Cerebellar Bottom-of-Fissure Dysplasia—a Novel Cerebellar Gray Matter Neuroimaging Pattern

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Abstract We report on seven patients with a novel neuroimaging finding that involves exclusively the cerebellar gray matter at the bottom of several fissures of both hemispheres but spares the vermis. The abnormal fissures were predominantly located in the lower and lateral parts of the cerebellar hemispheres. The affected cerebellar cortex was hypointense on T1-weighted and hyperintense on T2-weighted and fluid attenuation inversion recovery sequences. In some patients, the involved cerebellar gray matter was mildly thickened and the affected fissures slightly widened. In three of seven patients, the neuroimaging findings were unchanged on follow-up studies up to 6 years. The seven patients had various indications for the brain magnetic resonance imaging studies, and none of them had cerebellar dysfunction. Based on the similarity of the neuroimaging pattern with the cerebral "bottom-of-sulcus dysplasia," we coined the term "cerebellar bottom-of-fissure dysplasia" to refer to this novel neuroimaging finding. The neuroimaging characteristic as well as the unchanged findings on follow-up favors a stable "developmental" (malformative) nature. The lack of cerebellar dysfunction in the affected patients suggests that cerebellar bottom-of-fissure dysplasia represents most likely an incidental finding that does not require specific diagnostic investigation but allows a reassuring attitude.

Keywords Cerebellum · Cerebellar gray matter · Cerebellar fissure · Focal cortical dysplasia · Bottom-of-sulcus dysplasia · Incidental finding

Abbreviations

BOFD	Bottom-of-fissure dysplasia
BOSD	Bottom-of-sulcus dysplasia
FLAIR	Fluid attenuation inversion recovery
MRI	Magnetic resonance imaging

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Introduction

In the past decades, significant progress in neuroimaging techniques, particularly magnetic resonance imaging (MRI), has allowed to improve the evaluation of the various anatomical structures of the posterior fossa [1]. This resulted in the report of specific neuroimaging pattern characterization of new congenital structural cerebellar anomalies including pontine tegmental cap dysplasia [2], macrocerebellum [3], and cerebellar dysplasia with cerebellar cysts due to *LAMA1* mutations [4, 5].

In this article, we report on seven patients with a cerebellar gray matter pattern that, to our knowledge, has not been previously reported. This cerebellar pattern has some similarities with the supratentorial "bottom-of-sulcus dysplasia" (BOSD), but it seems to have no clinical correlate.

Patients and Methods

This retrospective study did not require approval by the institutional review boards.

Patient Cohort

The patients included in this study were collected by the senior author (EB) through patients with cerebellar anomalies from the own institution, personal contacts, and referrals for "second opinion inquiries" from different institutions based on his interest in cerebellar disorders.

Review of the clinical histories and clinical-neurological follow-up examinations provided information about neurological features and eventual complaints.

Qualitative Neuroimaging Analysis

In a retrospective analysis, two pediatric neurologists with experience in neuroimaging of the pediatric cerebellum (AP and EB) qualitatively analyzed all available neuroimaging data sets for morphological abnormalities of the posterior fossa structures. All MRI data have been acquired for clinical indication, and the local departmental protocols have been used. All initial MRI studies were performed on a 1.5 T MR scanner. The follow-up studies of two patients were acquired using a 3.0 T MR scanner.

Results

Patient Characteristics and Clinical Findings

Seven patients (five males) were included in this study. Three patients come from Switzerland, three from Germany, and one from Kosovo. At the last follow-up, the age of the patients ranged between 7.5 and 25 years. Relevant clinical information including indication for brain MRI and follow-up are summarized in Table 1. No patient had cerebellar dysfunction at any time of the course.

Qualitative Neuroimaging Findings

The age at first MRI ranged between 7 months and 18 years. In all patients, the key imaging finding consists of T2 and fluid attenuation inversion recovery (FLAIR) hyperintense and T1-hypointense signal abnormality confined to the cortical gray matter of the cerebellar hemispheres (Figs. 1, 2, and 3). This finding was generally best seen on coronal images. In all patients, both cerebellar hemispheres were involved (in one patient, the findings were slightly asymmetric), while the cerebellar vermis was consistently spared. In both cerebellar hemispheres, several fissures were involved, predominantly in their lateral and lower portions. In all patients, no postcontrast enhancement was seen. If available, diffusion-weighted imaging (DWI) and susceptibility-weighted imaging (SWI) did not reveal abnormal findings. In some, but not all involved fissures, the cerebellar cortex at the bottom of the fissure was obviously thickened and had an abnormal structure. The interfolial

