□ Case Report □

Basal cell nevus syndrome (gorlin syndrome) confirmed by *PTCH* mutations and deletions

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Basal cell nevus syndrome (BCNS), also known as Gorlin syndrome, is a rare autosomal dominant disorder characterized by variable manifestations, including multiple basal cell carcinomas, odontogenic keratocysts of the jaw, skeletal anomalies including scoliosis and bifid ribs, palmar and plantar pits, calcification of the falx cerebri, and biparietal frontal bossing. We report a case of a 9-year-old boy with the clinical features of basal cell nevus syndrome, in which a PTCH gene mutation was confirmed by DNA testing. **(Korean J Pediatr 2007;50:789-793)**

Key Words : Basal cell nevus syndrome, Odontogenic keratocyst, PTCH mutation

Introduction

Basal cell nevus syndrome (BCNS), also known as Gorlin syndrome, is a rare autosomal dominant disorder characterized by variable manifestations such as multiple basal cell carcinomas (BCC), odontogenic keratocysts of the jaw, skeletal anomalies including scoliosis and bifid ribs, palmar and plantar pits, calcification of the falx cerebri, and biparietal frontal bossing[1]. Most of the clinical features of BCNS become apparent during childhood and adolescence; however children with the syndrome may initially present with a wide range of congenital anomalies and/or dysmorphic features. Various diagnostic criteria have been used to diagnose BCNS[2-4], including major and minor clinical and radiological manifestations of the disease. The PTCH gene, the human homologue of the patched gene originally identified as a *Drosophila* segment polarity gene, has recently been shown to be involved in the development of BCNS[5]. The diagnosis can often be confirmed by mutation analysis; however, the diagnosis of BCNS can easily be overlooked in young patients, especially if there is no family history of the disease [6]. We report a 9-year-old boy with BCNS who initially presented with odontogenic keratogenic cysts. To the best of our knowledge, this is the first case of BCNS confirmed by PTCH gene in Korea.

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Case Report

A 9-year-old boy visited the Department of Otorhinolaryngology of Kangnam Sacred Heart hospital with a complaint of rapid swelling in the left side of the upper jaw area. He was subsequently transferred to the department of dentistry due to the presence of multiple odontogenic cysts of the jaw revealed by facial CT (Fig. 1). The dentist consulted with the pediatrician regarding the facial dysmorphism.

The patient was born at 40 weeks gestation with a birth weight of 3.5 kg following an uncomplicated pregnancy. A cesarean section was performed owing to suspected hydrocephalus diagnosed by fetal ultrasound. Hydrocephalus was confirmed by brain sonogram; however, because the patient showed no symptoms associated with hydrocephalus, the neurosurgeons decided to observe the patient for a while before taking any action. At the age of eight months, the patient showed normal brain magnetic resonance imaging (MRI) without any treatment. Both parents and his younger sister appeared to be healthy. There was no significant family history, except for a maternal uncle who died of skin cancer of unknown origin.

Physical examination revealed macrocephaly with a head circumference of 92 cm (>97 percentile), frontal bossing, depressed nasal bridge, hypertelorism, mandibular progna-

thism, and palmar pits. There was mild diffuse swelling in the right side of the face (Fig. 2). Chest radiography showed bifid rib anomaly (Fig. 3), and skull x-ray showed an intracranial calcification (Fig. 4). Brain MRI revealed small bilateral arachnoid cysts. The clinical suspicion of BCNS was confirmed by a chromosome study that revealed a mutation in the PTCH gene (Fig. 5). A mutation was found in this patient, which causes frameshift by AT deletion between 3364th and 3365th base in 20th exon of PTCH gene. Due to suspicion of mental retardation, psychiatric consultation was recommended and thorough neurological and mental examinations were carried out. His intelligence quotient was consistent with that of a 7-and-a-half-year-old boy. He showed borderline mental retardation and attention-deficit hyperactivity disorder (ADHD). Regular follow-up examinations are being conducted in the department of pediatrics

