

LETTER TO THE EDITOR

A new case of complete primary cerebellar agenesis: clinical and imaging findings in a living patient

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Sir,

We read with great interest the articles previously published in *Brain* by Glickstein (1994) and Boyd (2010) describing the clinical evidence and review of cerebellar agenesis. Here we report a new case of a living patient whom we believe to be another patient with cerebellar agenesis. Cerebellar agenesis is an extremely rare condition implying complete absence of the cerebellum. The pathogenesis and molecular basis of this disease remain unknown. There are very few reported cases of complete cerebellar agenesis, making it challenging and controversial to understand the degree of cerebellum development necessary to avoid deficits in motor and non-motor functions. Further, a detailed description of neurological findings in a living adult with cerebellar agenesis is almost non-existent; most cases are reported based on autopsy reports. The patient presents with mild mental impairment and medium motor deficits. CT and MRI scans revealed no remnants of any cerebellar tissues, verifying complete absence of the cerebellum. A comprehensive literature review reveals novel implications for differential diagnosis. We conclude that primary cerebellar agenesis is actually the same diagnosis as Chiari malformation IV.

A 24-year-old female patient was admitted to hospital complaining of dizziness and the inability to walk steadily for more than 20 years, and nausea and vomiting for ~1 month. She is married with a daughter, and her pregnancy and delivery were described as uneventful. Her parents had no history of neurological disorders. Her four sisters and one brother are described as neurologically normal. According to her mother, she was 4 years old before she could stand unassisted, and did not begin to walk unassisted until the age of 7, with a persistently unsteady gait. She never ran or jumped. Her speech was not intelligible until 6 years of age and she did not enter school. A neurological examination revealed she could cooperate and fully orientate. A verbal analysis test revealed her word comprehension and expression remained intact and she had no sign of aphasia, but mild to moderate signs of cerebellar dysarthria. The patient has mild voice tremor with slurred pronunciation and her voice quality is slightly harsh. Cerebellar ataxia including Romberg's sign, and there is evidence of heel-knee-tibia impairment. The patient experienced mild to moderate dysmetria in reaching the nose when administered the finger-to-nose test. Pronation-supination alternating movements were slightly irregular

