Unilateral Cerebellar Agenesis With Minimal Clinical Symptoms

Seyho C. Yucetas, MD,* Nergiz Huseyinoglu, MD,† Hatice Köse Özlece, MD,† Can H. Yildirim, MD,* Miktat Kaya, MD,* and Aytac Akbasak, MD*

Abstract: Unilateral cerebellar agenesis/hypoplasia is defined as total or partial lack of one of the cerebellar hemispheres and it may occur due to etiopathogenetically different mechanisms. Patients usually show cerebellar symptoms, yet patients may occasionally be asymptomatic. This study provides a discussion of 5 cases of unilateral, congenital, rather rare cerebellar agenesis in light of the related literature. Five cases with unilateral cerebellar agenesis/hypoplasia who were seen in the neurosurgery and neurology clinics between April 2010 to September 2013 were evaluated. The youngest patient was a 2-year-old, whereas the oldest one aged 37 years. Three patients were younger than 16 years, whereas 2 patients were older than 16 years; 4 patients were female, whereas 1 patient was male. All patients underwent detailed physical and neurological examinations as well as magnetic resonance imaging. The cerebellar tests of 4 of the patients revealed positive results, whereas one patient was asymptomatic and was diagnosed with cerebellar hypoplasia during examinations performed to find the cause of headaches. Of the 4 patients who had positive cerebellar tests of ataxia, dysdiadochokinesia, and dysmetria, 3 were children and 1 was an adult. Wherever necessary, the patients were subjected to additional examinations of electroencephalography, electromyography, blood tests, abdominal ultrasonography, ophthalmological examination, and psychiatric evaluation. The aim of this study was to point out the fact that unilateral cerebellar agenesis/hypoplasia, which is a rare cerebellar anatomical disorder, may occasionally show minimal clinical cerebellar findings, or may be asymptomatic.

Key Words: cerebellum, agenesis, unilateral, hypoplasia

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The cerebellum is a unique part of the central nervous system. In comparison with the other regions of the central nervous system, the cerebellum has a more homogenous neuroanatomic structure and includes only several types of neurons (granule, unipolar brush, Purkinje, Golgi, Lugaro, stellate, basket, candelabrum cells, and interneurons). Yet, the role of the cerebellum in functions such as mood, motor, sensory, and balance are not fully clear. The common view is that the cerebellum provides not only upregulation of motor and sensory functions but also integration between regions responsible for cognition in the cerebral hemispheres. Clinical symptoms of cerebellar dysfunction are ataxia, dysmetria, dysdiadochokinesia, and yssynergia. In addition, psychiatric syndromes such as schizophrenia, attention deficit hyperactivity disorder, and autism are identified in cerebellar syndrome. Although various congenital and acquired diseases are accompanied by cerebellar dysfunction, unilateral cerebellar agenesis is a rather rare finding. Unilateral cerebellar agenesis is defined as the total or partial lack of one of the cerebellar hemispheres. Patients with unilateral cerebellar agenesis generally show cerebellar symptoms; however, they may occasionally be asymptomatic. In the present study, 5 cases with rather rare cerebellar agenesis/hypoplasia that showed minimal or mild clinical findings were discussed in light of the related literature.

CASE REPORTS

Case 1

Herein, we report on a 2-year-old female patient. The reason for application to our outpatient clinic was for stumbling. Routine blood tests of the patient (including vitamin B12) were normal. Family history in terms of ataxia was negative. There was nothing significant in the antenatal, prenatal, and postnatal history. The mother, although she did not have any serious diseases or infections during pregnancy, had not been under a regular doctor’s care, and had not undergone the usual ultrasonographic tests. Neurological examination revealed a left-sided ataxia. Other cerebellar tests could not be performed because of the young age of the patient. Other than that, the results of the cranial nerve, motor, sensory, and reflex examinations of the patient were appropriate for her age. Magnetic resonance imaging (MRI) was performed on the patient and left cerebellar agenesis was detected. The psychiatric examination of the patient performed by the department of child psychiatry revealed age-appropriate results.

Case 2

The second case we report is of a 5-year-old male patient. The reasons for applying to the hospital were for an intermittently appearing unbalanced walk and a speech impediment. His complaints, which started 2 years before, were not frequent
and therefore disregarded by the family. However, as the complaints became severe in the previous weeks, they applied to the hospital. Mental development of the patient was normal, and there were no motor or sensory deficiencies. The patient showed dysarthria and ataxic gait. In MRI, agenesis of the right cerebellar hemisphere was detected (Figs. 1, 2). EEG results were normal. No other family members reported similar complaints. Neurological examinations of the patient’s 2 brothers were normal. The patient was examined by the department of child psychiatry; the mental and behavioral stages of the patient were appropriate for his age.