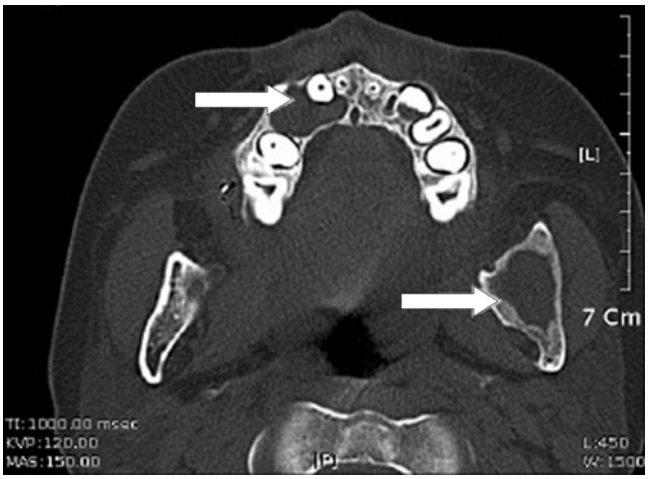

Fig. 1. Axial CT scan at mid-maxilla level shows multiple odontogenic cysts in the left mandibular angle and right parasymphysis (arrows).

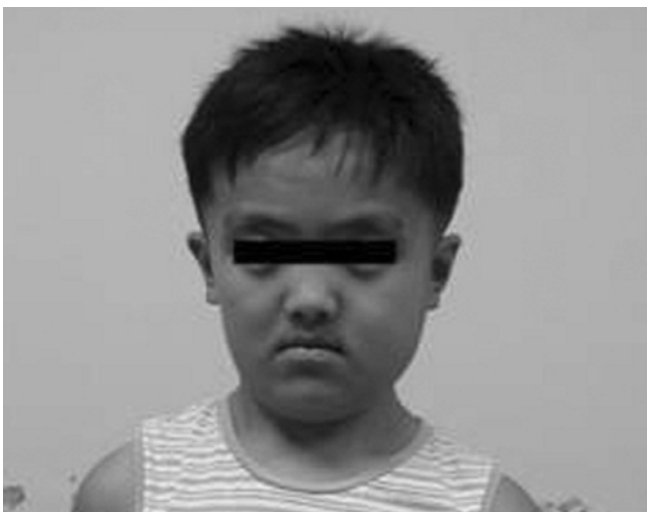

Fig. 2. Patient shows relative macrocephaly, facial dysmorphism.

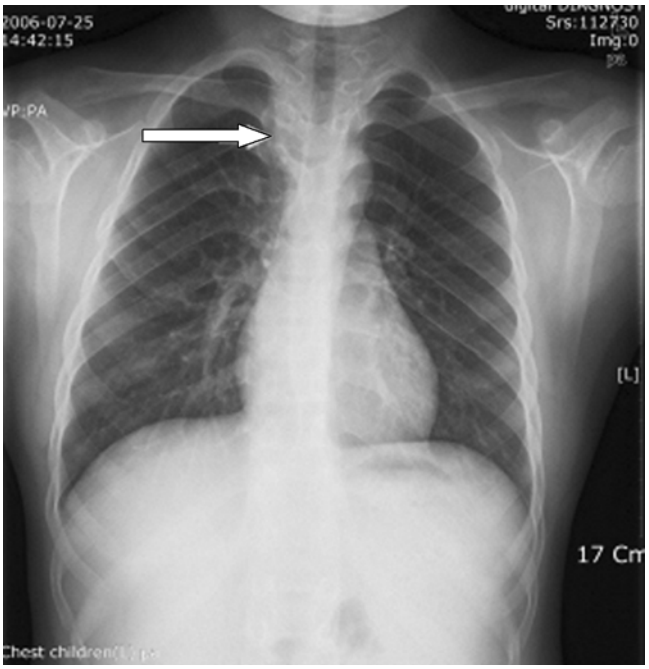

Fig. 3. Chest x-ray shows bifidity of ribs.

