

Congenital Mirror Movements in Gorlin Syndrome: A Case Report With DTI and Functional MRI Features

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Congenital mirror movements are rare conditions that define the inability to perform unimanual movements. Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is a genetic disorder with multiple nevi predisposing to basal cell carcinoma, odontogenic keratocysts, and skeletal malformations. Herein we report on an adolescent patient with Gorlin syndrome and coexisting congenital mirror movements. To our knowledge, this is the first patient in the literature who has both of these very rare conditions.

Congenital mirror movements are rare conditions characterized by the inability to perform unimanual movements and unintentional mirroring of voluntary movements on the opposite side of the body, mainly at the upper extremity.¹ This phenomenon is usually isolated, which means that it is not part of a syndrome, or it may be syndromic as a component of several conditions such as Kallmann syndrome, Klippel-Feil syndrome, Joubert syndrome, Moebius syndrome, and congenital hemiplegia,²⁻⁵ and individual patients with Seckel syndrome and Wildervanck syndrome have also been reported with this condition.⁶⁻⁹ However, to our knowledge, this disorder was not previously described in patients with Gorlin syndrome.

Gorlin syndrome, also known as nevoid basal cell carcinoma syndrome, is an autosomal dominant disorder characterized by multiple basal cell carcinomas, jaw keratocysts, and skeletal malformations.¹⁰ The syndrome is a cancer-prone condition, which may predispose to, in addition to basal cell carcinomas of the skin, malignant or benign tumors such as

medulloblastoma, uterine and ovarian fibromas/fibrosarcomas, meningioma, and cardiac fibromas.¹¹ Herein, an adolescent patient with Gorlin syndrome and coexisting congenital mirror movements is reported as the first patient in the literature, to the best of our knowledge, who has both conditions.

PATIENT PRESENTATION

A 16-year-old right-handed male patient was referred to the pediatric outpatient clinic by his dentist with the radiologic finding of multiple odontogenic cysts. Past medical history revealed his inability to perform unimanual hand movements, starting from early infancy. His birth was uneventful as the second child of healthy nonconsanguineous parents. There was no familial history of any neurologic disease, odontogenic keratocysts, basal cell carcinomas, or any other significant disorder. Growth parameters and developmental milestones were normal.

Physical examination revealed short stature (height of 153 cm, below the third centile), macrocephaly (head

abstract



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Dr Sag followed the patient as the primary doctor, drafted the initial manuscript, and revised and finalized the manuscript; Dr Gocmen performed the radiologic analysis; Drs Yildiz and Temucin conducted the electrophysiologic studies; Dr Ozturk took the photos and video of the patient and drafted the initial manuscript with Dr Sag; Dr Teksam followed the patient as the primary doctor with Dr Sag, coordinated and supervised data collection, and revised and reviewed the manuscript; Dr Utine diagnosed the patient with Gorlin syndrome, coordinated and supervised data collection, and critically reviewed the manuscript; and all authors approved the final manuscript as submitted.

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circumference of 58 cm, above the 97th centile), incomplete unilateral cleft lip, coarse facial characteristics with prominent eyebrows, and mild hypertelorism. He also had multiple nevi over the trunk, Sprengel deformity, mild pectus deformity, and mild scoliosis, as well as a few palmar pits (Fig 1). Neurologic examination was normal except for the bilateral mirror movements of the hands (Supplemental Video).

On chest radiograph, there were 3 bifid costae, including fourth costa on the left, third and fifth costae on the right. Skull radiograph revealed multiple mandibular odontogenic keratocysts and supernumerary teeth (Fig 1). Neurophysiologic assessment with the WISC-R (Wechsler Intelligence Scale for Children-revised edition) revealed a verbal IQ of 62 and a performance IQ of 101, with an overall IQ of 80. The evaluation of family members for features of Gorlin syndrome and congenital mirror movements revealed negative results. The structure and function of the brain were evaluated with structural MRI, diffusion tensor imaging (DTI), functional MRI (fMRI), and electrophysiologic tests such as transcranial magnetic stimulation (TMS), as described below.