Case 3

Fifteen-year-old female patient applied to our hospital with complaints of headaches. In the neurological examination of the patient, who had been having headaches intermittently for about 3 years, minimal ataxia was detected. She was a successful student. She had no history of any serious illness. Because the headaches were resistant, patient underwent MRI and showed left cerebellar agenesis. Accordingly, advanced examinations, EEG, nerve conduction studies, and abdominal USG were requested, all of which revealed results in normal ranges. The family history was negative in terms of hereditary neurological diseases.

Case 4

A 19-year-old female patient was previously followed up in the neurology and neurosurgical outpatient clinics because of a diagnosis of ataxia and mild mental retardation. MRI revealed right cerebellar agenesis. There were no neurological complaints in the immediate family members.

Case 5

A 37-year-old female patient applied to the neurosurgery polyclinic because of headache complaints. She had been suffering from headaches for a long time and had no other distinct neurological complaints. The neurological examination of the patient was normal. Hemogram and biochemical tests (including vitamin B12 and thyroid function tests) were in

FIGURE 1. Right cerebellar agenesis in T1A sagittal magnetic resonance imaging (MRI) (case 2).

FIGURE 2. Right cerebellar agenesis in T1A axial magnetic resonance imaging (MRI) (case 2).
normal ranges. Cranial MRI showed left cerebellar agenesis (Figs. 3, 4).

The common characteristics of all patients were lack of similar complaints among family members, no effect on motor functions, and normal intellect, except for 1 patient.

FIGURE 3. Left cerebellar agenesis in T2A axial magnetic resonance imaging (MRI) (case 5).

FIGURE 4. Left cerebellar agenesis in T2A coronal magnetic resonance imaging (MRI) (case 5).

DISCUSSION

Formation of the cerebellum starts at week 5 of gestation. Cerebellar hemispheres develop at the center of the rhombic flaps of the metencephalon and form the vermis by uniting in the intermedial line.\(^3\) In a 12-week embryo, in the middle of this plaque a small region is present as the vermis and both hemispheres are at the sides. Such formation occurs from anterosuperior to posteroinferior and finally the posteroinferior of the vermis develops. Thereafter, the posterolateral fissure and cranial and caudal regions form. The caudal region forms the most primitive structure of the cerebellum, namely the flocculonodular region, whereas the cranial region forms the cerebellar vermises.\(^4\) The fissure deepens at the end of month 3 and divides the vermis and the hemispheres into lobes. The surface of the lobules is shaped like leafy structures called folia. Some neuroblasts that are present in the intermedial region of the alar plates migrate to the marginal zone and differentiate as neurons of the cerebellar cortex. The cerebellum consists of 3 regions anatomophysiologically: vestibulocerebellum, spino-cerebellum, and cerebrocerebellum. The flocculonodular area of the cerebellum is responsible for direct vestibular connections and is called the “vestibulocerebellum.” Medial vestigial and interposed nuclei (spinocerebellum) that settle in the vermis and intermediate region join the control of the motor system and are called “spino-cerebellum.” The lateral regions of the cerebellum connect through the dentate nucleus to thalamus and thereby to the cerebral cortex and, therefore, are known as the “cerebrocerebellum.”\(^2\)

