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Case Report

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Autopsy report of Dandy-Walker malformation: A rare anomaly of the brain

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ABSTRACT

Dandy-Walker malformation is a rare congenital anomaly of the posterior fossa of the skull and cerebellum. The pathology includes hypoplasia or agenesis of the vermis of the cerebellum, cystically dilated fourth ventricle, and an enlarged posterior fossa of the skull. This anomaly of the cerebellum can lead to a wide spectrum of clinical presentations ranging from mild developmental delay to severe hydrocephalus, seizures, and fatality. It is usually diagnosed prenatally using anomaly scans. A detailed study of morphological and microscopic findings is necessary for a better understanding of the etiopathogenesis of this anomaly.

Autopsy is considered the gold standard for confirmation of findings associated with this anomaly. It can also help to explore other associated anomalies which can further help in genetic studies and patient counseling.

Herein, we present an autopsy report of a 20-week-old male fetus with Dandy-Walker malformation diagnosed prenatally and sent for autopsy with informed consent after medical termination of pregnancy. Gross and microscopic findings were studied and compared with those of previous studies done in the past.

Keywords: Dandy-Walker, Vermis, Ventricle, Cerebellum

1. INTRODUCTION

Dandy-Walker malformation is a rare congenital anomaly of the brain that particularly affects the posterior fossa of the skull and cerebellum [1,2]. It involves hypoplasia or agenesis of the vermis of the cerebellum, cystically dilated fourth ventricle, and an enlarged posterior fossa of the cranium [3,4]. This condition may result from the interplay of genetic and environmental factors during pregnancy, leading to abnormal development of the cerebellum and the fourth ventricle [5,6]. According to epidemiological data, approximately 1 in 25,000 – 30,000 live births are affected by this anomaly [7]. The prognosis of this condition depends on two factors: the severity of the defect and the quality of treatment given to the patient [8,9]. Females were more affected than males. Dandy-Walker malformation is also associated with a few Dandy-Walker variants, which are less severe. Clinically, patients with Dandy-Walker malformation may present with developmental disabilities, hydrocephalus, seizures, and motor and coordination deficits [10,11]. A detailed understanding of the etiopathogenesis of Dandy–Walker malformation is essential, as it provides insights into the developmental, genetic, and morphologic basis of the disorder, as demonstrated in clinicopathologic and genetic correlation studies [12,13]. Here, we present an autopsy report of a 20-week-old male fetus diagnosed prenatally with Dandy-Walker malformation and sent for autopsy.

2. CASE REPORT

A 25-year-old female, 20 weeks primigravida visited the obstetrics outpatient department for a routine antenatal checkup. There was no history of trauma, infections, consanguinity or alcoholism. Blood sugar levels were normal. Anomaly scan reports revealed the following findings: head circumference (HC) was 18.5 cm which was larger for gestational age. The abdominal circumference (AC) was 14 cm. The HC/AC ratio was 1.3, which was higher than that for the gestational age. The cisterna magna measured 4.4 mm. Both lateral ventricles of the brain appeared dilated, measuring 15mm. Thinning of the cerebral cortex and corpus callosum was also observed.

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The cerebellum appeared to be splayed with the absence of the vermis. These findings were suggestive of Dandy-Walker malformation. The thorax, heart, abdominal viscera, spine, face, and limbs were all normal. Uterine artery screening was negative for pregnancy-induced hypertension.

The patient was counseled about the prognosis of the condition. Medical termination of pregnancy was performed and the fetus was sent for autopsy with informed consent.

Table I. *Comparison of neuropathologic findings in reported cases of Dandy–Walker malformation*

Author (Year)	Gestational age of fetus (weeks)	Purkinje heterotopia / disorganization	Choroid plexus findings	Genetic / molecular findings
Pasquier, et al., Acta Neuropathologica, 2009 [13]	18 – 24	Not specifically described; main focus on vermian hypoplasia	Enlarged and occasionally cystic; attributed to hydrocephalus	Karyotyping normal in most
Aldinger, et al., Nature Genetics, 2009 [5]	20 – 23	Ectopic Purkinje cells within cerebellar core; disrupted layering	Marked choroid plexus expansion	FOXC1 deletions / mutations (6p25)
Haldipur, et al., eLife, 2017 [1]	18 – 22	Prominent Purkinje heterotopia and cortical disorganization	Expanded, vascularized choroid plexus	FOXC1 loss → altered BMP/TGFβ signaling
Phillips JJ et al., Prenatal Diagnosis, 2006 [12]	19 – 25	Not detailed; mainly macroscopic vermian absence	Cystic expansion of 4th ventricle and choroid plexus	Not done
Present case	20	Distinct ectopic Purkinje clusters with disrupted layering	Expanded choroid plexus with vascular proliferation	Not available

FOXC1: Forkhead box C1, BMP/TGFβ : Bone morphogenetic protein (BMP)/ transforming growth factor-beta (TGF-β).

Autopsy findings of the fetus

Received a male fetus weighing 300 g and measuring 32 cm in length, with an attached umbilical cord measuring 5 cm in length.

External examination: The measurements were as follows: HC-18.5 cm; chest circumference (CC) – 15.5 cm; AC – 14 cm; crown rump length (CRL) – 17 cm; rump heel length (RHL) – 15 cm; hand length – 2.5 cm and foot length – 3.5 cm with all fingers and toes in situ. The HC was larger for gestational age (Figure 1). No other external abnormalities were present.



Figure 1. *Anterior view of the fetus*

Gross examination: The posterior aspect of the cerebellum showed absence of vermis (Figure 2A). Posterior view of the brain of a normal baby of the same gestational age and sex was used as a control for comparison (Figure 2B).

