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Craniofrontonasal dysplasia associated with Chiari malformation

Report of 3 cases

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Craniofrontonasal dysplasia (CFND) is a rare developmental anomaly associated with an X-linked inheritance. It is predominantly expressed in females. A Chiari malformation (CM) has not been reported in such patients earlier. The authors report on a family with 3 female members who have marked and generalized CFND. The generalized bone dysplasia/hypertrophy resulted in reduction in the posterior cranial fossa volume in all 3 patients, and in a CM associated with syringomyelia in 2 of them. One of the 2 affected family members who had a CM and syringomyelia was symptomatic and was treated by foramen magnum decompression surgery. The 3 family members had remarkable similarity in their external facial features and in their radiologically revealed morphological features. A review of the relevant literature, genetic abnormalities, and pattern of inheritance is presented.
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Key Words • Chiari malformation • craniofrontonasal dysplasia • craniofrontonasal syndrome • X-linked inheritance

Craniofrontonasal dysplasia or CFNS is characterized by severe hypertelorism, with a central nasal groove, frontonasal dysplasia, and unilateral or bilateral coronal craniosynostosis.[19] The typical manifestations of this syndrome are noted predominantly in females; this is an X-linked developmental disorder that shows paradoxically greater severity in heterozygous females than in homozygous males.[16]

We report on a family of 4, with 3 female members who had CFND that was associated with a CM, and with syringomyelia in 2. Our literature search did not reveal any similar association.

Case Report

History. In this 46-year-old housewife, there had been a swelling at the root of her nose since birth. She had a history of continuous, dull aching pain in the nape of the neck and left upper extremity, which had lasted for approximately 8 years. There was slowly progressive weakness and numbness of the left upper limb over the same period. For 1 year, she had suffered facial asymmetry and bilateral hearing impairment. For a period of approximately 3 months, she had experienced progressive quadriparesis, with the left side being weaker than the right. When admitted to the hospital, she needed support to walk and preferred wheel-chair ambulation.

Examination. On neurological examination she had right lower motor neuron facial paresis and bilateral partial sensorineural hearing loss. There was hypotonia in the left upper limb and spasticity in the legs. There was no clear muscle wasting. There was Grade 4 hemiparesis on the left side. There was a dissociated cervicodorsal sensory loss in the left upper limb and left half of the trunk between the C-3 and T-12 dermatomes. The joint position sense was impaired in all limbs. The Romberg sign was positive. She had a broad-based gait and required bilateral support to walk. She had a characteristic facies with frontal bossing, prominent supraorbital ridges, broad nasal root, bilateral epicanthic folds, hypertelorism, hypoplastic maxillae, and small ear lobules (Fig. 1). She had bilateral pseudophakia due to previous cataract surgery,

Abbreviations used in this paper: CFND = craniofrontonasal dysplasia; CFNS = craniofrontonasal syndrome; CM-I = Chiari malformation Type I.

retrognathia, and torus mandibularis. The swelling at the root of the nose was nontender, hard, and bony. Her neck showed pseudowebbing due to long clavicles. She also had pectus carinatum, scoliosis of the thoracic spine with convexity to the right, a single palmar transverse crease in the left hand, and cutaneous syndactyly of the right hand. Audiography demonstrated bilateral mild sensorineural hearing loss. The patient had no male offspring and had experienced no miscarriages or abortions.

Family History. On inquiry, the patient reported that she had 2 daughters, ages 23 (Fig. 1, seated on left) and 21 years (Fig. 1, seated on right), who had also had similar swellings at the root of the nose since birth. On examination, both daughters had prominent supraorbital ridges, broad nasal root, bilateral epicanthal folds, hypertelorism, hypoplastic maxillae, small ear lobules, pectus carinatum, and torus mandibularis (Fig. 1). In addition, the elder daughter had a single palmar transverse crease in her right hand, her right scapula was higher than the left, and she had thoracic scoliosis. There was no Sprengel deformity. Although the coronal sutures appeared sclerosed, there was no deformation of the skull that suggested coronal craniosynostosis. None of the 3 women had any ridging or longitudinal splitting of the nails. The serum alkaline phosphatase level of all 3 family members was assessed, with normal results.

Neither daughter had any neurological symptoms or deficit. Neuroradiological examination was performed for the entire family. The affected patient and her daughters had similar findings on CT scanning of the cranium and face, which showed diffuse hyperostosis and sclerotic thickening of calvaria and skull base (including both petrous bones), and also of nasal and lacrimal bones, with hypoplasia of maxillae and mandibles (Figs. 2–4). Magnetic resonance imaging studies of the patient and her elder daughter revealed CM-I and cervicodorsal syringomyelia (Figs. 2C, 3B, and 3C). The younger daughter did not have a CM (Fig. 4 right). A skeletal survey was performed in all 3 women, which did not reveal any other abnormality.

