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Case Report

Is unilateral cerebellum sufficient? Insights from new cases of cerebellar agenesis and literature review

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Abstract

The clinical manifestations of adult-acquired cerebellar diseases often surpass those of congenital cerebellar diseases, suggesting the significant role of the cerebellum in the developing brain. Moreover, emerging evidence from structural and functional magnetic resonance imaging indicates that the cerebellum is implicated not only in motor functions but also in non-motor domains such as cognition, emotion, and language. However, delineating the specific extent of cerebellar development required to prevent deficits in either motor or non-motor functions remains challenging. In this study, we present two new cases of unilateral cerebellar agenesis. One individual leads a nearly normal life, while the other exhibits mild cognitive impairment, mild depression, and severe autism, but maintains normal motor function. Van der Heijden *et al*. (2023) revealed that the brain can compensate for some, but not all, perturbations to the developing cerebellum, including motor deficits and impairments in social behaviors. Therefore, we hypothesize that comparing structural images from our patients and reviewing pertinent literature may elucidate the reasons for the varied clinical manifestations observed in patients with cerebellar agenesis.

Case reports

Case 1

A 22-year-old right-handed male patient underwent a magnetic resonance imaging (MRI) scan (GE 3.0 T SIGNA Pioneer) following a traffic accident. The scan revealed a complete absence of the left cerebellum, as well as the absence of the inferior cerebellar vermis and enlargement of the ipsilateral pons and cerebral peduncle (Fig. 1). Furthermore, diffusion tensor imaging (DTI) demonstrated a complete lack of the efferent and afferent pathways of the left cerebellum (Fig. 1). No abnormalities were observed in the supratentorial brain morphology on routine MRI.

According to his mother, he began to walk at the age of 1 but was unstable and prone to falls, especially during the first 2 years. However, his walking gradually improved after the age of 6. In comparison to his peers, he exhibits normal reading, writing, and calculating abilities, but experiences difficulties with memory and presents with strabismus. The patient was able to cooperate during the neurological examination, and his comprehension and verbal expression were unaffected. Neuropsychological testing, including assessments of cognitive function, depression, and autism severity, was conducted on the patient using the Montreal Cognitive Assessment, Hamilton Depression Rating Scale, and Childhood Autism Rating Scale, respectively. The test results indicated moderate cognitive impairment (with a score of 17 on the Montreal Cognitive Assessment), mild depression (score of 12 on the Hamilton Depression Rating Scale), and severe autism symptoms (score of 38 on the Childhood Autism Rating Scale). There is no reported history of other illnesses in the patient, and there is no reported history of neurological disorders in his family. It is noteworthy that his mother experienced a severe intrauterine infection during her pregnancy with him.

Case 2

A 57-year-old right-handed female presented to the hospital with complaints of intermittent dizziness, which she had experienced over the preceding 15 years. Laboratory tests revealed no significant abnormalities. An MRI scan (GE 1.5 T Signa HDe) showed a near-total absence of the left cerebellum, with remnants representing the anterior quadrangular lobule (Fig. 2). Additionally, there was isolated normal inferior vermis lobulation with small volume, contralateral enlargement of the cerebellar hemisphere, and ipsilateral enlargement of the pons and cerebral peduncle (Fig. 2). DTI demonstrated afferent and efferent fibers connecting the pons and remnants of the cerebellum (Fig. 2E, F). Routine MRI showed no abnormalities in supratentorial brain morphology. She is employed as a manual laborer and demonstrates proficient performance of associated daily tasks, showing no apparent functional deficits. Neurological examination showed no abnormalities. Despite recommendations for additional comprehensive neurological assessments, she declined further evaluation.

The two patients included in this study did not present the expected clinical symptoms, suggesting potential functional compensation in the absence of unilateral cerebellar hemisphere.