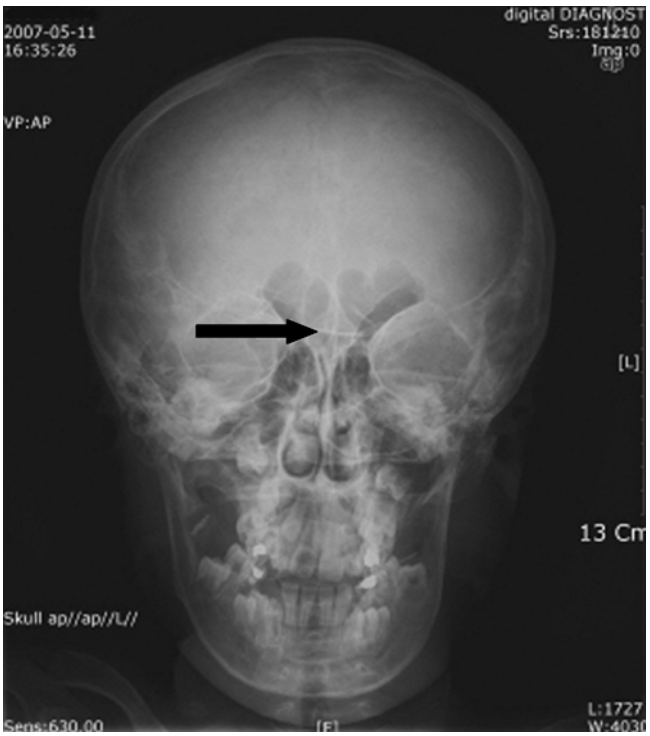

Fig. 4. Skull x-ray shows tentorial calcification.

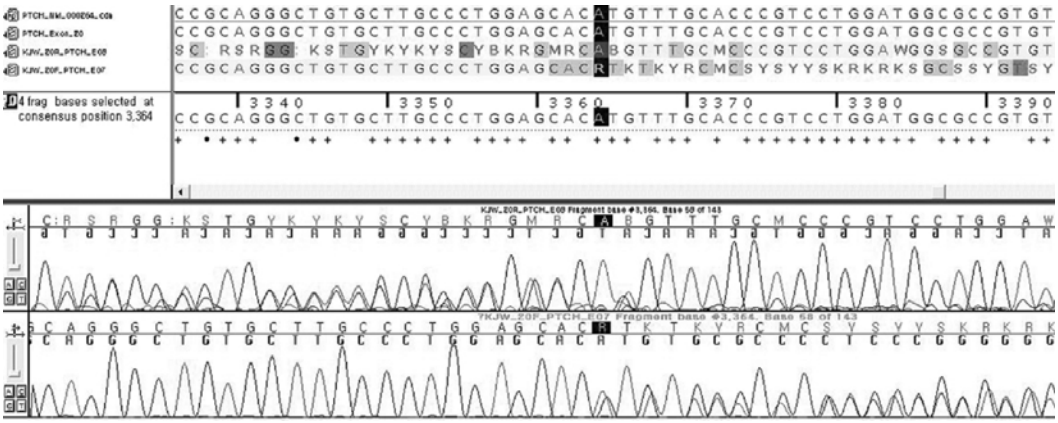

Fig. 5. PTCH mutation analysis. A mutation was found in this patient, which causes frameshift by AT deletion between 3364th and 3365th base in 20th exon of PTCH gene.

Table 1. Diagnostic Criteria for Gorlin Syndrome

Major criteria
Multiple (two or more) basal cell carcinomas or one under 30 years, or ten or more basal cell naevi
Odontogenic keratocysts or polyostotic bone cysts
Three or more palmar or plantar pits
Ectopic calcification; lamellar or early falx calcification
Family history of Gorlin syndrome
Minor criteria
Congenital skeletal anomaly; bifid, fused, splayed or missing rib, or bifid, wedged or fused vertebra
Macrocephaly
Congenital malformation: cleft lip or palate, frontal bossing, 'coarse face', polydactyly, hypertelorism, eye anomaly (cataract, coloboma, microphthalmia)
Cardiac or ovarian fibroma
Medulloblastoma
Lymphomesenteric cysts

Lo Muzio L. Gorlin Syndrome. Orphanet Encyclopedia 2002 Jan [WWW document] Available from:URL://http://www. orpha.net/data/patho/GB/uk-gorlin.pdf

Table 2. Clinical Protocol in BCNS

Family history
Past medical and dental history
Clinical examinations
Oral
Skin
Central nervous system
Head circumference
Interpupillary distance
Eye
Genitourinary system
Cardiovascular system
Respiratory system
Skeletal system
X-ray
Chest
AP and lateral skull
Orthopantogram
Spine
Hands
Pelvic (female)
Ovarian ultrasound (female)
Echocardiogram (children)

Lo Muzio L. Gorlin Syndrome. Orphanet Encyclopedia 2002 Jan [WWW document] Available from:URL://http://www. orpha.net/data/patho/GB/uk-gorlin.pdf

and department of dentistry.

