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Noonan syndrome with giant cell lesions

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Summary. Noonan syndrome is characterised by short stature, unusual facies, congenital heart disease, chest deformity and mild mental retardation. It may be sporadic or inherited as an autosomal dominant trait and occurs between one in 1000–2500. Cherubism is a giant cell lesion of the jaws thought to be transmitted as an autosomal dominant trait. It is usually recognised by age two to four years, follows a variable course, and is not known to be related to other genetic disorders. The purpose of this article is to report a case of multiple giant cell lesions of the mandible that occurred in a patient with phenotypic features of Noonan syndrome. The emerging relationship between these cherubism-like findings and Noonan syndrome will be discussed.

Introduction

Noonan syndrome was first described in 1963 by Noonan and Ehmke1 [1], although the condition was first reported by Kobylinski in 1883 [2]. By 1987, more than 300 cases had been reported. The link with cherubism derives from the presence of multiple giant cell lesions within the mandible and maxilla. The following is a report of one such case.

Case report

A nine-year-old girl was referred to the Oral and Maxillofacial Unit at the Royal Liverpool Children's Hospital (Alder Hey) by her General Dental Practitioner for an opinion concerning a 2-month history of swelling and tenderness affecting the left side of her mandible. She had previously been prescribed oral antibiotics (amoxicillin) by her General Dental Practitioner for what was thought initially to be a dental abscess arising from the left mandibular dentoalveolar area. When the swelling did not subside, and remained painful on palpation and with discomfort on eating, she was subsequently referred for a second opinion.

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The patient's medical history included Noonan syndrome, and she had previously undergone cardiac surgery at the age of two and a half years, which included a balloon valvuloplasty for a dysplastic pulmonary valve stenosis. Her facial characteristics included hypertelorism, downslanting palpebral fissures and posteriorly angulated low-set ears.

Initial clinical examination confirmed the presence of a localized swelling within the substance of the lower left cheek (Figs 1 and 2). Extraorally the swelling was hard on palpation with some discomfort but with no associated inflammation. Intraorally, the buccal sulcus in the lower left first permanent molar region was extended with a palpable hard swelling, which was painful along the lower border of the mandible. The gingivae were not inflamed nor were any of the teeth grossly carious, tender to percussion or showed any signs of a history of trauma. Radiographic investigations revealed extensive cystic lesions involving both mandibular ramal areas (Figs 3 and 4).

Subsequent specialized imaging, with CT scanning of the mandible and facial bones, confirmed the presence of bilateral expansile cystic lesions in the mandible occupying both angles and mandibular rami (Fig. 5). The individual lesions appeared to be thin-walled and expansive and the contents showed soft tissue attenuation. The largest individual cyst measured between 2 and 3 cm in diameter and, although polycystic, did not involve the mandibular

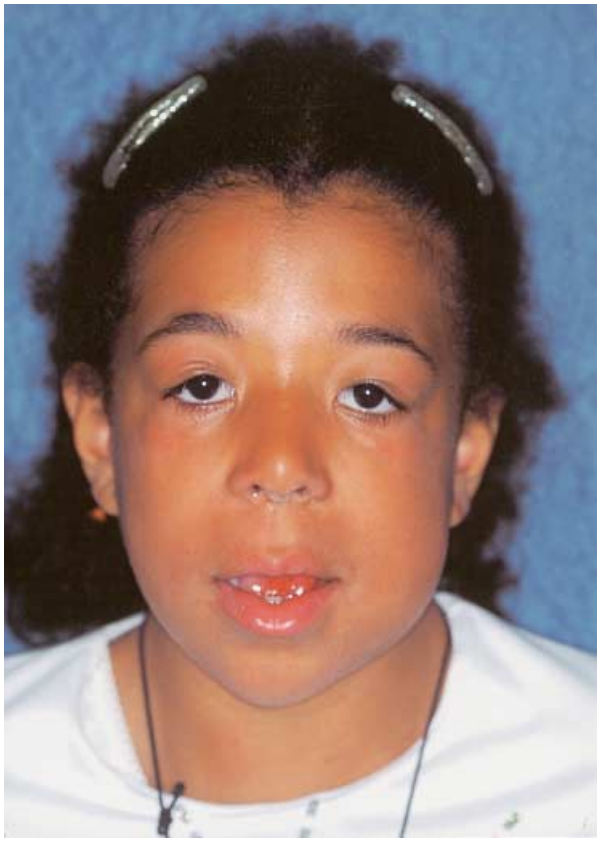

Fig. 1. Front view: patient presenting with a swelling in the left mandibular region. Note the characteristic downslanting of the palpebral fissures, hypertelorsim and posteriorly angulated lowest ears.