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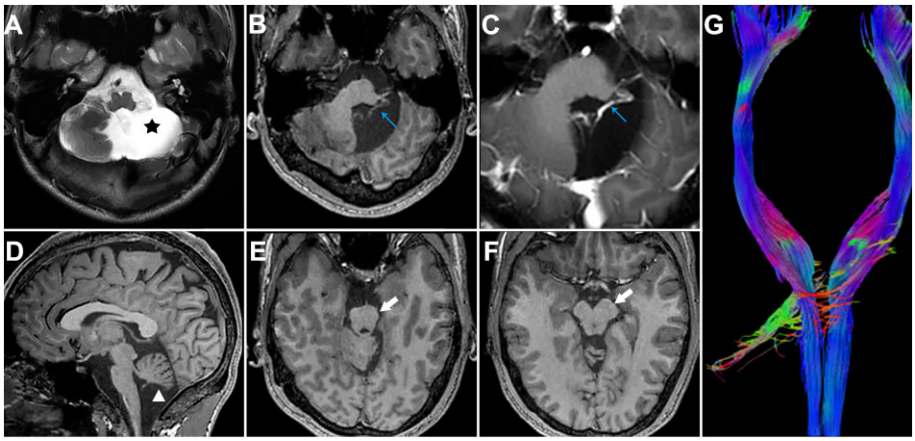

Figure 1: (**A**) An axial T2-weighted image shows hyperintensity in posterior fossa and no cerebellar tissue (black star). Axial 3D-T1-weighted image (**B**) and axial T1-enhanced image (**C**) reveal that there is no recognizable cerebellar structure, the left posterior fossa is filled by CSF and a cerebrovascular in the left cerebellar hemisphere (blue arrow). (**D**) A sagittal 3D-T1-weighted image shows the absence of the inferior cerebellar vermis (white triangle). Axial 3D-T1-weighted images (**E**, **F**) show ipsilateral enlargement of the pons and cerebral peduncle (thick, white arrow). (**G**) DTI shows complete lack of the efferent and afferent limbs of the left cerebellum.

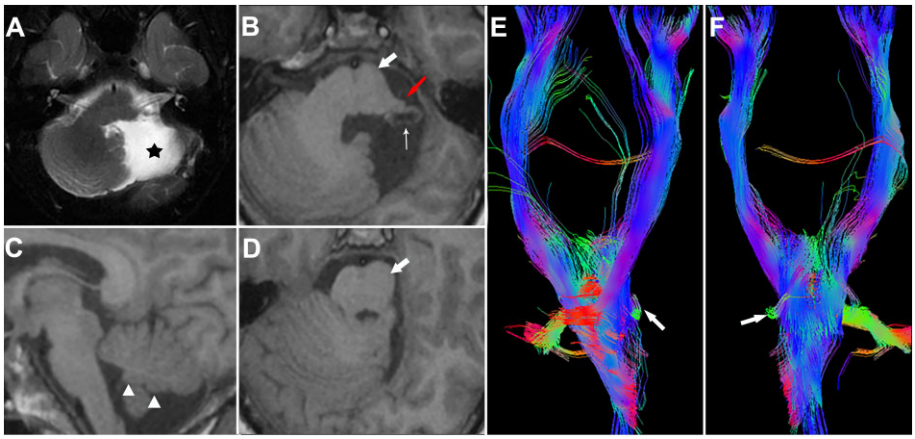

Figure 2: (**A**) An axial T2-weighted image shows the absence of the left cerebellum with CSF filled the posterior fossa (black star). (**B**) An axial 3D-T1-weighted image shows the remaining cerebrovascular in the left cerebellar hemisphere (thin white arrow), similar to Fig. 1(B, C) and shows the remaining cerebellar remnant (red arrow). (**C**) A sagittal 3D-T1-weighted image shows the hypoplasia of the inferior cerebellar vermis (white triangle). Axial 3D-T1-weighted images (**B**, **D**) show ipsilateral enlargement of the pons and cerebral peduncle (thick, white arrow). (**E**, **F**) DTI shows fibrous connections between the pons and cerebellar remnants (white arrow).