Discussion

Basal cell nevus syndrome (BCNS) was first described by Jarish and White in 1894[7] and was later established as a unique syndrome by Gorlin and Goltz in 1960[1]. The syndrome initially consisted of the triads of basal cell carcinomas, jaw cysts, and skeletal anomalies. BCC usually begin to appear around puberty and usually involve the face, back and chest. Odontogenic keratocysts develop in more than 50% of BCNS patients, often in the first decade of life.

BCNS, or Gorlin syndrome, is essentially a clinical diagnosis. 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 manifestations are present[2, 3]. The minor manifestations of BCNS include congenital skeletal anomalies, cardiac fibroma, medulloblastoma, cleft lip and/or palate and macrocephaly (Table 1). In addition, Kimonis et al.[5] added bifid/splayed/synostosed ribs as a major criterion; an important discriminating feature that can be detected at birth. Lo Muzio et

al[8] suggested the clinical examination protocol for patients with suspected BCNS (Table 2). In our case, we could diagnose Gorlin syndrome clinically by 2 major manifestations such as odontogenic keratocysts of jaw, ectopic calcifications and 3 minor manifestations such as macrocephaly, frontal bossing, bifid rib anomaly. Although mental retardation is one of the known clinical manifestations of BCNS, it remains unclear whether ADHD is a related symptom, as in our case.

Early diagnosis of BCNS is crucial to affected children and their families, especially considering the risk of developing malignancies such as medulloblastoma and aggressive skin cancers. Recent studies have estimated the frequency of medulloblastoma in BCNS patients to be approximately 3-5%[2, 5], while BCNS in medulloblastoma patients is estimated to be approximately 1-2% overall and 4.5% in patients younger than five years of age[9]. Evans et al[2] reported an average age of diagnosis ranging from 2 months to 7 years. Thus, it is very important to screen for medulloblastoma in the early years of life in patients with BCNS. Although most individuals develop their first BCC in their early 20s, children as young as 1.5 years have been noted to have BCCs in the absence of radiation therapy. Therefore, regular dermatological surveillance from an early age with the frequency of visits increasing as needed during and after adolescence is important. Advising patients to reduce exposure to ultraviolet radiation may lessen their risk of developing BCCs.

The genetic abnormality underlying Gorlin syndrome was first identified in 1996. The responsible gene, called Patched 1 (PTCH1), is located on chromosome 9q22.3[10, 11]. PTCH encodes an integral membrane protein, Patched 1 (Ptc1), which behaves as a membrane receptor in the Shh-Ptc-Gli signaling pathway, a cascade that is crucial in embryonic development and is involved in the patterning of vertebrate structures[12]. Confirming the diagnostic suspicion by mutation analysis at an early age is important in view of the recommended clinical surveillance and genetic counseling of relatives. In our case, a mutation causing frameshift by AT deletion between 3364th and 3365th base in 20th exon of PTCH gene was confirmed.

A negative family history could hamper the early clinical recognition of patients with BCNS; nonetheless, patients can be diagnosed during early childhood if the clinician is also aware of the minor clinical signs of this disease[6].

Guidelines for follow-up have been established and include the following: neurologic examinations twice yearly, yearly cerebral MRI between ages 1-7 years, orthopantomograms every 12-18 months starting at the age of eight years, yearly skin examination, and cardiologic examination according to the signs and symptoms[13].

In conclusion, since most symptoms of BCNS begin to appear during childhood and adolescence, the dentist would most likely be the first doctor to suspect the disease since an odontogenic cyst of the jaw might be the first sign, as in our case. Pediatricians should be aware of this disease since confirming the diagnosis at an early age may reduce the severity of complications, including cutaneous and cerebral malignancy and oromaxillofacial deformation and may allow genetic counseling of relatives.

한 글 요 약

PTCH 유전자 검사로 확진된 기저세포 모반 증후군 1례

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기저세포 모반 증후군은 피부의 기저세포 암종, 악골의 치성 각화낭종, 손, 발바닥의 소와, 이소성 석회화, 기저세포 모반 증후군의 가족력 등을 주요 특징으로 하는 상염색체 우성 유전 질환이다. 저자들은 갑자기 커지는 좌측 안면부 종물을 주소로 내원한 9세 남자 환아에서 외관상 특징적인 소견 관찰되고 분자유전학적 검사에서 PTCH 유전자의 결손 확인되어 기저세포 모반 증후군 확진된 1례를 경험하였기에 보고하는 바이다.

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