Imaging Studies

Structural MRI, DTI, and fMRI were performed with the use of a 3.0 Tesla magnet (Philips Healthcare, Ingenia, Netherlands). Structural MRI showed a left anterior temporal arachnoid cyst and bilateral hippocampal incomplete rotation. fMRI with blood oxygen level-dependent protocol data was acquired with a slice thickness of 4 mm without gap; a 128 × 128 acquisition matrix; a 23-cm field of view; repetition and echo times of 3000 and 35 milliseconds, respectively; and with a “high force hand clenching test” for 240 seconds. fMRI data were obtained by subtracting the

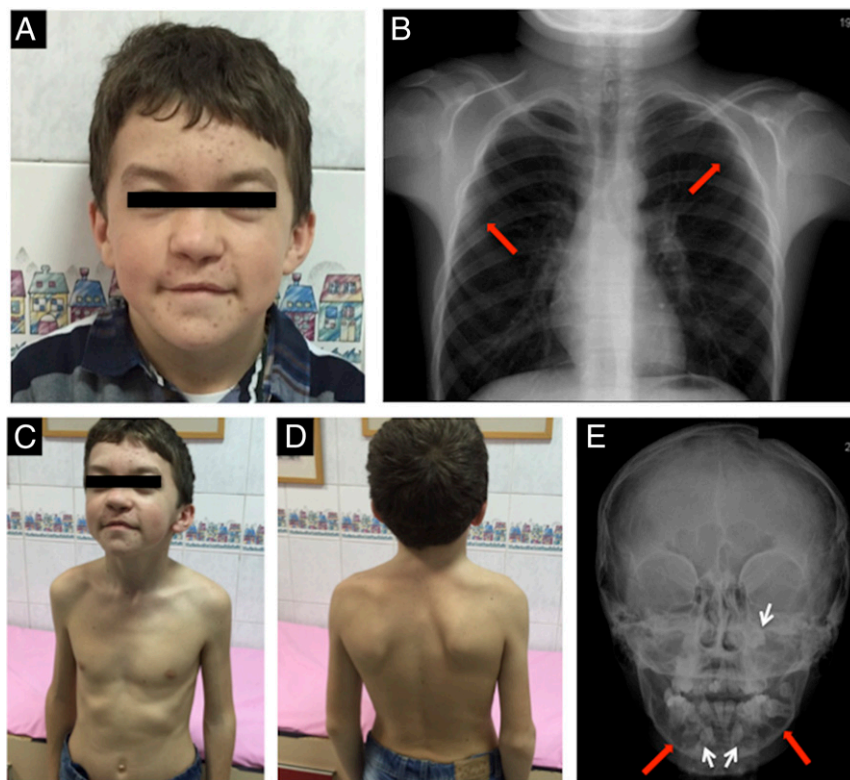


FIGURE 1

A, An incomplete left unilateral cleft lip, coarse face with thick eyebrows, minimal frontal bossing, and mild hypertelorism are shown. B, Posteroanterior chest radiograph showing a bifid fourth rib on the left, a fifth rib on the right (arrows), and right high scapula (Sprengel deformity). C and D, Multiple small nevi on the trunk are shown. E, Skull radiograph showing odontogenic keratocysts in the mandibula (red arrows) and mandibular and maxillary supernumerary and unerupted teeth (white arrows).

motor activity periods from the rest periods. All functional images were then coregistered with the subject's anatomic images. DTI data were acquired with 30 diffusion-encoding directions; 5.0- × 5.0- × 5.0-mm isotropic voxel resolution; a 160 × 160 acquisition matrix; repetition and echo times of 2065 and 92 milliseconds, respectively; and a b-value of 800 seconds/mm². DTI fiber tracking showed a lack of the decussation of bilateral corticospinal tracts at the medulla oblongata (Fig 2A). fMRI showed bilateral activation in the precentral gyri and supplementary motor areas during both an ipsilateral and a contralateral hand-clenching task (Fig 2 B and C).