Motivated by this observation, our study aimed to comprehensively investigate the mechanisms of functional compensation corresponding to structural changes. Initially, we assessed the gray matter volume (GMV) of supratentorial brain structure using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/vision v.5.3.0). The detailed process of GMV reconstruction using FreeSurfer v.5.3 has been described and validated elsewhere (Bigl *et al.*, 1982; Boddaert *et al.*, 2003). In brief, the T1-weighted imaging data were preprocessed using FreeSurfer software, and the bilateral brain hemispheres were segmented according to the Desikan–Killiany atlas to calculate the average GMV of each brain region. Then, we compared the GMV of the two patients with age-matched controls from a normal brain model. This model was constructed based on a sample of >600 healthy participants aged 12 to 65 years old from West China Hospital of Sichuan University and validated in other hospitals. It was tailored for age groups spanning 10 years, with the 95% confidence intervals (CI) of GMV serving as the lower and upper thresholds for each group. Subsequently, we utilized BrainNet Viewer to visualize the GMV ratio between abnormal brain regions and their corresponding normal counterparts. The GMV in Case 1 was compared with the normal range of GMV determined by age-matched controls in this model. The GMV over the normal upper threshold indicated an increase in GMV (represented as a positive ratio), while the GMV below the normal lower threshold indicated a reduction in GMV (represented as a negative ratio). The GMV values within the normal range were represented by "0." So was Case 2. As illustrated in Fig. 3 (Case 1), Fig. 4 (Case 2), as well as summarized in Table 1, both patients exhibited increased GMV in multiple brain regions, with significant alterations observed in the frontal and temporal lobes, as well as the cingulate gyrus. Additionally, changes were noted in the accumbens, pallidum, and thalamus. These findings highlight both commonalities and differences, with more extensive and pronounced alterations observed in Case 2. Furthermore, our analysis revealed a slight decrease in GMV in the five regions, as detailed in Table 1.

Discussion

Cerebellar agenesis (CA) was initially reported by Combettes (1831) and has since been sporadically documented, manifesting

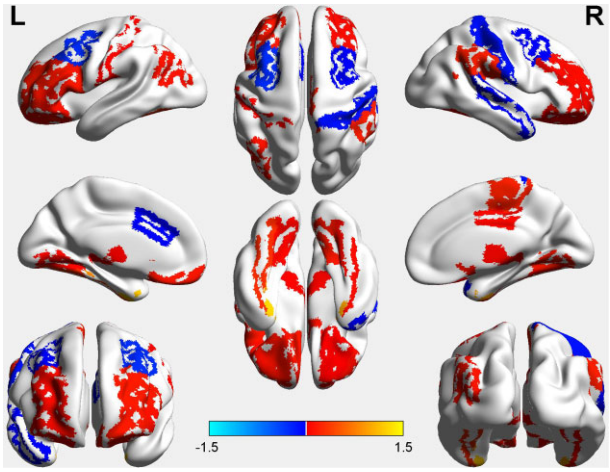

Figure 3: Brain regions showing significantly altered GMV in the patient in Case 1. Warm colours indicate increased GMV, and cool colours represent decreased GMV when compared with an age-matched normal brain model.

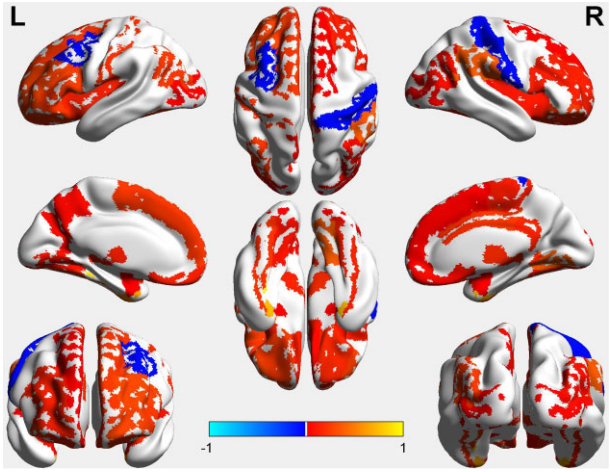

Figure 4: Brain regions showing significantly altered GMV in the patient in Case 2. Warm colours indicate increased GMV, and cool colours represent decreased GMV when compared with an age-matched normal brain model.