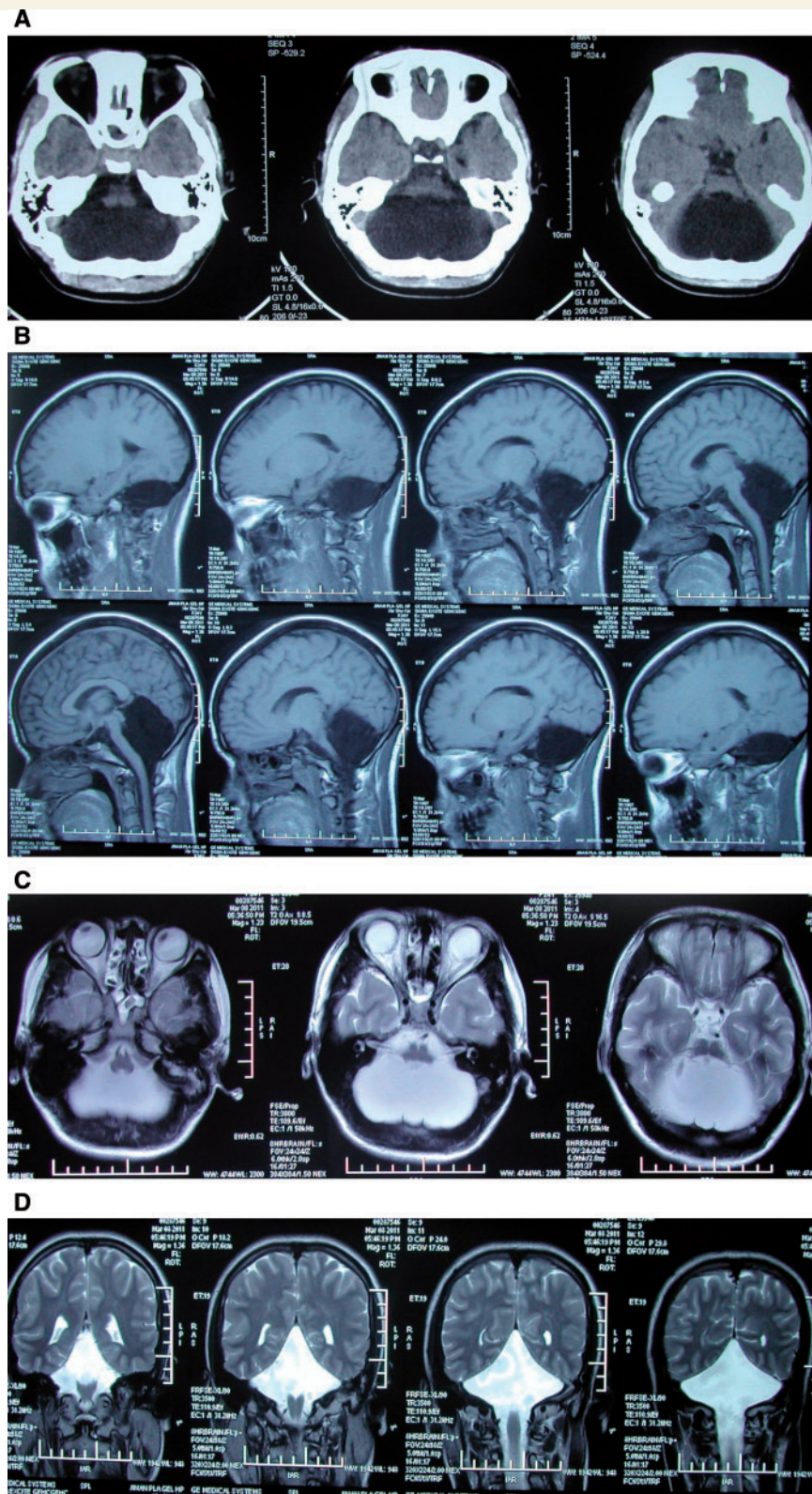


Figure 1 (A) Consecutive axial CT images show a large low density in posterior fossa and no cerebellar tissue. (B) Consecutive T₁-weighted sagittal MRI reveals that there is no recognizable cerebellar structure and the posterior fossa is filled by CSF with no mass effect. Mesencephalon, pons, and medulla oblongata were present. The mesencephalon had a normal aspect, and the Sylvian aqueduct seemed patent. The pons, medulla oblongata was attenuate and no hindbrain herniation. Tentorial attachment and straight sinus are normal. Supratentorially, the pattern of cortical gyri was normal as was the corpus callosum, aqueduct. The shape and relative proportions of the third ventricle and lateral ventricle were preserved and no hydrocephalus. (C and D) Consecutive axial and coronal T₂-weighted MRI demonstrates no structures in posterior fossa, which means the absence of a cerebellum.



Figure 2 Magnetic resonance angiography demonstrates that the posterior inferior cerebellar artery, anterior inferior cerebellar artery and superior cerebellar artery are absent bilaterally, meaning the posterior fossa is avascular.

and slowed. While she is able to walk unsteadily without support, her gait is moderately unsteady. The patient has evidence of tandem gait and moderately reduced gait speed. There is no focal paresis but the muscle tone is mildly increased. Evaluation of the sensory system showed no abnormalities, no deformities of the fingers and toes were observed, and her complete blood count and urinalysis were normal.

