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Unusual Neurological Presentation of Nevoid Basal Cell Carcinoma Syndrome (Gorlin-Goltz Syndrome)

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Dear Editor,

Nevoid basal cell carcinoma syndrome (NBCCS; also called Gorlin-Goltz syndrome, MIM: 109400) is a rare autosomal dominantly inherited disorder caused by defects in the hedgehog signaling resulting in constitutive pathway activity and tumor cell proliferation.[1] In addition to basal cell carcinoma from a young age, distinguishing features are keratocystic odontogenic tumors, dyskeratotic palmar and plantar pitting, skeletal and other developmental abnormalities, and neurological involvement (e.g., meningeal calcifications, intracranial tumors, seizures, congenital hydrocephalus, intellectual disability, and movement disorders).[1,2] Here we report two patients with unusual neurological presentations of NBCCS. Written informed consent was obtained from both patients, and their family histories were negative.

A 24-year-old female was referred because of bilateral frontal-temporal headache of mild-to-moderate intensity without signs of increased intracranial pressure and which responded to non-steroidal anti-inflammatory drugs with short-lasting relief. She had a prenatal diagnosis of macrocephaly with mild ventriculomegaly and a mild delay in motor development, but no intellectual disability. She had undergone surgery for keratocystic odontogenic tumors in her infancy. A physical examination revealed a prominent forehead, mild hypertelorism, macrocephaly (head circumference 60 cm, ≥97th percentile), mandibular prognathism, and pits on the palms (Fig. 1A). The findings of a neurological examination were normal. Extensive laboratory testing, including of pituitary and parathyroid hormones, produced negative results. Electroencephalography (EEG) results were also normal, and skeleton X-rays and cardiac and pelvic ultrasonography produced unremarkable findings. A maxillofacial computed tomography (CT) scan revealed a cystic lesion in the body of the left mandible (Fig. 1B). Head CT showed diffuse calcifications of the falx cerebri and tentorium cerebelli (Fig. 1C), and a microadenoma of the pituitary gland and a choroid plexus papilloma of the left lateral ventricle were evident in magnetic resonance imaging (MRI). Dermoscopy showed multiple melanocytic nevi (Fig. 1D) and a basal cell carcinoma of the trunk (Fig. 1E). *PTCH1* mutations were ruled out.

The second patient, a 16-year-old female, was admitted because of developmental delay and behavioral disturbances. She had previously received surgery for two nodular basal cells carcinomas below the eyelids (Fig. 1F). Her full IQ was 55 on the Wechsler Intelligence Scale for Children (revised edition). A physical examination revealed short stature (height 158 cm, ≤3rd percentile), prominent eyebrows, scapular winging, and marked scoliosis of the dorsal-lumbar spine with hyperkyphosis of the dorsal tract. A neurological examination disclosed moderate-to-severe intellectual disability, stereotypical motor behavior (e.g., swinging and clapping the hands), and sphincter incontinence. Several hyperpigmented basal cell carcinomas were observed over her face, especially around the eyes (Fig. 1G). Dermoscopy also revealed multiple pits on the palms and a melanocytic nevus of the right shoulder. The findings