a spectrum of clinical features ranging from severe neurological deficits to cases with normal or nearly normal development. Vascular events during pregnancy, genetic factors, and intrauterine infection are widely recognized as the most common etiologies. The possibility of a vascular event in Case 1 was ruled out based on the presence of the residual posterior inferior cerebellar artery in the left cerebellar hemisphere (Fig. 1B, C). Moreover, intrauterine infection was hypothesized to be the primary etiology, given the significant intrauterine infections during pregnancy. Additionally, in Case 2, the likelihood of vascular or infectious events was excluded, considering the uneventful pregnancy and the presence of a residual artery (Fig. 2B), consistent with the findings in Case 1.

The highlight of this study is the comparison of GMV between the two patients and an age-matched normal brain model, respectively, which has not been reported before. We observed varying degrees of increased GMV in multiple brain regions, particularly in the frontal, temporal, cingulate gyrus, and some deep brain nuclei. According to van der Heijden *et al.* (2023), the brain can compensate for some, but not all, perturbations to the developing cerebellum, including motor deficits and impairments in social behaviors. We speculate that the relatively mild clinical symptoms observed in our patients are largely attributed to functional compensation resulting from increased GMV.

Both patients demonstrated a notable increase in GMV within the frontal lobe, particularly in Case 2. In addition, the patient in Case 1 exhibited no significant increase in the superior frontal gyrus, a region implicated in emotional processing (Hong *et al.*, 2024) and previously reported to show abnormal function among individuals diagnosed with major depressive disorder (Liu *et al.*, 2024). Therefore, we hypothesize that the presence of depressive symptoms in Case 1 may be attributed, at least in part, to the lack of compensatory changes in the superior frontal gyrus.

Another region that exhibited significant differences between the two patients was the cingulate gyrus. A recent study used electrical cortical stimulation found that the cingulate gyrus is involved in a variety of complex functions, including sensory, affective, and motor functions (Xue *et al.*, 2023). The symptomatic patient exhibited no significant volume change in the cingulate gyrus, whereas the asymptomatic patient demonstrated a significant volume increase in the right cingulate gyrus. Hence, the potential compensatory effects of the cingulate gyrus cannot be disregarded.

The increased GMV in the temporal lobe was mainly located in the parahippocampal, entorhinal, and fusiform areas, which are part of the limbic circuit and associated with neuropsychiatric symptoms, cognitive abilities, and communication skills (Kolc *et al.*, 2019). Within the parietal lobe, regions showing increased GMV were mainly located in the inferior parietal, postcentral, and supramarginal areas, which play important roles in the arousal system (Jiang *et al.*, 2022), somatosensory processing and integration, coordination of upper limb movements (Kenzie *et al.*, 2024), and tactile categorization and decision-making (Lee *et al.*, 2023). GMV changes in these brain regions exhibited similarity between the two patients.

In addition to the cerebral cortex, the pallidum and thalamus of asymptomatic patient exhibited a marked increase in GMV. The outputs from the pallidum re-enter corticolimbic loops via direct projections to prefrontal cortex and dense projections to the mediodorsal nucleus of the thalamus, which then relays to prefrontal cortex (Bigl *et al.*, 1982; Pirot *et al.*, 1994; Churchill *et al.*, 1996; Zahm, 2000). Such limbic-related anatomical connectivity lays the foundation for mediating reward and facilitating the translation of movement at the brain level. Unlike the pallidum and thalamus, the accumbens exhibited similar GMV changes in both patients.