The patient has low posterior fossa density and no cerebellar tissue following CT analysis (Fig. 1A). No recognizable cerebellar structures are present, and the posterior fossa was filled by CSF when analysed by cranial MRI (Fig. 1B–D). The mesencephalon, pons, and medulla oblongata were present. The mesencephalon had a normal aspect, and the aqueduct of Sylvian seemed patent. The pons was hypoplastic, due to volume reduction of the pontine prominence. The medulla oblongata was attenuated and no hindbrain herniation was detected. A membranous structure present at both lateral sides of the pons formed a large cyst, which occupied most of the normal-sized posterior fossa. Tentorial attachment and straight sinus were normal, as was the pattern of cortical gyri, the corpus callosum, the cerebral peduncle and aqueduct. The shape and relative proportions of the third ventricle and lateral ventricle were preserved with no hydrocephalus. In addition to CT and MRI findings, magnetic resonance angiography also demonstrated vascular characteristics of this patient consistent with complete cerebellar agenesis. The posterior inferior cerebellar artery, anterior inferior cerebellar artery and superior cerebellar artery were absent bilaterally, indicating an avascular posterior fossa. The basal artery, posterior cerebral artery and their branches were normal (Fig. 2). Complete lack of the efferent and afferent limbs of the cerebellum was diagnosed by diffusion tensor

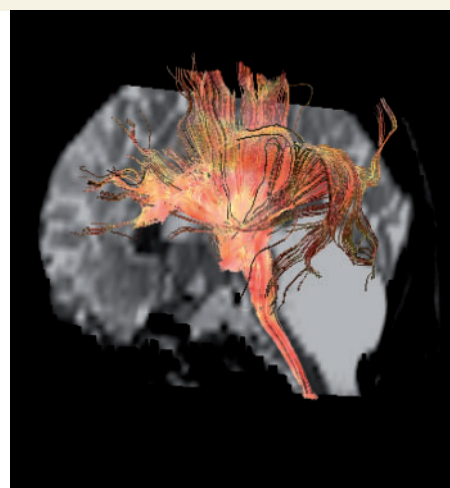


Figure 3 Diffusion tensor imaging shows the ascending and descending fibres are integrated but no ponto-cerebellar fibres enter the cerebellum, which means complete lack of the efferent and afferent limbs of the cerebellum.

imaging analysis (Fig. 3). With these findings, the patient was diagnosed with complete primary cerebellar agenesis.

A lumbar puncture and CSF test revealed the patient's CSF pressure was 210 mm H₂O and her CSF chemistry was normal. The patient experienced significant relief of symptoms with dehydration therapy and non-surgical management. The patient maintained consistent symptom management and relief of symptoms at her 4-year follow-up.

Research on cerebellar function is evolving rapidly, prompting many additional questions regarding the role and necessity of the cerebellum (Manto, 2008). Is normal cerebellar function possible in the case of total or subtotal cerebellum damage? If one part of the cerebellum is damaged, can another part take over? The opportunity to study cases of complete primary cerebellum agenesis, especially in a living adult, will provide some answers to these questions. Primary cerebellum agenesis, a rare condition marked by absence of the cerebellum, was first described by Combettes (1831). Only eight living cases have been reported prior to this study (Yoshida and Nakamura, 1982; Sener and Jinkins, 1993; Sener, 1995; Van Hoof and Wilmink, 1996; Velioglu *et al.*, 1998; Deniz *et al.*, 2002; Timmann *et al.*, 2003). The clinical presentation of primary cerebellum agenesis varies from degrees of cerebellar dysfunction and developmental delay at an early age. Oftentimes, primary cerebellum agenesis is diagnosed as Chiari malformation type IV, a condition defined by an incomplete or underdeveloped cerebellum (Sener and Jinkins, 1993). Primary cerebellum agenesis is associated with severe developmental anomalies resulting in a high mortality rate; few reports on the subject have been published. The 24-year-old female we report, with mild mental retardation and cerebellar ataxia, was diagnosed with complete primary cerebellar agenesis based on CT and MRI scans.