Table 1 Relevant clinical data and time at MRI of seven patients with cerebellar bottom-of-fissure dysplasias

Patient	Age at MRI	Indication for MRI	Age at MRI FU	Actual age	Actual status
1	7 mo	Recurrent apnea after liver transpl because of biliary atresia	None	10 y 6 mo	No symptoms
2	2 y 9 mo	Workup for CI and kidney transpl, cong nephrotic syndrome, Galloway-Mowat like, mutation-negative	6 y 9 mo	7 y 6 mo	Stable
3	10 y 9 mo	Headache, vomiting	11 y 3 mo	12 y 6 mo	No symptoms
4	11 y 6 mo	Staging for abdominal NH lymphoma	None	17 y	No symptoms
5	11 y 2 mo	Moderate ID	None	11 y 2 mo	Stable
6	13 y 6 mo	Seizures, mild ID	None	14 y 6 mo	Stable
7	18 y	Headache	24 y 8 mo	25 y	No symptoms

CI cochlea implant, *cong* congenital, *FU* follow-up, *ID* intellectual disability, *mo* month, *MRI* magnetic resonance imaging, *NH* non-Hodgkin, *transpl* transplantation, *y* year

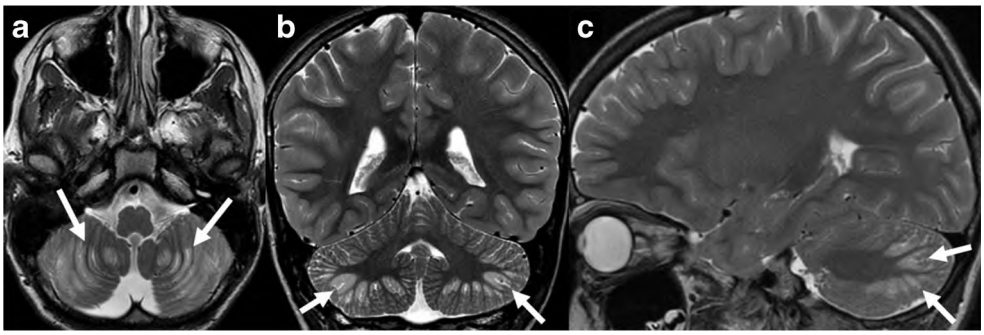

Fig. 1 **a** Axial, **b** coronal, and **c** sagittal T2-weighted images of patient 3 at the follow-up age of 11 years and 3 months show a bilateral, multifocal thickening and T2-hyperintense signal of the deep gray matter of the inferior cerebellar fissures (*arrows*), which are mildly widened

spaces were slightly enlarged in some affected fissures. The cerebellar white matter had normal signal, and its arborization and foliation was normal. No anomalies were identified in the brain stem and supratentorial brain in all patients.

Patients 2, 3, and 7 had a follow-up MRI after 6 months, 4 years, and 6 years 8 months, respectively. Follow-up MRI studies showed unchanged findings in the hemispheric cerebellar gray matter.

Discussion

We report on seven patients with a novel, peculiar neuroimaging pattern consisting of multiple T2- and FLAIR-hyperintense, T1-hypointense, partially thickened fissural gray matter involving the cerebellar hemispheres. No enhancement after intravenous injection of gadolinium-based contrast agent was noted, and DWI and SWI revealed normal findings. This neuroimaging finding is reminiscent of cerebral BOSD [6]. Therefore, we suggest the descriptive term "cerebellar bottom-of-fissure dysplasia" (BOFD) to delineate the neuroimaging findings in our patients, taking anatomic terminology into account that supratentorial gyri are separated by *sulci*, while cerebellar folia are separated by *fissures*.

Cerebellar BOFD however differs in some aspects from cerebral BOSD. Cerebellar BOFDs are usually multiple, do not have a "tail" into the white matter, and are preferentially located within the inferior and lateral aspects of the cerebellar hemispheres. In addition, cerebellar BOFDs are not epileptogenic.

Cerebral BOSDs are seen in patients with focal seizures that are stereotyped, predominantly nocturnal, and mostly drug-resistant [7, 8]. The majority of the patients becomes seizure-free without antiepileptic medication and has an excellent outcome after lesionectomy [7]. Small cerebral BOSDs are often initially overlooked on conventional MRI, and a high index of suspicion is required to make the diagnosis [9]. In addition, high-resolution images, high magnetic field strength, application of morphometric MRI analysis, correlation with neurophysiological findings, and co-registration with fluorodeoxyglucose positron emission tomography may be helpful for the identification of small focal cortical dysplasias located at the bottom of a deep sulcus [10, 11]. The dysplastic nature of BOSD has been confirmed by neuropathology. BOSD as well as focal transmantle dysplasia have histological features of focal cortical dysplasia type IIa/IIb and are likely different names for the same entity [12–14]. BOSD is thus considered as a subtle but distinct malformation of cortical development [15]. Cortical thickening at the bottom of a

