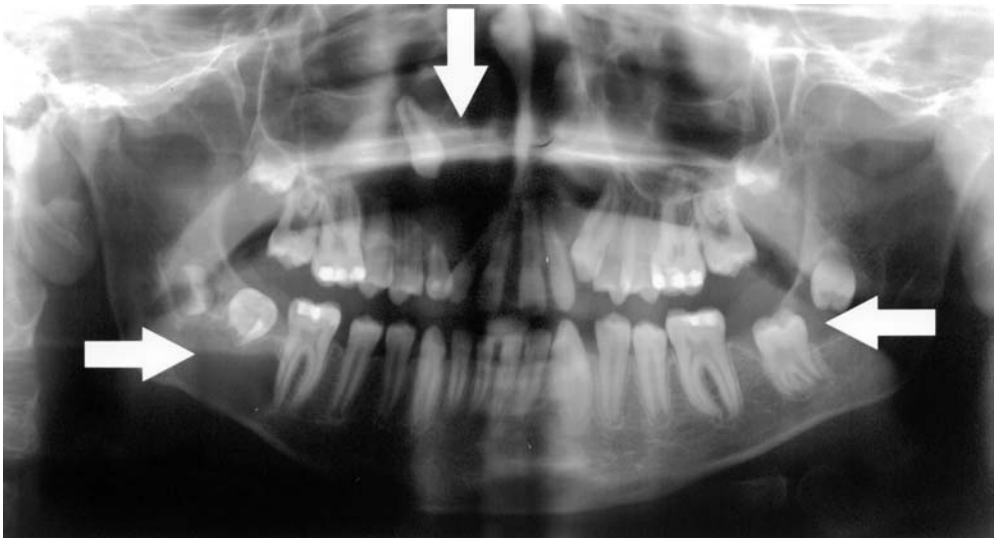

Fig. 4 Case 3 showing radiological features of odontogenic keratocysts in both left and right angles of the mandible and right maxilla

Table 1 Clinical and radiological criteria for BCNS, including detected *PTCH* mutations, adapted from Evans et al. [4] and Kimonis et al. [9]. A diagnosis can be made when two major or one major and two minor criteria are fulfilled

Major criteria	Case 1	Case 2	Case 3
Basal cell carcinomas >2 or 1 before age 20 years	–	–	–
Odontogenic keratocyst	–	–	+ (Age 12 years)
Pits (three or more)	–	–	–
Ectopic calcification (lamellar or early falx)	+ (Scalp[a])	–	+ (Falx)
Bifid/fused/markedly splayed ribs[b]	+	+	+
Positive family history	–	–	–
Minor criteria			
Macrocephaly (OFC >97th percentile)	+	+	+
Other skeletal anomalies (Sprengel deformity, pectus deformity, syndactyly digits)	–	–	–
Radiological abnormalities (bridging sella turcica, vertebral anomalies (hemivertebrae, fused or elongated vertebral bodies), modelling defects of hands and feet	+	–	–
Fibroma (cardiac/ovarian)	–	+ Cardiac	–
Medulloblastoma	–	–	–
Congenital malformations			
Cleft lip/palate	+	–	–
Polydactyly	+ Postaxial	–	+ Postaxial
Eye anomaly (cataract, coloboma, microphthalmia)	Transient cataract Absent right kidney	Ectopic pupil[a] Immobile thumbs[a]	
PTCH mutation	290insA	2619C > A[c]	3139delC

[a]Feature previously described in BCNS but not counted as a diagnostic criterion
[b]Minor diagnostic criterion according to Evans et al. [4]
[c]Nonsense mutation already reported [3,12]

diagnosis of BCNS made definite. In the second patient the combination of a cardiac tumour, macrocephaly and immobile thumbs triggered our suspicion and we looked for other features of BCNS, which were indeed present (congenital rib anomalies) (Table 1). The diagnosis of BCNS was not suspected in the third patient until he developed odontogenic cysts at the age of 12 years. In retrospect, his earlier manifestations (macrocephaly, falx calcifications and latent polydactyly) were all part of the BCNS picture, but it was only after a specific examination that he was also seen to have a bifid rib.

The clinical suspicion of BCNS was confirmed by mutation analysis in all three patients: they each carried a de novo deleterious mutation in the *PTCH* gene, which was compatible with the negative family histories. We were therefore able to report a low recurrence risk to the parents. The nonsense mutation 2619C > A (Y873X) in case 2 has already been reported [3,12], but cases 1 and 3 proved to be novel frame shift mutations.

The *PTCH* gene (gene map locus 9q22.3) is the human equivalent of the Patched (PTC) gene in *Drosophila*. *PTCH* functions as a tumour suppressor gene but

also interacts with the Sonic Hedgehog signalling pathway, important in determining embryonic patterning and cell fate in multiple structures of the developing embryo [1].

Wicking et al. [12] estimated the new mutation rate to be at least 14% in those families in which both parents had been examined, and perhaps as high as 81%. No founder mutations or hotspots have been identified so far [3]. Patients who are the first person in the family to be affected may have milder signs because of somatic mosaicism. It is therefore likely that the estimated prevalence of 1 in 57, 000 in the United Kingdom is too low [4].

A negative family history could hamper early clinical recognition of patients with BCNS; nonetheless, patients can be diagnosed in early childhood if the clinician is also aware of the minor clinical signs of this disease. We recommend looking for other manifestations of BCNS in patients who present with cardiac fibroma, cleft lip/palate, polydactyly, or macrocephaly. Confirming the diagnostic suspicion by mutation analysis at an early age is important in view of the recommended clinical surveillance and genetic counselling of relatives. Our patients illustrate the importance of using bifid/splayed/synostosed ribs as a major diagnostic criterion especially in a paediatric population.

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