Clinically Mild, Atypical, and Aged Craniofacial Syndrome is Diagnosed as Crouzon Syndrome by Identification of a Point Mutation in the Fibroblast Growth Factor Receptor 2 Gene (FGFR2)

Toyoki MAEDA, Masamitsu HATAKANAKA*, Hiromi MUTA, Masaharu NAKAYAMA, Yukoh NAKAZAKI, Takashi HIROYAMA, Tomokazu SUZUKI and Kenzaburo TANI

Abstract

A 53-year-old Japanese woman presented with mild mental retardation, short stature, hypertelorism, saddle nose, vertebral fusion, and hydrocephalus, implying an underlying bone growth impairment mainly of the head and neck. A point mutation in fibroblast growth factor receptor 2 (FGFR2) was identified that had previously been seen only in sporadic cases of Crouzon syndrome. This patient did not exhibit any of the typical features of Crouzon syndrome primarily seen in affected infants, such as a severely deformed skull, an apical shaped skull, or severe mental retardation. The patient was diagnosed with a mild form of Crouzon syndrome. The patient’s symptoms very early in life may have been ameliorated and modified through growth and aging. The age-related phenotype modifications in Crouzon syndrome are discussed.

Key words: aged case, craniofacial syndrome, vertebral fusion, fibroblast growth factor receptor 2

Introduction

Since its description by Crouzon in 1912, craniofacial syndrome has been subcategorized into over 100 syndromes based on the severity of the craniofacial and associated congenital malformations. Different classifications include Crouzon, Pfeiffer, Jackson-Weiss, Apert, and Saethre-Chotzen syndromes to name a few. Molecular genetic studies demonstrated that mutation of the FGFR (fibroblast growth factor receptor) 1, 2 and 3 genes is a crucial molecular factor in craniofacial syndrome development (1, 2). The FGFR2 locus also encodes keratinocyte growth factor receptor; this protein results from alternative splicing. Mutations causing craniofacial syndrome are almost exclusively localized to exon 9, a region specific for the FGFR2 gene product. Associated anomalies, such as syndactyly, have been observed in craniofacial syndrome patients with mutations in the same exon; this cluster of features is known as Pfeiffer syndrome. Mutation of FGFR2 seems to be involved not only in craniofacial syndrome, but also in other associated congenital anomalies. This variation may originate from identical mutations, a phenomenon referred to as ‘variable expressivity’. Variable expressivity of an FGFR2 mutation manifests in craniofacial syndrome as the presence or absence of associated anomalies. Cases of Crouzon syndrome have been reported in conjunction with fusion of vertebrae, suggesting that the FGFR2 mutation could be a common underlying cause of craniofacial syndrome and vertebral fusion (3). The phenotypic features of craniofacial syndrome also appear to change with growth and aging (4). The clinical manifestations of this syndrome vary in the severity of malformation, patient age of onset, and accompanying complications. This variety often confuses diagnosis. In the case described, genetic analysis for Crouzon syndrome provided a definitive diagnosis in a patient of advanced age with wide-range vertebral fusion and no typical skull deformities.
Case Report

A 53-year-old Japanese woman presented in October 1997 with back pain, urinary incontinence, and gait disturbance lasting for six months or longer. She often fell down as a result of the gait disturbance. She has healthy parents and 12 healthy siblings. Paternal and maternal ages at the patient’s birth were 43 and 38 years old, respectively. Her learning ability in elementary school was below average but was not severely disturbed. She graduated from junior high school. The patient was 153 cm in height and 60 kg in weight. We observed hypertelorism, saddle nose, and brachydactyly in both fifth fingers but no syndactyly (Fig. 1). Tendon reflexes were hyperactive at extremities with no laterality. Babinski’s reflex was positive bilaterally. We also observed Lasegue’s sign and spastic gait. The patient had an IQ of 75 according to the Wechsler Adult Intelligence Scale. Ocular fundus revealed no sign of optic nerve atrophy. Skull roentgenogram could not detect an apical skull (Fig. 2A). Brain CT revealed enlarged lateral ventricles, indicating hydrocephalus (Fig. 2B). Magnetic resonance imaging of the spine revealed fusion of the cervical and thoracic vertebrae (C1–4, C5–6, C7-Th1, Th4–5) (Fig. 2C). The patient possessed a 46 XX karyotype with a normal G-banding pattern. Cerebrospinal fluid pressure was 17.5 cmH2 O. Lumbar traction effectively improved the urinary incontinence, gait disturbance, and lumbago. The lumbago disappeared gradually within three months with daily traction on admission. The patient’s balanced gait was recovered, and she seldom fell down after additional administration of muscle relaxant. The urinary incontinence was partly improved by further administration of oxybutinin.

A genomic DNA specimen was extracted from the patient’s peripheral white blood cells. After obtaining informed consent, a DNA fragment, including exon 9 of FGFR2, was amplified from the genomic DNA of the patient and two siblings by polymerase chain reaction with specific primers for exon 9 of FGFR2, the region in which the majority of point mutations associated with Crouzon syndrome have been identified (1). Sequence analysis of the amplified samples was performed by cycle sequencing, according to the manufacturer’s protocol (TAKARA, Otsu). While the two siblings did not contain a mutation in the region of exon 9, analysis of the patient’s samples revealed a G to A point mutation at position 1,073 leading to an amino acid substitution from serine to cysteine at position 354. This point mutation has been previously identified as a single allele mutation associated with sporadic Crouzon syndrome reported by Reardon et al (5) (Fig. 3).