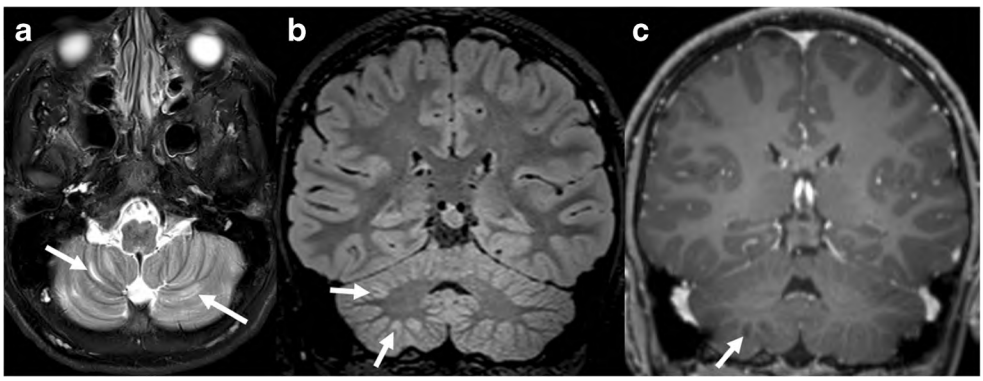

Fig. 2 **a** Axial T2-weighted, **b** coronal FLAIR, and **c** coronal postcontrast T1-weighted images of patient 6 at the age of 13 years and 6 months show a bilateral, asymmetric (involving mostly the right cerebellar hemisphere) multifocal thickening and T1-hypointense and T2-/FLAIR-hyperintense signal of the deep gray matter of the lateral and inferior cerebellar fissures (*arrows*). No postcontrast enhancement is noted

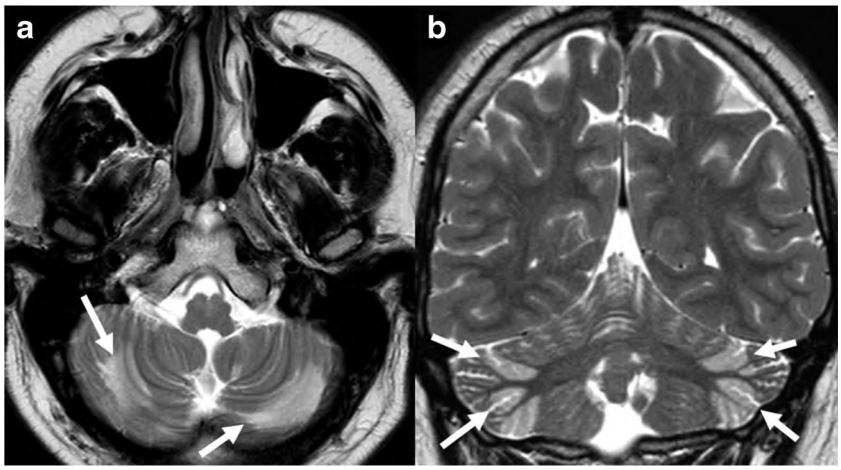

Fig. 3 **a** Axial and **b** coronal T2-weighted follow-up images of patient 7 at the follow-up age of 24 years and 8 months show a bilateral, multifocal thickening and T2-hyperintense signal of the deep gray matter of the lateral cerebellar fissures (*arrows*), which are mildly widened

sulcus, a funnel-shaped extension of the lesion toward the ventricular surface, commonly with abnormal T2-/FLAIR-hyperintense signal intensity, and an abnormal gyral pattern related to the bottom-of-sulcus dysplasia, sometimes with a puckered appearance, are the characteristic neuroimaging findings [6, 16]. BOSDs are single lesions and are most commonly located within the frontal, parietal, and insular cortex [7]. BOSDs most likely result from a combination of abnormal migration and abnormal apoptosis, but the pathomechanisms responsible for the selective vulnerability of the sulcal buttom are still unknown.

Involvement of the cerebellar gray matter is a key finding of cerebellar dysplasia as reported in Chudley-McCullough syndrome [17, 18], *GPR56*-associated cerebellar dysplasia [19], and *LAMA1*-associated cerebellar dysplasia with cerebellar cysts [4, 5]. Cerebellar dysplasia is defined by abnormal cerebellar foliation and fissuration, white matter arborization, and gray-white matter junction [20]. The neuroimaging pattern of cerebellar BOFD differs substantially from cerebellar dysplasia. In cerebellar dysplasia, the involved cerebellar cortex is usually not thickened and has a normal signal intensity on T1-, T2-weighted, and FLAIR sequences.