Furthermore, unilateral CA patients may not consistently present with ipsilateral cerebellar remnants, contralateral cerebellar hemisphere enlargement, or ipsilateral enlargement of the pons and cerebral peduncle. However, the patient in Case 2 exhibited all three conditions, consistent with those reported in asymptomatic CA patients by Erdogan *et al.* (2002) and Kilickesmez *et al.* (2004). Additionally, the absence or hypoplasia of the vermis warrants attention. Tavano *et al.* (2007) observed that malformations involving the cerebellar vermis often lead to affective and social disorder, frequently associated with autism, presenting similar MRI changes and clinical symptoms to those of our symptomatic patient. Moreover, literature reports indicate that ~50% of children with Dandy–Walker malformations have normal cognitive development, which is linked to normal vermian lobulation (Boddaert *et al.*, 2003). Although the involvement of the cerebellar vermis often, but not consistently, correlates with poorer cognitive

Table 1: Altered cerebrum GMV in each patient compared to an age-matched normal model brain.

Brain region	Case 1		Case 2	
	Left	Right	Left	Right
Increased regions				
frontal lobe				
lateral orbitofrontal	0.125	0.025	0.233	0.172
medial orbitofrontal	0.153	0	0.139	0.054
parsopercularis	0.155	0	0.258	0.127
parsorbitalis	0.096	0.112	0.273	0.264
parstriangularis	0.114	0	0.224	0
rostral middle frontal	0.166	0.087	0.279	0.137
superior frontal	0	0	0.229	0.022
temporal lobe				
entorhinal	1.178	1.005	0.676	0.769
fusiform	0.286	0.088	0.208	0.137
parahippocampal	0.809	0	0.857	0
parietal lobe				
inferior parietal	0.140	0	0.230	0.073
postcentral	0.051	−0.115	0.201	−0.05
supramarginal	0	0.203	0	0.367
occipital lobe				
lateral occipital	0	0	0.016	0.032
lingual	0.068	0.170	0.093	0.370
cingulate gyrus				
caudal anterior cingulate	−0.030	0	0	0.200
isthmus cingulate	0	0.007	0	0.153
posterior cingulate	0	0.071	0.009	0.227
basal ganglia				
pallidum	0	0	0.126	0.106
accumbens	0	0.130	0	0.105
thalamus				
thalamusproper	0.039	0.063	0.141	0.184
Decreased regions				
caudal anterior cingulate	−0.030	0	0	
caudal middle frontal	−0.276	−0.016	−0.050	0.200
postcentral	0.051	−0.115	0.201	0
precentral	0	−0.010	0	−0.050
superiortemporal	0	−0.028	0	0

outcomes, an intact vermis typically corresponds to normal clinical manifestations.

Some limitations of this artical should be considered. First, we refrained from providing a summary of previously reported cases of CA due to the potential for duplicate reporting. For example, Poretti *et al.* (2010) reported seven patients with absent cerebellar hemisphere from seven different institutions; however, it remains unclear whether these cases have been reported on elsewhere. Additionally, CA is heterogeneous condition that may manifest as an isolated anatomical anomaly or as part of a more complex cerebral malformation. Moreover, the nomenclature used in previous studies to describe the absence of cerebellar hemispheres is inconsistent. Some authors refer to this condition as CA, whereas others use the term "cerebellar hypoplasia" or describe it directly as the absence of cerebellar hemispheres. Therefore, to avoid duplication or incomplete data, we have opted not to provide a detailed summary of CA cases. Instead, our focus is on exploring potential compensatory mechanisms underlying the diverse clinical manifestations of this condition.

In conclusion, it is plausible to assert that unilateral CA, in the absence of other comorbidities, is compatible with an honorable existence, even allowing for a normal or nearly normal life. However, the type and extent of cerebral reorganization processes in CA patients are challenging to predict and could contribute to the variability in clinical phenotypes.

Author contributions

Dingmei Deng (Writing – original draft), Bo Tao (Methodology), Yizhi Yuan (Methodology), Yongsheng Ao (Formal analysis), and Lihua Qiu (Writing – review & editing)

Conflict of interest

None declared.

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