Electrophysiologic Examinations

To identify the motor organization of mirror movements, we studied

motor pathways by using focal TMS. TMS was performed with parabolic coil connected Magstim (MagPro-stimulator, Medtronic A/S, Copenhagen, Denmark) with the TMS coil placed over the motor cortex (M1), motor-evoked potentials (MEPs) were obtained from ipsi- and contralateral relaxed abductor digiti minimi (ADM) muscles simultaneously by surface Ag-AgCl electrodes. MEP signals were amplified and filtered (20–2000 Hz). In cortical stimulation, we measured the cortical motor latency and MEP amplitudes. The MEP amplitude was measured from 100% stimulator output during rest. An average of 3 trials was used to analyze MEP amplitude and latency. To measure cortical latency, we calculated the onset of averaged MEPs and obtained

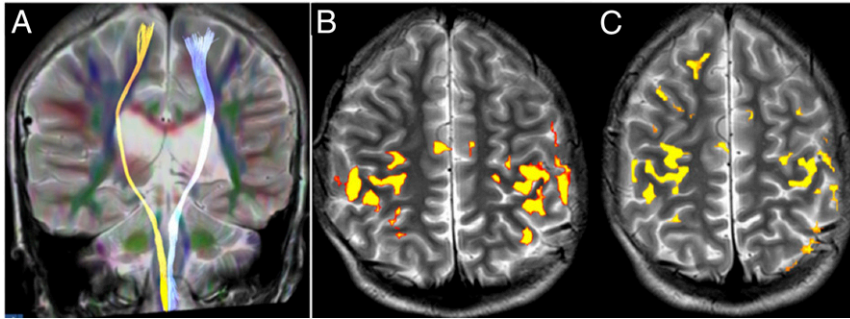


FIGURE 2

A, DTI fiber tractography images show lack of the decussation of bilateral corticospinal tracts. B, Blood oxygen level–dependent fMRI image shows activation of bilateral, symmetrically precentral and postcentral gyrus and supplementary motor area during a right-hand clenching task. C, Blood oxygen level–dependent fMRI image shows bilateral, asymmetrically precentral and postcentral gyrus and supplementary motor area activation during a left-hand clenching task.

the averaged response of amplitude values.

The left focal TMS evoked an ipsilateral MEP of ADM muscle (latency: 19.3 milliseconds; amplitude: 0.7 mV). However, there was a smaller MEP on the contralateral ADM muscle (latency: 22.8 milliseconds; amplitude: 0.2 mV). Similarly, right TMS of the right hemisphere evoked ipsilateral MEPs from the ADM muscle (latency: 18.9 milliseconds; amplitude: 0.8 mV) and small contralateral MEPs (latency: 22.1 milliseconds; amplitude: 0.3 mV). On the basis of these neurophysiologic findings, it can be hypothesized that most corticospinal axons do not cross the midline but travel ipsilaterally.

DISCUSSION

Congenital mirror movements represent an interesting, rare congenital condition, which may persist into adulthood and are usually isolated. Although dominant and recessive inherited mutations in a few genes have been identified recently, these are present in only a minority of the patients and the genetic etiology remains to be elucidated in most of the cases. Several rare syndromes are known to accompany congenital mirror movements in a small subset of

patients, with unclear molecular and genetic implications. Until now, to our knowledge, this condition has not been reported in a patient with Gorlin syndrome.