Unilateral cerebellar agenesis is defined as total or partial lack of one of the cerebellar hemispheres. The first report of cerebellar agenesis was given by Combettes in 1831.\(^4\) One of the latest classifications of the pathologies of the cerebellum was developed by Barkovich et al.\(^5\) According to this classification, in the group “malformations secondary to early anteroposterior and dorsoventral patterning defects, or to misspecification of mild-hindbrain germinal zones,” cases of cerebellum agenesis with near normal development and pancreatic with cerebellar agenesis are observed.\(^3\) These cases involve genetic defects that effect multiple dorsoventral subregions and cerebellar GABAergic neurons. The other group, “generalized brain malformations that significantly affect the brain stem and cerebellum,” includes the syndromes of isolated cerebellum agenesis, X-linked nonprogressive cerebellar hypoplasia, mental retardation, epilepsy with cerebellar hypoplasia, and AD or X-linked cerebellar hypoplasia with improvement.\(^5\) In yet another group identified as “combined hypoplasia and atrophy in putative prenatal onset degenerative disorders,” cerebellar hemisphere hypoplasia due to prenatal injury rather than genetic causes is observed. As for genetic causes, Sellick et al\(^6\) and Hoshino et al\(^7\) reported that pancreatic and cerebellar agenesis may be present in gene mutations. The *PTF1A* gene encodes helix-loop-helix transcription factor and therefore plays a role in the formation of GABAergic cells of the cerebellum (Purkinje...
cells and interneurons). Granular cells are also formed, based on the number of GABAergic cells. Therefore, if the number of GABAergic cells is insufficient, then granular cells will also be scarce, thereby causing cerebral agenesis/hypoplasia to develop. Cerebellar agenesis/hypoplasia is also observed in certain X-linked genetic malformations and it is accompanied by clear clinical findings. X-linked cerebellar dysgenesis may progress in an isolated way or together with malformations of the other areas of the brain and even many organ involvements. Up until now, in the medical literature, at least 15 genetic defects in chromosome X were found responsible for pathologic cerebellar phenotype. Several families with X-linked cerebellar dysgenesis were reported and 8 genes responsible for this were mapped. There are certain defined gene mutations, which are linked to X and related to cerebellar agenesis/hypoplasia; these are oligophrenin-1 (OPHN1), calcium/calmodulin-dependent serine protein kinase (CASK) gene, and Xp11.21-Xq24, Xq25-q27.1 gene mutations. In addition, in Hoyeraal-Hreidarsson, Fragile X, Opitz, and oral-facial-digital type I/X-linked Joubert syndromes, cerebellar dysgenesis is often observed in addition to mental retardation, cancer predisposition, dimorphism, epilepsy, retinitis pigmentosa, and other clinical symptoms. The fact that the cases in our present study had no family history, insignificant clinical symptoms, and unaffected state of other organs leads away from the diagnosis of any X-linked genetic syndromes described above. In contrast, it must be kept in mind that the existence of a sporadic gene mutation is still a possibility because of the fact that genetic examinations have not been carried out. It is also possible that these patients with similar radiologic findings may yet have different etiopathogeneses.

As explained above, in some cases, cerebellar dysgenesis may be linked to prenatal cerebellar infarct. In a review study, clinical and imaging findings of 7 cases diagnosed in different clinics between the years 1995 to 2005 were reviewed retrospectively and long-term follow-ups were studied. Five of 7 patients had their left cerebellar hemisphere affected and all 5 of them had their vermis affected as well. On neurological examination, 5 patients showed truncal ataxia and muscle hypotonia, whereas 3 had extremity ataxia and 2 had titubation. Five patients had speech impediments, 3 had learning disabilities, and 1 had a severe behavioral disorder. Although none of the follow-up imaging of the patients showed hemosiderin deposits and there were no findings that supported cerebellar infarct radiologically, the authors considered prenatal hemorrhagic infarct as the cause of unilateral cerebellar hypoplasia. They supported this conclusion by the fact that weeks 20 to 24 of gestation was a risky period for cerebellar infarct and hemorrhage and that hemosiderin can be detected in a premature brain in <6 weeks. Our cases were different from the study of Portelli and colleagues in that there were no distinct cerebellar findings, most of the complaints were nonspecific, and one patient was even arbitrarily diagnosed with cerebellar agenesis from MRIs, which together lead away from a prenatal cerebrovascular incident. Yet, particularly in pediatric cases, such etiology cannot be discarded. To detect specific etiopathogenetic mechanisms, Zanni and colleagues recommended performing complete physical and neuroimaging examinations, metabolic work-up, nerve conduction studies, and standard karyotype followed by array-CGH studies on patients with a neurologically documented cerebellar agenesis/hypoplasia and with ≥2 dysmorphic features. In addition, we believe that in etiologically indefinite cases, clinic and radiologic follow-ups are very important in defining the nature and prognosis of the disease. In terms of prognosis, it has been suggested that the life span of patients with cerebellar agenesis or hypoplasia may be normal and such patients may be employed as unskilled labor.

Some authors claim that patients with cerebellar agenesis may be completely asymptomatic, whereas others assert that neurological deficits may be revealed through detailed examination and, in addition, patients may show various psychological and behavioral disorders. The fact that in the cases submitted above the clinical findings were not distinct, and no pathologic findings were detected in the detailed examination of one of the patients, is a clear indicator that compensatory mechanisms of the cerebellum have not been discovered yet. In fact, the medical literature reported a patient with total cerebellar agenesis, which was detected in autopsy, who lived his life independently and without specific cerebellar findings. It is our hope that developments in molecular biology and medical genetics will enable detailed examination of the molecular mechanisms of the formation of cerebellar agenesis or hypoplasia and exposition of the cerebellar compensatory mechanisms.

REFERENCES