Discussion

Craniofacial syndrome is characterized by premature synostosis of cranial sutures, resulting in a deformed skull with reduced intracranial volume, hydrocephalus, and mental retardation. Some cases are accompanied by additional anomalies, including syndactyly of fingers or toes and rostral vertebral fusion, such as the fusion of the cervical or upper thoracic vertebrae. In this case, skull bone deformity was not obvious and facial bones showed hypertelorism and saddle nose, but the facial deformity was not prominent. Even though the patient’s appearance was not typical, hypertelorism, saddle nose, vertebral fusion and short fifth fingers implied bone growth impairment as the underlying pathology of this disorder. Facial and vertebral anomalies are sometimes commonly observed in craniofacial syndrome. Taken together, these observations led us to attempt a genetic diagnosis of craniofacial syndrome. The observed mutation G1073A has been detected exclusively in sporadic cases of Crouzon syndrome. This mutation was detected in 1 of 9 Japanese cases of sporadic Crouzon syndrome (6), one sporadic Crouzon case in the report of Reardon et al (5), 2 of 30 German craniosynostosis patients (7), and one of 259 craniosynostosis patients in the United Kingdom (8), but there are no reports of the G1073A mutation in familial Crouzon syndrome or other types of craniofacial syndrome [H]. The high paternal age in the present case may be associated with de novo FGFR2 mutation as previously described (9).

The FGFR2 mutation seen in Crouzon syndrome appears to be a potent promoter of fusion of the bones of the skull and the vertebrae proximal to the skull. In this patient,
hypertelorism and saddle nose were also observed, although these are not specific to Crouzon syndrome. The typical physical features of this syndrome, including severely deformed skull, intracranial volume reduction, and severe mental retardation, were lacking in this patient. The patient’s skull shape might be modified by hydrocephalus. Hydrocephalus is thought to develop in craniofacial syndrome as a result of increased cerebrospinal pressure secondary to intracranial venous hypertension via premature fusion of the cranial base and stenosis of the jugular foramen (10).

Conversely, a primary defect of cranial and neural tube development at embryonic stages may lead to hydrocephalus (11). Intracranial volume in Crouzon syndrome increases during growth to reach normal values by six months of age (4). The reduced intracranial volume of this mild case may have been compensated for by such postnatal changes. The severity of mental retardation may be ameliorated by lifelong experiences of daily social activities. The patient’s saddle nose and hypertelorism could be caused by mild hypoplasia of center part of facial bone. Severe central facial

Figure 2. Radiological images of the patient’s skull (A), brain scan (B), and magnetic resonance image of spine (C). The skull shape reveals neither an apical skull nor a reduced head size (A). Enlarged lateral ventricles are prominent (B). Cervical and thoracic vertebral fusions at C1–4, 5–6, 7-Th1, and Th4–5 are observed (C).
hypoplasia is often brought on by premature sagittal synostosis in craniofacial syndrome. In addition to the mild phenotype at birth, postnatal compensatory cranio-structural change would lessen the extent of facial hypoplasia in this patient.

Neither fusion of the bones of the digits nor deformity of the extremities was seen, and the genetic mutation identified in this case has been detected only in Crouzon syndrome. Therefore, we diagnosed this patient with Crouzon syndrome with a mild and atypical phenotype.

This patient exhibited vertebral fusion encompassing the cervical and thoracic parts. The unexpected, wide-range spinal fusion encompassing the cervical vertebrae and the middle portion of thoracic vertebrae is a rare observation in Crouzon syndrome. Vertebral fusion in Crouzon syndrome is thought to progress with increasing age (3). The thoracic vertebral fusion may result from postnatal long-term progression of such bone fusion. To our knowledge, this is the first report of a patient with Crouzon syndrome possessing accompanying vertebral fusion of the middle thoracic spinal column. These atypical clinical features made an initial diagnosis of Crouzon syndrome difficult.

As the initial diagnosis of Crouzon syndrome was made at an advanced age, this patient is a very rare case. The mild phenotype observed in this case may have made correct diagnosis in early life difficult. The FGFR2 mutation was not identified in two siblings and all of her family members are healthy, thus the patient is likely a sporadic case of Crouzon syndrome. The atypical features of this patient with accompanying vertebral fusion and lack of skull deformity are likely the result of variable expressivity of the FGFR2 mutation. Moreover, age-related changes modified the phenotype of this syndrome, resulting in atypical expression usually not observed in infantile cases. In this patient, phenotypic modifications occurring throughout the course of her life must be considered as factors contributing to the abnormal presentation.

Careful observations and the consideration of age-related modifications in conjunction with genetic analysis are necessary for the correct diagnosis of atypical craniofacial syndrome cases that include mild or atypical symptoms and advanced age.

References