The present patient had some features of Gorlin syndrome, including facial and cranial findings, costal anomalies, borderline intellectual disability, and palmar pits. However, it was the detection of mandibular odontogenic keratocysts that prompted the clinical consideration of a syndromic condition. Odontogenic keratocysts are one of the common presentations of the disease, most often encountered in adolescents. A wide range of developmental abnormalities including some skeletal abnormalities may coexist; however, a predisposition to neoplasms including basal cell carcinomas is usually the main concern.^{10,12,13} Other manifestations of the disease include hyperkeratosis of palms and soles, skeletal abnormalities (rib, vertebral column, skull, and extremities), intracranial ectopic calcifications, and craniofacial dysmorphic features including macrocephaly, cleft lip/palate, severe eye anomalies, and, in some patients, intellectual disability.¹²

The prevalence of Gorlin syndrome has been reported to range between 1 in 56 000 and 1 in

256 000 in different studies, with a male to female ratio of 1:1.^{5,14} The molecular pathogenesis of Gorlin syndrome is attributed to mutations in the *PTCH1* gene at 9q22.3q31.^{15,16} However, the diagnosis is mostly clinical and requires the presence of 2 major or 1 major and 2 minor criteria.¹⁷ Major criteria include the following: (1) >2 basal cell carcinomas or 1 basal cell carcinoma under the age of 20 years; (2) odontogenic keratocysts proven by histopathology; (3) ≥3 palmar or plantar pits; (4) bilamellar calcification of the falx cerebri; (5) bifid, fused, or splayed ribs; (6) a first-degree relative with the condition. Minor criteria include (1) macrocephaly after adjustment for height; (2) congenital malformations including cleft lip or palate, frontal bossing, coarse facies, or moderate to severe hypertelorism; (3) skeletal abnormalities including Sprengel deformity, pectus deformity, or syndactyly; (4) radiologic abnormalities including bridging of the sella turcica; vertebral anomalies such as hemivertebrae, fusion, or elongation of the vertebral bodies; modeling defects of the hands and feet; or flame-shaped radiolucencies of the hands or feet; (5) ovarian fibroma; and (6) medulloblastoma. The present patient met 3 major (odontogenic keratocysts of the jaw, palmar pits, and bifid ribs) and 3 minor (macrocephaly and congenital malformations such as cleft lip, coarse face, hypertelorism, and Sprengel deformity) criteria.

Congenital mirror movements are rare conditions characterized by the inability to perform unimanual movements and unintentional mirroring of voluntary movements on the opposite side of the body.¹ It is often nonsyndromic and persists through adulthood with no other associated abnormalities, or rarely,

it may be a component of several syndromes.²⁻⁵ Congenital mirror movements usually affect the distal upper extremities, especially the muscles that control the fingers. Mutations in 3 genes, *DCC*, *RAD51*, and *DNAL4*, are known to be responsible for the disorder.¹ The *DCC* gene encodes the DCC protein, a receptor for Netrin-1, which guides the axons across the midline of the body.¹⁸ The *RAD51* gene product is thought to affect the development of corticospinal axons at the pyramidal decussation.¹⁹ An underlying genetic defect may be revealed in only a minority of affected individuals and the pathogenesis is better understood by TMS, DTI, and fMRI. An abnormal decussation of the corticospinal tract, abnormal interhemispheric inhibition and bilateral cortical activation of primary motor areas during intended unimanual movements, and an abnormal involvement of the supplementary motor area during both unimanual and bimanual movements are the 3 possible mechanisms.¹⁹ TMS and DTI revealed the presence of the first phenomenon, and fMRI revealed the presence of the second and third phenomena in the present patient.

The neurologic involvement in Gorlin syndrome usually manifests with ectopic calcifications, central nervous system tumors, seizures, congenital hydrocephalus, intellectual disability, and Huntington chorea.¹² In a report from Switzerland, a patient presented with extrapyramidal findings, Gorlin syndrome, and parkinsonism.²⁰ However, to the best of our knowledge, there are no reported patients diagnosed with both Gorlin syndrome and congenital mirror movements in the English-language literature. The present patient should remind clinicians once again about the importance of integrative evaluation

of patients, with a full physical examination. These individual observations would also be of clinical and molecular importance in elucidating the underlying genetic etiologies of rare conditions.

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ABBREVIATIONS

ADM: abductor digiti minimi
DTI: diffusion tensor imaging
fMRI: functional MRI
MEP: motor-evoked potential
TMS: transcranial magnetic stimulation

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