Follow-up MRI studies were available for three patients at a time interval of 6 months, 4 years, and 6 years 8 months, respectively, and showed unchanged findings. The similarity between cerebellar BOFD and cerebral BOSD and the unchanged imaging findings on a rather long follow-up favor a malformative nature of cerebellar BOFD. The pathogenesis of cerebellar BOFD is unknown. We were not able to find a mouse model that may elucidate it. We hypothesize that cerebellar BOFD may result from an abnormality affecting the complex folding mechanism of the cerebellar cortex. It is unknown whether this abnormality might be caused by a genetic predisposition and/or result from a prenatally acquired lesion.

Involvement of the cerebellar gray matter that is remotely reminiscent of cerebellar BOFD has been reported in selected metabolic and autoimmune disorders. Band-like T2-hyperintense signal abnormalities of the cerebellar gray matter has been reported in autoimmune polyglandular syndrome type 1 [21]. The signal abnormalities however involved not only the gray but also the white matter. In addition, the neuroimaging findings diffusely involved both cerebellar hemispheres and were associated with atrophy of the cerebellar vermis. Finally, the clinical presentation was completely different compared to our patients. Multifocal T2-hyperintense signal changes within the cerebellar cortex have been described in biotin-responsive basal ganglia disease due to *SLC19A3* mutations [22]. In biotin-responsive basal ganglia disease, however, the gray matter cerebellar involvement does not involve only the "bottom of sulcus" and the entire spectrum of neuroimaging findings is highly different compared to cerebellar BOFD. Finally, T2-hyperintense signal of the cerebellar gray matter has been reported in complex I deficiency due to *NUBPL* mutations and severe hypomagnesemia [23, 24]. In these patients, however, the entire cerebellar gray matter was diffusely involved. In patient 7 (Fig. 3), the gray matter T2-hyperintense signal is located in the watershed zone between the three cerebellar artery territories. Hypoperfusion in the cerebellar watershed areas, however, is not a likely pathomechanism for BOFD because (1) the white matter in the cerebellar watershed areas has a normal T2 signal, while injury to both the gray and white matter is expected in wathershed hypoperfusion; (2) there is variability of the anatomical distribution of the gray matter T2-hyperintense signal between our patients; and (3) three patients had a follow-up MRI study that showed unchanged imaging findings (a dynamic alteration is expected for a wathershed hypoperfusion). Diffuse T2-hyperintense signal of the cerebellar gray matter may be seen in cerebellitis. In cerebellitis, however, there is involvement not only of the cerebellar gray matter but also of the white matter. In addition, follow-up MRI studies in three patients revealed unchanged findings. Therefore, we conclude that cerebellitis in not a pathomechanism for BOFD. The clinical and neuroimaging findings as well as the stable clinical

and imaging follow-up in cerebellar BOFD do not suggest an underlying postnatal metabolic (including infantile neuroaxonal dystrophy, congenital disorder of glycosylation, and Marinesco-Sjoegren syndrome, that are characterized by cerebellar atrophy with global T2-hyperintense signal of the cerebellar gray matter not confined to the bottom of sulci) or neoplastic origin.

In our small cohort of patients, cerebellar BOFD was never associated with cerebellar dysfunction, neither at presentation nor at follow-up. The indication for the brain MRI studies was quite variable. Follow-up neuroimaging studies did not show any suspicion of progression. We suggest that cerebellar BOFD may be considered as an incidental and stable finding. Therefore, the recognition of cerebellar BOFD is of important practical significance. No specific (e.g., metabolic or immunologic) diagnostic workup is needed. A long-term neuroimaging follow-up might be considered. A reassuring attitude toward the parents and the child is justified.

We are aware of some limitations of our study, including the small number of patients and the diversity of the imaging acquisition protocols. The cerebellar BOFDs however were unequivocally seen in all studies. Conversely, this report has the strength of a long-term clinical follow-up in most patients and the availability of three follow-up neuroimaging studies.

In conclusion, cerebellar BOFD is a novel cerebellar gray matter neuroimaging finding that most likely represents an incidental stable finding of malformative origin and does not require specific diagnostic workup. Additional future studies with larger numbers of patients and high-resolution brain MRI studies ideally on a 7.0 T MR scanner may potentially help to further characterize cerebellar BOFD and understand its pathomechanism.

Compliance with Ethical Standards

Conflicts of Interest All co-authors do not report conflicts of interest.

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