The patient's parents, grandparents, siblings, and husband were normal. Imaging studies of the mother and the 2 daughters were performed, but the parents, grandparents, and siblings did not undergo imaging because they had no physical or neurological manifestation of the syndrome.

Operation and Postoperative Course. The patient underwent suboccipital, foramen magnum, and posterior arch of atlas decompression. The bone was markedly thick and hard, and it was moderately hypervascular. Postoperative recovery was uneventful. On follow-up review at 13 months, the patient reported a significant improvement in her limb numbness on the left side and relief of her neck pain. She was able to walk unaided. During the period of observation, the patient's 2 daughters developed no neurological symptoms.

Discussion

The term CFND was first introduced by Cohen[4] in 1979 to describe a patient with coronal craniosynostosis, hypertelorism, limitation of shoulder movements, and digi-

Fig. 1. A photograph of the affected family. The mother and her daughters (front row) harbor CFND. The husband and the patient's mother (back row) are normal.

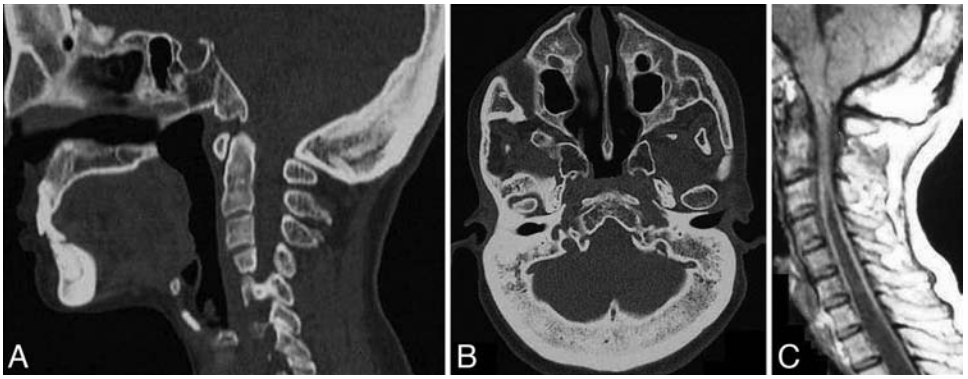

Fig. 2. Neuroimages obtained in the affected patient (mother). **A:** Sagittal CT scan of cranium, upper cervical spine, and face showing diffuse hyperostosis and sclerotic thickening of skull, nasal, and lacrimal bones, with hypoplasia of maxillae and mandibles. Marked hyperostosis of the suboccipital bone can be observed. **B:** Axial CT scan of the cranium showing diffuse hyperostosis of the skull bones, and the nasal and frontal bones. Reduction in the posterior cranial fossa volume due to hyperostosis of the bones can be clearly seen. **C:** A T1-weighted sagittal MR imaging study of the craniovertebral junction demonstrating the CM-I and syringomyelia.

tal abnormalities. It has also been referred to as CFNS. The typical manifestations of this syndrome in female patients are severe hypertelorism (frequently asymmetrical) with a central nasal groove, frontonasal dysplasia, and unilateral or bilateral coronal craniosynostosis (brachycephaly or plagiocephaly). The 3 female family members described in our case report had the abovementioned characteristics and could be labeled as having this syndrome phenotypically. Males are usually affected mildly, with hypertelorism only. A proportion of cases also have a host of thoracic abnormalities such as webbed neck, rounded shoulders, abnormal modeling of the clavicles causing apparent webbing of neck, raised scapulae, pectus excavatum, scoliosis, and asymmetrical breast development.[8,10–13] These patients may also have longitudinal splitting of the nails, syndactyly, preaxial polydactyly, clinodactyly, deviated distal phalanges of the fingers and toes, digital hypoplasia, and a wide space between the first and second toes.[4] Cleft lip and palate, diaphragmatic hernia, agenesis of the corpus callosum, cardiomyopathy, intracranial dermoid, duplex kidneys, and cerebellar dysplasia have also been recorded.[17]

This condition needs to be differentiated from other similar defects such as craniodiaphyseal dysplasia, craniometaphyseal dysplasia, Paget disease, osteopetrosis, and hyperostosis frontalis interna. In craniometaphyseal dysplasia there is mild to moderate overgrowth of the craniofacial bones, which can lead to asymmetry of the mandible, cranial nerve compression, variable hearing loss, and facial palsy. Along with this, there is widening of the metaphysis of the long bones.[1] In craniodiaphyseal dysplasia, in addition to the generalized hyperostosis and sclerosis involving the skull and facial bones, there is diaphyseal, endosteal cortical thickening, and the long bones are generally cylindrical.[2] These two conditions can be distinguished from each other and from CFND on the basis of a radiological survey of the long bones. None of the family members had any radiological abnormality on the skeletal survey or any raised enzyme levels.