Table 1 Summary of all published living cases with primary cerebellar agenesis

Author	Age	Gender	Motor	Aphasia	Ataxia	Mental and development	Notes
Yoshida and Nakamura, 1982	4 mths	Female	Retardation	–	–	Retardation	Consanguinity, total absence
Sener and Jenkins, 1993	58 years	Female	Normal	N	N	Normal	Subtotal absence
Sener, 1995	6 years	–	Retardation	Y	Y	Normal	Moderate cerebellar symptom
Sener, 1995	–	–	Retardation	Y	Y	Normal	Moderate cerebellar symptom
Van Hoof and Wilmink, 1996	46 years	Male	Spasticity	Dysarthria	Y	Mild Retardation	Total absence, confirmed by surgery
Velioglu <i>et al.</i> , 1998	22 years	Male	Retardation	Dysarthria	Y	Retardation	Subtotal absence
Deniz <i>et al.</i> , 2002	7 years	Female	Retardation	Dysarthria	Y	Retardation	Total absence
Timmann <i>et al.</i> , 2003	59 years	Female	Retardation	Dysarthria	Y	Retardation	Total absence

This patient presents with complete cerebellum agenesis with a complete lack of the efferent and afferent limbs of the cerebellum, a relatively normal-sized posterior fossa, a normal brain and spine without syringomyelia or encephalocele. This case is the ninth reported case of this diagnosis.

The cerebellum is a complex region of the human brain responsible for primarily motor, but also non-motor functions. Following birth, the cerebellum continues to develop for many months, making it vulnerable to developmental disorders (Alkan, 2009). Details of cerebellar development may provide clues as to whether cerebellar remnants contribute to normal function even after agenesis. The cerebellum arises from the caudal-most segment of the midbrain and the rostral-most segment of the hindbrain, and the medulla from the caudal segment of the hindbrain. The mesencephalon differentiates from the midbrain and the pons from the rostral segment of the hindbrain. Cerebellar agenesis accompanied by reduction in brainstem size is most likely a consequence of severe loss of cerebellar radiations (Barkovich *et al.*, 2007; Alkan, 2009). The vermis and the flocculonodular lobe are the oldest portions during the development of the cerebellum, therefore, commonly observed cerebellar remnants are usually flocculus, anterior quadrangular lobe or vermis, possibly providing some remaining cerebellar function in patients with subtotal cerebellar agenesis (Sener and Jenkins, 1993).

Most individuals with complete primary cerebellar agenesis are infants or children with severe mental impairment, epilepsy, hydrocephaly and other gross lesions of the CNS. In even more rare instances, adults have been discovered with apparent complete primary cerebellar agenesis, but detailed neurological descriptions of these findings in a living adult are lacking. Complete primary cerebellar agenesis diagnosis usually occurs by autopsy. Cerebellar deficiency arises very early in embryogenesis and the developmental plasticity and functional compensation with the remaining brain tissue is remarkable. In our case, complete absence of the cerebellum results in only mild to moderate motor deficiency, dysarthria and ataxia, although clearly present, were less than would be expected in complete absence of the cerebellum. This surprising phenomenon supports the concept of extracerebellar motor system plasticity, especially

cerebellum loss, occurring early in life. In this series of nine living cases (Table 1), three patients were male, six female. One patient was noted of consanguinity whereas others had no family history of genetic disorders and their siblings were reported as neurologically normal. All patients were related with uneventful pregnancy and delivery and blood count, chemistry and serological test were normal. Only one patient (Sener and Jenkins, 1993) was completely normal in neurological examinations (three mental development normal). The other eight patients all showed cerebellar symptoms from motor, language to mental development. One patient's diagnosis of complete agenesis of cerebellum was testified by surgery of opening the posterior fossa. In the nine living patients, eight patients having complete or near-complete cerebellar agenesis were characterized by motor dysfunction and impaired development. We conclude that the cerebellum is necessary for normal motor, language functional and mental development even in the presence of the functional compensation phenomenon. Future studies using functional MRI may help answer whether some functional activity remains in the small cerebellar remnants in subtotal cerebellar agenesis or in the cortex in complete cerebellar agenesis. From the family history of this series we can also infer that primary cerebellum agenesis is not an inherited disease and most likely it is a heterogeneous condition. This disease is not candidate for surgery, and heteropathy treatment would provide a good result.