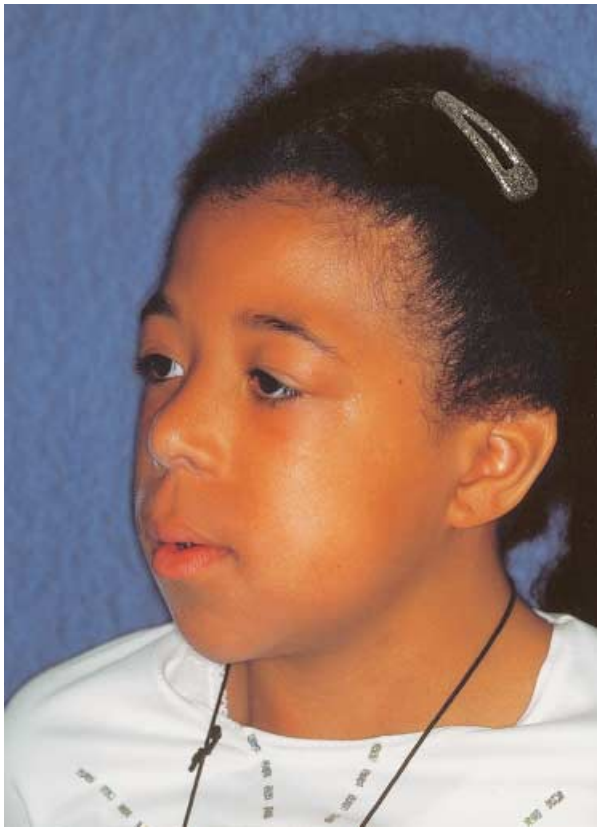

Fig. 2. Left lateral view.

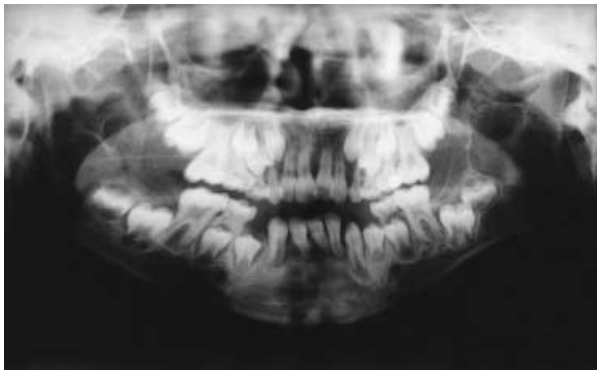

Fig. 3. An OPG showing the multoloculated cystic regions in the mandilble.

condyles, which appeared normal and symmetrical. No skull base or maxillary abnormalities were observed.

In view of these findings, and the known association of Noonan syndrome with odontogenic keratocysts and possibly cherubism, arrangements were made for a surgical exploration and biopsy of the more extensive, and symptomatic, left-sided mandibular cystic lesion under general anaesthesia. The appropriate haematological and biochemical investigations, including serum calcium studies, were also undertaken to eliminate other disorders, such as brown tumours of hyperparathyroidism, and these results were all within the normal range.

During the surgical exploration, it was seen that most of the bone in the posterior body and ramus of the mandible had been replaced by a soft, brown and vascular lesion, which on enucleation of a single cystic lesion appeared to be friable (Fig. 6). There was no obvious capsule surrounding the cavity and the lesion extended inferiorly to the lower border of the mandible. The inferior alveolar neurovascular bundle was seen to be intact at the deep periphery of the cystic cavity. The large excavated bony cavity was then packed with half-inch ribbon gauze, soaked in Whitehead's varnish and sutured accordingly (Fig. 7). The patient was discharged home 2 days later with oral analgesics and antibiotics. At subsequent outpatient review appointments, she was