Craniofrontonasal dysplasia is a rare, familial, X-linked syndrome. The precise mode of genetic transmission is unclear. The culprit gene *(EFNB1)* has been mapped on chromosome Xq12, which encodes ephrin B1.[16–18] The

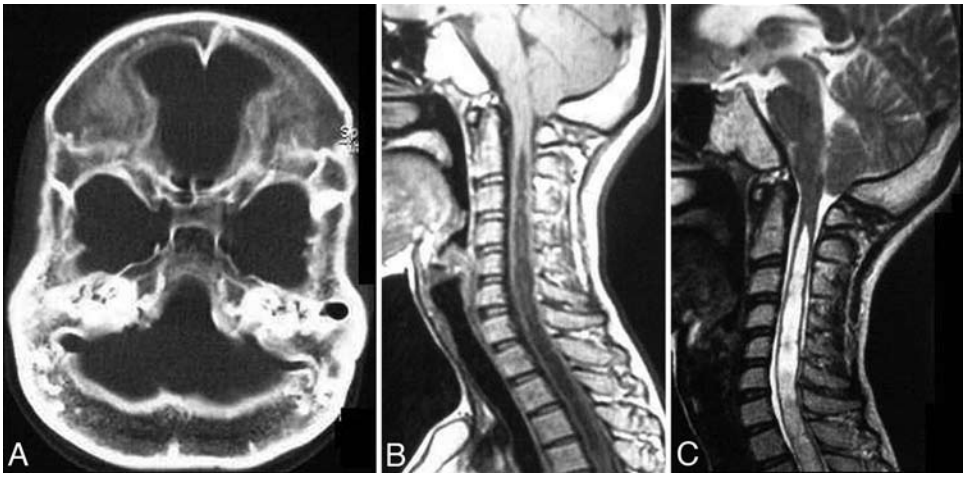

Fig. 3. Neuroimages obtained in the patient's elder daughter. **A:** Axial craniofacial CT scan showing diffuse hyperostosis and thickening of bones identical to the mother's. **B:** A T1-weighted sagittal MR image showing CM-I and syringomyelia. **C:** A T2-weighted sagittal MR image showing CM-I and syringomyelia.

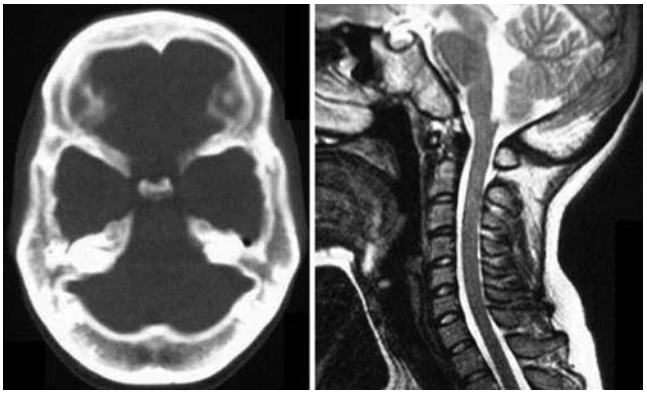

Fig. 4. Neuroimages obtained in the patient's younger daughter. **Left:** Axial craniofacial CT scan also showing diffuse hyperostosis and thickening of bones. **Right:** A T2-weighted sagittal MR image showing absence of a CM.

CFNS phenotype is caused by heterozygous loss-of-function mutations in *EFNB1*, which encodes a member of the ephrin family of transmembrane ligands for Eph receptor tyrosine kinases. Loss of function of this protein leads to broadening of median facial structures (developed from the frontonasal eminence) and shortening of lateral facial structures (branchial arch derivatives). There is diffuse hyperostosis and an increased amount of dense lamellated bone in the craniofacial skeleton.