Embryologically, the human cerebellum develops as a cellular proliferation from the dorsal region of the rhombencephalon. Gross cerebellar anomalies may be associated with many malformations in the posterior fossa, including the cortical layer, vascular, ascending and descending fasciculus of the telencephalon with the cerebellum, etc. The vascular changes induced by cerebellum malformations are not well characterized, and few data are available addressing the effect of complete primary cerebellum agenesis on the vascular system. Pascual-Castroviejo (1978) reported his study of arterial changes in different types of cerebellar defects and found that the posterior inferior cerebellar artery was hypoplastic or aplastic in a large number of cases. In cases of extremely severe cerebellar malformation with almost complete agenesis of the vermis and the

hemispheres, the circulation is quite poor and the posterior fossa arteries are very thin. In this case, we find that all of the posterior circulation blood vessels, including the bilateral posterior inferior cerebellar artery, anterior inferior cerebellar artery and superior cerebellar artery, are completely defected. The conclusion that the severity of the posterior fossa's vascular alterations is directly related to the degree of cerebellar hypoplasia, may be reasonable. At least, our case demonstrates this fact.

The superior, middle, and inferior cerebellar peduncles are the major white matters tracts that can be identified connecting the brainstem with the cerebellum at 1.5 T magnetic field strength. The superior cerebellar peduncle, originating from the dentate nucleus, is the main pathway that connects the cerebellum with the thalamus. The middle cerebellar peduncle is part of the pontocerebellar tract, while the inferior cerebellar peduncle, which has afferent and efferent connections related to the cerebellum, originates in the caudal medulla oblongata, traverses the pons, and sends branches into the cerebellar cortex. To date, there are no published reports in which the authors describe diffusion tensor imaging findings in primary cerebellum agenesis. Unpublished data from our own research projects demonstrate an abnormal, no afferent or efferent fibres connecting the pontine nuclei with the cerebellum. The pons hypoplasia, manifesting as volume reduction of the pontine prominence in MRI, ascribed to deficiency of these fibres. But are the orientation and the decussation fibres preserved in subtotal cerebellum agenesis? The cortico-pontine fibres that project to pontine nuclei descended through the cerebral peduncle resulting in the normal shape of cerebral peduncle.

Congenital conditions that affect the cerebellum are not uncommon, the most common forms being the Dandy-Walker malformation and the Chiari malformation. Therefore, the differential diagnosis of primary cerebellum agenesis includes these two malformations. Dandy-Walker is easily diagnosed on the basis of the classic triad: (i) complete or partial agenesis of the vermis; (ii) cystic dilation of the fourth ventricle; and (iii) enlarged posterior fossa, with upward displacement of the transverse sinuses, tentorium and torcula. Also it may be accompanied by other developmental anomalies such as callosal agenesis, but the brainstem is normal. Chiari malformation, subdivided into four types, is a common malformation of the brain where the cerebellum protrudes into the spinal canal, causing many symptoms, mostly due to obstruction of CSF outflow. Type I, typically difficult to diagnose and not apparent often-times until adulthood, refers to elongation of the cerebellar tonsils forcing protrusion through the base of the skull. Type II includes the herniation of the cerebellar vermis,

brainstem and fourth ventricle through the foramen magnum, associated with myelomeningocele and multiple brain anomalies. Hydrocephalus and syringomyelia are common, and the posterior fossa is often small. Type III, the most severe form of hindbrain herniation, covers cases with herniation of the cerebellum and brainstem into posterior encephalocele. Type IV is an extremely rare condition with few patients reported in the literature. It is characterized by loss of cerebellar development, hypoplasia, and reduced cerebellum size. It may occur as a rare autosomal recessive disease (Wichman *et al.*, 1985; Mathews *et al.*, 1989). Considering the previous descriptions of anatomical changes related to Chiari malformation IV, it is our opinion and conclusion that it actually represents primary cerebellar agenesis.

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