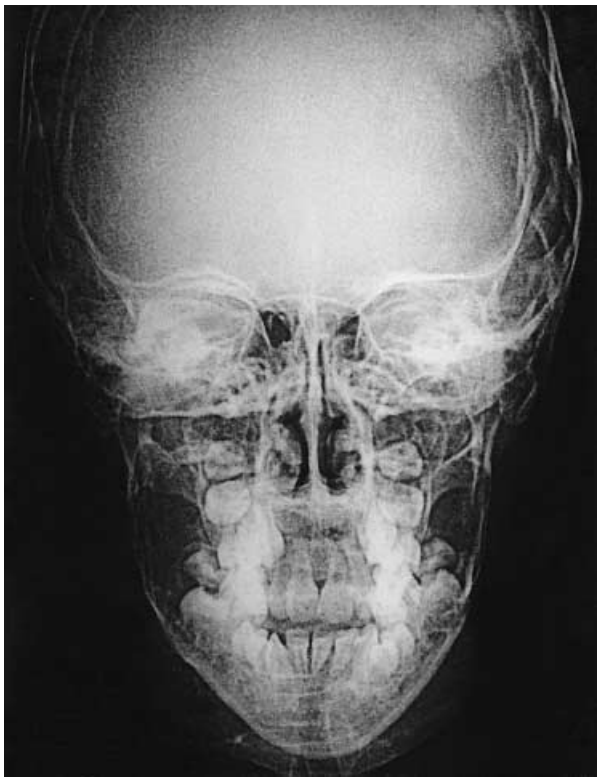

Fig. 4. Posterior–anterior view of the mandible showing the extensive lesion.

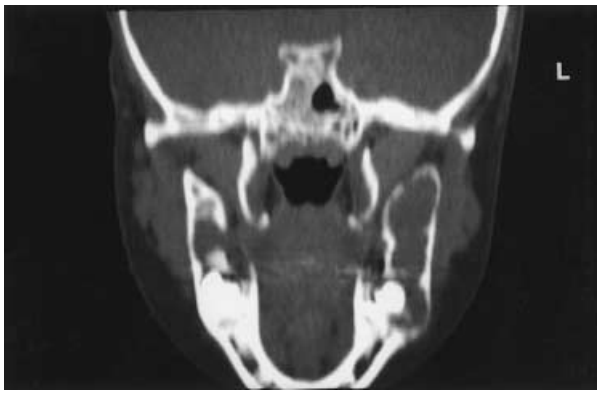

Fig. 5. CT views of the bilateral cystic lesions – axial.

progressing well and the Whitehead's varnish pack was removed, a few centimetres at a time at weekly intervals, for four consecutive weeks, in order to allow healing by secondary intention.

Following histopathological examination, a lesion was reported to be composed of cellular stroma, predominantly ovoid and spindle shaped, without obvious atypia and mitotic activity, in which osteoclast-like giant cells were scattered throughout

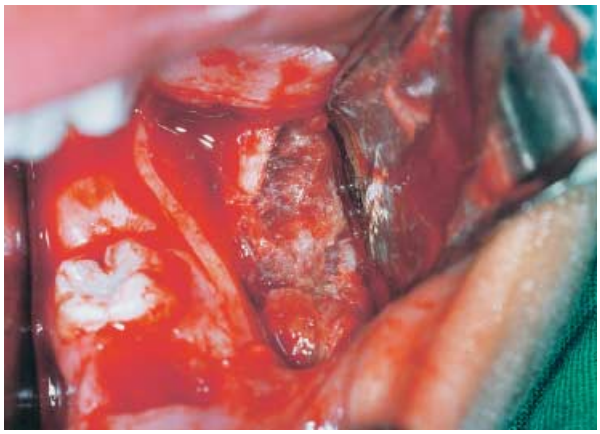

Fig. 6. Intraoral view of the lesion, showing replacement of mandibular bone by the brown vascular lesion.

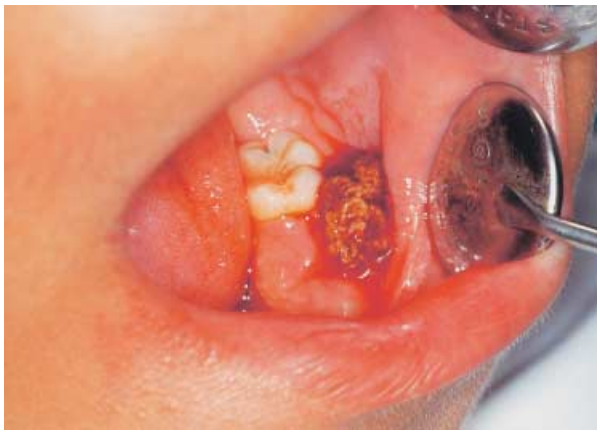

Fig. 7. Intraoral view of the healing site following the excisional biopsy of the left angle and the body of the mandible. The Whitehead's varnish pack can be seen in the buccal sulcus.

but in a clustered distribution. Fibrillary collagen, haemosiderin deposition and haemorrhage, residual bone and foci of osteoid were also observed (Fig. 8).