The bones and connective tissue of the throat, jaws, and front of the skull derive largely from the neural crest. The base of the skull derives from paraxial mesoderm. Cells in the neural crest of rhombomeres 1 and 2 migrate, forming the first branchial arch, which in turn gives rise to 2 maxillary and mandibular prominences of the nasal placode that, together with the ventral mesenchyme of the encephalon (frontal eminence), result in the frontonasal prominence.[7]

The following anomalies comprise the first arch syndrome: Treacher Collins syndrome (mandibulofacial dysostosis), Pierre Robin syndrome (hypoplasia of the mandible with glossoptosis), mandibular dysostosis, deformities of the external and middle ear, congenital deaf-mutism, cleft lip and palate, hypertelorism, and congenital deafness. Except for the hypertelorism, our patients did not have features of the first arch syndrome.[9]

In CFND there is a paradoxically greater severity in heterozygous females than in homozygous males. The usual proposed mechanism for this sex-linked bias in manifestation is the segregation of an X-linked male-lethal mutation.[17] This was the initial mechanism proposed for CFNS, but the explanation became untenable with the description of multiple pedigrees in which classically affected females were linked through an intermediate male relative. These carrier males were always affected less severely than females, with a nonspecific phenotype comprising hypertelorism and occasionally a cleft lip. It was later proposed by Twigg et al. that the major factors accounting for the relative scarcity of carrier males are as follows: the predominant paternal origin of germ line mutations, because they can affect only females in the first generation; the lower genetic fitness of heterozygous females compared with homozygous males, because carrier males in X-linked disorders can inherit a mutation from their affected mother only; and last of all, the occurrence of postzygotic mutations, which are more likely to occur in female embryos and are also likely to manifest clinically because of X inactivation. Genetic testing is imperative in this instance, not only for the molecular test for CFND, which is available in the US and England, but also for karyotype and microarray analyses, which would be beneficial.

The affected patients have a normal life span, with average intelligence. The quality of life is impaired by cranial neuropathies, cosmetic deformity, and depression.

A CM as noted in our patients has not been hitherto reported.[4,11,13,19] The CM-I is a syndrome of hindbrain malformation manifesting with foramen magnum neural displacement, primarily of the cerebellar tonsils and lower medulla. In the majority of patients with CM-I, the disease is sporadic. A review of the literature reveals few previously reported familial cases.[3,5,15] A CM-I with or without syrinx has been associated with a wide range of syndromal conditions, including velocardiofacial syndrome, Goldenhar syndrome, achondroplasia, X-linked aqueductal stenosis, Klippel-Feil syndrome, Williams syndrome, and several others; however, all syndromic cases together account for < 1% of the total cases.[14] Cavender and Schmidt[3] reported on monozygotic triplets, one of whom presented with symptoms of CM-I and syringomyelia, which were confirmed by imaging. The MR imaging studies of the asymptomatic siblings revealed tonsillar descent of 4 and 2.5 mm, respectively. However, it was Coria et al.[5] who first suggested an origin for familial CM-I syndrome by describing a family in which 17 members in 3 generations were studied using high-resolution CT scanning. Seven members exhibited occipital dysplasia and a small posterior fossa. Of these, 3 were proven to have a CM-I deformity, and 2 members were strongly suspected of having an asymptomatic variant of CM-I deformity. Stovner et al.[15] described the presence of a CM-I in DNA-proven monozygotic twins, their mother, and possibly 2 of their children. The MR imaging revealed tonsillar descent of 6 mm in the mother and 1 of the twins; however, neither exhibited any tonsillar impaction. The other 3 patients revealed tonsillar descent between 2 and 5 mm below the foramen magnum, and all were asymptomatic.

Recent studies of posterior fossa morphological features in patients with sporadic CM-I suggest that occipital hypoplasia results in posterior fossa overcrowding, and that this promotes herniation of lower hindbrain contents through the foramen magnum.[6]

Our literature search did not reveal any patient with CFND who had a CM. We hypothesize that a spontaneous mutation might have occurred in the patient, which has manifested in both of her daughters through X-linked Mendelian inheritance. Our cases support the suggestion that diffuse hyperostosis and sclerotic thickening of skull base produces overcrowding of posterior fossa structures and promotes hindbrain herniation through the foramen magnum. Facial nerve paresis and bilateral sensorineural hearing loss in our patient may be due to the narrowing of the skull base foramina through which the seventh and eighth cranial nerves pass.

The second daughter had no CM-I at the time the family was evaluated for CFNS. Whether she will develop a CM-I in future is a matter of speculation.

Conclusions

Symptomatic CM-I may be seen in patients with CFND. Early recognition of the syndrome is important for genetic counseling as well as for detection of a CM and syringomyelia in an asymptomatic stage. This will permit close neurological monitoring and appropriate surgical intervention at an incipient stage.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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