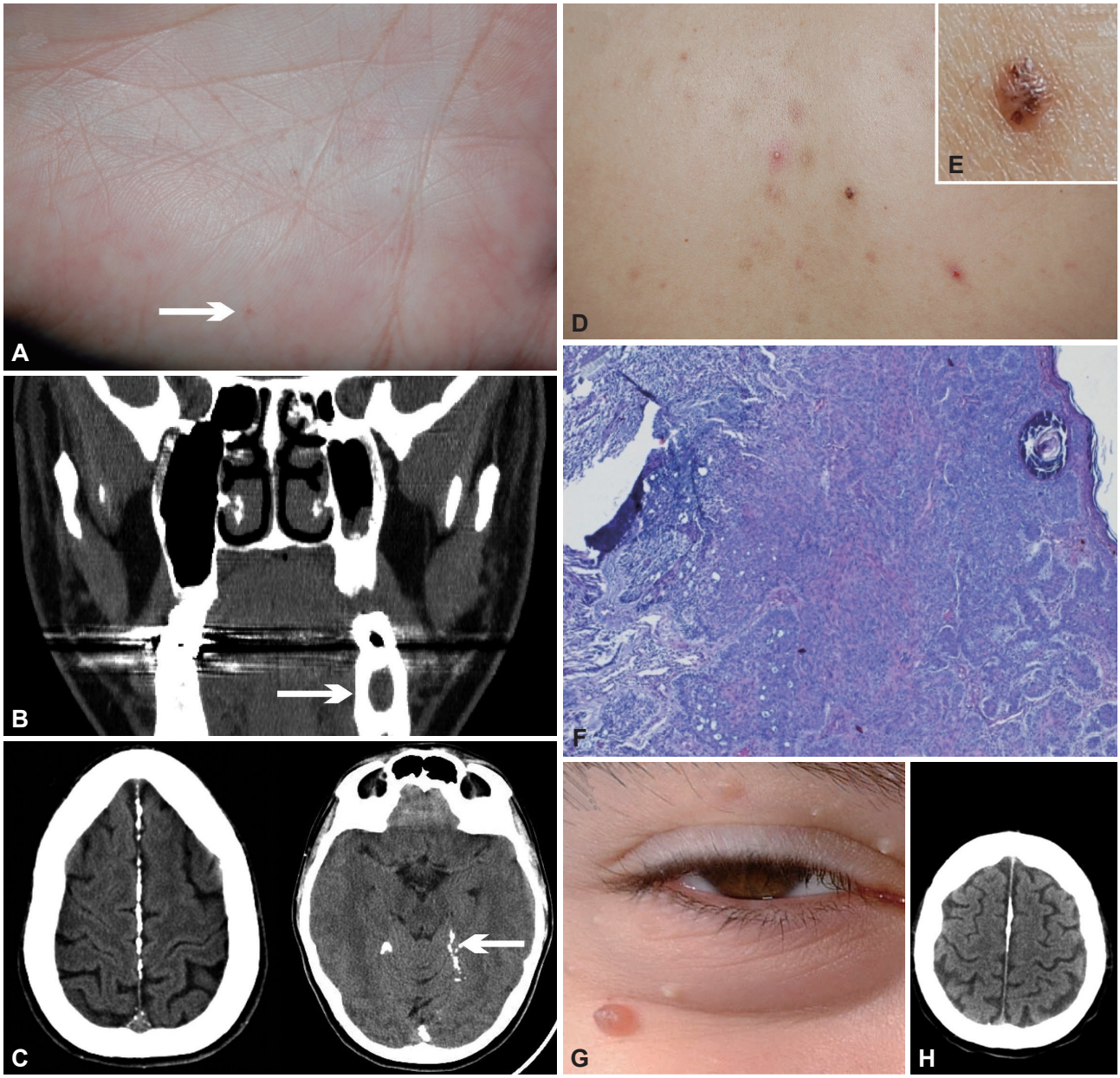

Fig. 1. Clinical and radiological findings. Images of the first patient. A: Palmar pits (arrow). B: Odontogenic cystic (arrow) lesion of the left mandible in maxillofacial CT. C: Falcine and tentorial calcifications (arrow) in brain CT. D: Melanocytic nevi and basal cell carcinoma of the trunk. E: Magnification of the basal cell carcinoma in panel D. Images of the second patient. F: Histopathology of a nodular basal cell carcinoma. G: Multiple hyperpigmented basal cell carcinomas around the right eye. H: Calcifications of the falx cerebri in brain CT. CT: computed tomography.

of laboratory, cardiac, and pelvic examinations were normal. EEG excluded epileptic abnormalities. X-rays showed three bifid ribs on the right side and bilateral mandible cystic lesions. Brain CT showed calcification of the falx cerebri (Fig. 1H). The patient did not cooperate with MRI, and refused genetic testing.

Both the phenotype and imaging results for these patients supported the clinical diagnosis of NBCCS. It was particularly interestingly that they had first sought neurologist attention, which highlights the importance of the awareness of this multifaceted neurocutaneous disorder and a multidisciplinary approach.[1] Although diagnostic criteria for NBCCS have been established,[3] the racial and genetic background may contribute to different levels of expressivity, even within the family.[4] It is worth remembering that headache in NBCCS–in the absence of disease-related causes (e.g., medulloblastoma, meningioma, and hydrocephalus)–might be coincidental. Similarly, intracranial calcifications, which are rare in young patients, can be due to trauma, infection, meningioma, or hypo-

parathyroidism (which were all excluded in the present cases).

In conclusion, neurological and neuroimaging findings associated with NBCCS might be crucially important for obtaining a better pathophysiological understanding, an early diagnosis, and appropriate management of the related malignancy. The take-home message is that neurologists should examine the skin and bones of patients with meningeal calcifications.

Conflicts of Interest

The authors have no financial conflicts of interest.

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