These histopathological features were considered to be indistinguishable from a central giant cell lesion; however, given the lateral position and symmetry of the lesions, a diagnosis of cherubism could reasonably be reached.

The patient has subsequently been regularly followed up as an outpatient and the previously noted swelling affecting the left mandibular ramal region has subsequently resolved. A radiograph, taken 6 months postoperatively, has shown that the previous cystic area in the left mandibular ramal region has subsequently commenced to resolve and bony regeneration is now clearly visible (Fig. 9). In view

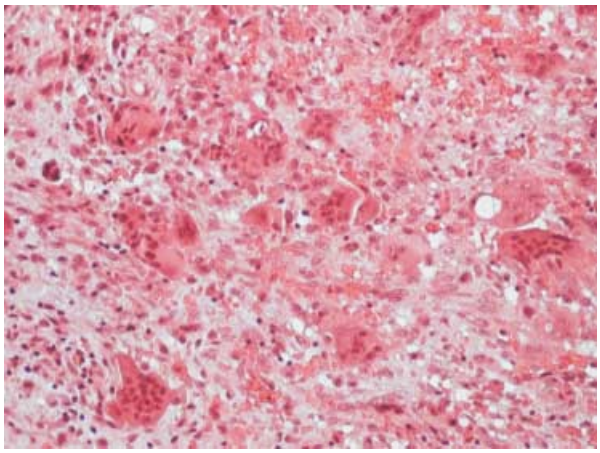

Fig. 8. Histopathology of the lesion shows the osteoclast-like giant cells scattered throughout a cellular stroma.

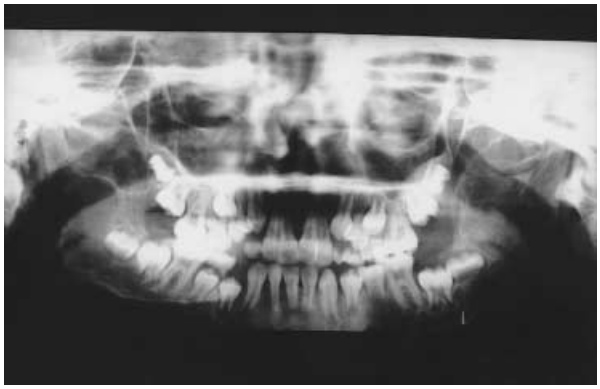

Fig. 9. An OPG taken 6 months postoperatively. Note the bony infill in the left angle, body and ramus of the mandible.

of this initial satisfactory progress, the right-sided mandibular region is merely being kept under close review, both clinically and radiologically, although if the lesion increases in size and gives rise to symptoms in the future, this particular cystic area will also undergo surgical intervention and enucleation; however, if the lesion solely increases in size, but remains asymptomatic, then this will be monitored at regular follow-up out-patient appointments.

Discussion

Noonan syndrome is not an uncommon disorder and Nora *et al*. [3] suggested a prevalence of one in 1000–2500. The condition affects both males and females and most cases are sporadic but occasionally autosomal dominant inheritance occurs (Collins and Turner [4], McKusick [5]). The general body appearance is that of Turner syndrome, and hence Noonan syndrome has been known as 'pseudo-Turner' syndrome in affected females and 'male-Turner' syndrome in males.

Noonan syndrome is characterized by short stature, various congenital heart defects (most commonly pulmonary stenosis), a broad or webbed neck, chest deformity, hypertelorism, antimongoloid slant, ptosis, low-set ears and in some cases mild mental deficiency. Oral features include micrognathia, high arched palate, dental malocclusion, dental anomalies, bifid uvula and rarely cleft palate (Gorlin *et al*. [6]).

Cherubism is a rare dysplasia of bone, which was first reported in 1933 by Jones [7], and is an uncommon disease with only approximately 145 cases reported in 45 years since the first report. Anderson *et al*. [8] and McClendon *et al*. [9] concluded that it is an autosomal dominant trait with 100% penetrance in males and 50–70% penetrance in females. Cherubism is a painless, disfiguring disease affecting bones of the jaws almost exclusively. It manifests during early childhood and progresses until puberty when it spontaneously regresses. Lesions are usually bilaterally symmetric and involve the mandible either alone or with the maxilla. The fullness of the lower half of the face and the retraction of the lower lids gives the characteristic 'eyes raised to heaven' cherubic appearance. By the age of 7 years, the lesions become static and begin to regress, with progressive reduction in the facial deformity as the patient passes from puberty into adult life (Fairclough *et al*. [10]).

Early lesions occur in the posterior body of the mandible and ascending rami. Maxillary lesions may occur simultaneously but are obscured from radiographic detection by the overlapping sinus and nasal cavities. Radiographically, the lesions are radiolucent and multilocular, rarely unilocular, with expansion and thinning of the cortical plates.

The typical histopathological features of cherubism include proliferation of spindle cells, presumably fibroblasts among scattered aggregates of multinucleated giant cells; however, histology cannot guarantee a definite diagnosis, as some lesions such as giant cell granuloma, giant cell tumour and brown tumour of hyperparathyroidism show similar macroscopic and microscopic features. Differential diagnosis is by comparative evaluation of clinical, radiological and biochemical evidence only.

As mentioned previously, cherubism is self-limiting and there is improvement in the facial

features after puberty. Cosmetic jaw surgery may be indicated post puberty. Radiographically, the improvement in appearance is accompanied by bony infilling of the lesions.

Noonan syndrome and cherubism are so essentially different that a common link is difficult to foresee; however, a syndrome has been defined by Cohen and Gorlin [11] which combines patients with a phenotype of Noonan syndrome with multiple giant cell lesions. It seems likely that they are independent diseases transmitted by genes closely linked on the same chromosome. Other similar case reports have been published by Connor *et al*. [12], Dunlap *et al*. [13] and Betts *et al*. [14] and two cases in a publication by Chuong *et al*. [15]. To date, this rare syndrome still requires considerable investigation; to be fully delineated.

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Résumé. Le syndrome de Noonan est caractérisé par une petite taille, un facies inhabituel, une maladie cardiaque congénitale, une déformation du buste et un léger retard mental. Il peut être sporadique ou transmis de façon autosomique dominante et survient dans un cas sur 1000–2500. Le chérubinisme est une lésion à cellules géantes des mâchoires qui serait transmise selon un mode autosomique dominant. Il est généralement mis évidence à l'âge de 2 à 4 ans, se développe de façon variable et n'est pas connu pour être relié à d'autres désordres génétiques. Cet article a pour objectif de rapporter un cas de lésion à cellules géantes de la mandibule survenue chez un patient présentant les caractéristiques d'un syndrome de Noonan. Le lien entre ces caractéristiques de type chérubinisme et le syndrome de Noonan sera discuté.

Zusammenfassung. Noonan-Syndrom ist durch Minderwuchs, eine charakteristische Facies, Herzfehlbildungen, Deformationen des Brustkorbs und leichte geistige Behinderung charakterisiert. Es kann sporadisch oder als autosomal dominant vererbte Form beobachtet werden bei einem von 1000–2500 Kindern. Cherubismus ist eine Riesenzellläsion der Kiefer, die autosomal dominant vererbt wird. Üblicherweise wird die Diagnose im Alter zwischen zwei und vier Jahren gestellt, der Verlauf ist variabel, die Assoziation mit anderen genetisch bedingten Störungen ist nicht bekannt. In der vorliegenden Untersuchung soll ein Fall multipler Riesenzellläsionen des Unterkiefers bei einem Patienten mit dem Phänotyp eines Noonan-Syndroms beschrieben werden. Eine mögliche Beziehung zwischen diesem dem Cherubismus ähnlichen Bild zu Noonan-Syndrom wird diskutiert.

Resumen. El síndrome de Noonan se caracteriza por estatura corta, facies especial, enfermedad cardíaca congénita, deformidad del tórax y ligero retraso mental. Puede ser esporádico o heredado como un rasgo autosómico dominante y ocurre en uno de cada 1000–2500. El querubismo es una lesión de células gigantes de los maxilares que se cree transmitida como un rasgo autosómico dominante. Se manifiesta generalmente entre los 2–4 años de edad, sigue un curso variable y no se conoce que esté relacionado a otras alteraciones genéticas. El propósito de este artículo es informar de un caso de múltiples lesiones de células gigantes en la mandíbula que aparecieron en un paciente con rasgos fenotípicos del síndrome de Noonan. Se discutirá la relación surgida entre los hallazgos semejantes al querubismo y el síndrome de Noonan.

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