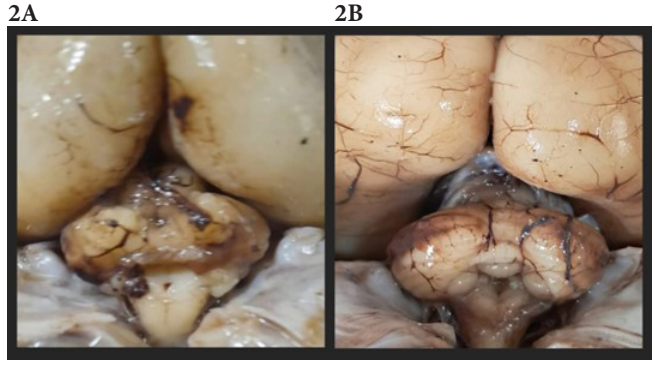


Figure 2. (2A) *Posterior view of the brain in the present case showing Dandy-Walker malformation with absence of the cerebellar vermis and hypoplastic cerebellar hemispheres.* ***(2B)*** *Posterior view of the brain of a normal baby of the same gestational age and sex, used as a control for comparison.*

The sagittal section of the brain showed dilated lateral ventricles, thinned-out cerebral cortex, and malformed corpus callosum (Figure 3). The transverse section of the cerebellum showed an enlarged fourth ventricle cavity measuring 1.5x1.5 cm, thinned-out cerebellar cortex, and the absence of vermis (Figure 4A). Transverse section of the cerebellum of a normal baby of the same gestational age and sex, was used as a control for comparison (4B). The heart, lungs, liver, spleen and kidneys were normal on gross examination.

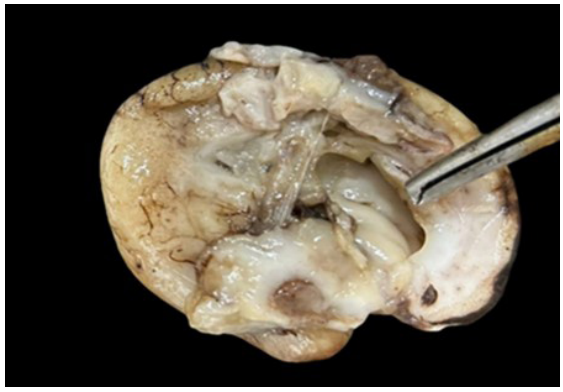


Figure 3. *Sagittal section of the brain showing a dilated lateral ventricle, agenesis of the corpus callosum and thinned-out surrounding cerebral cortex*

4A **4B**

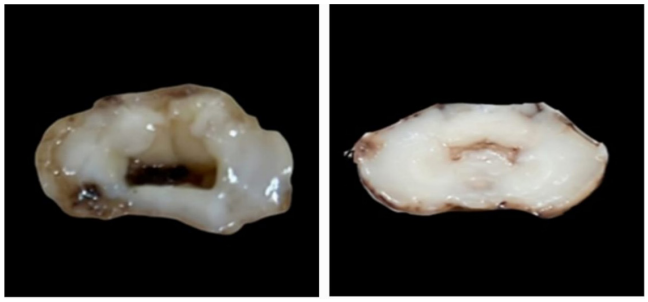


Figure 4. ***(4A)*** *Transverse section of the cerebellum in the present case showing Dandy-Walker malformation with a dilated fourth ventricular cavity, absence of the cerebellar vermis, and thinning of the cerebellar cortex.* ***(4B)*** *Transverse section of the cerebellum of a normal baby of the same gestational age and sex, as a control for comparison.*

***Microscopic examination*:** The cerebellum showed ectopic clusters of Purkinje cells in the parenchyma (Figures 5 and 6). Expansion of the choroid plexus was observed in the fourth ventricular cavity (Figure 7). The liver, spleen and kidneys showed congestion. Lungs and heart appeared normal.

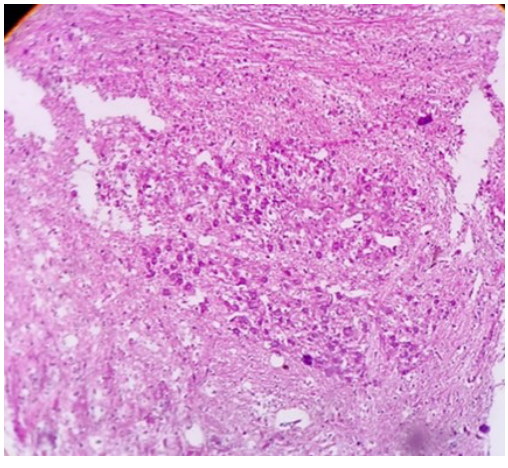


Figure 5. *Ectopic clusters of Purkinje cells in the core of the cerebellum*

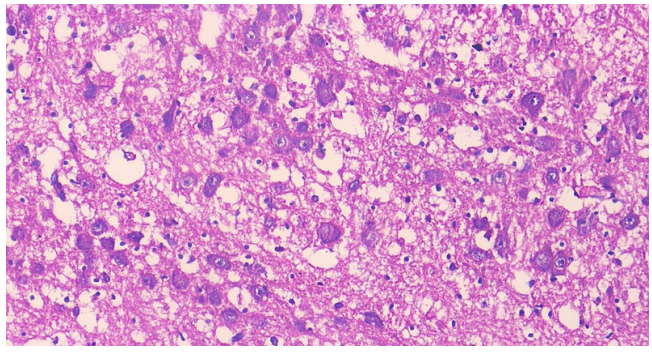


Figure 6. *High-power image of Purkinje cells*

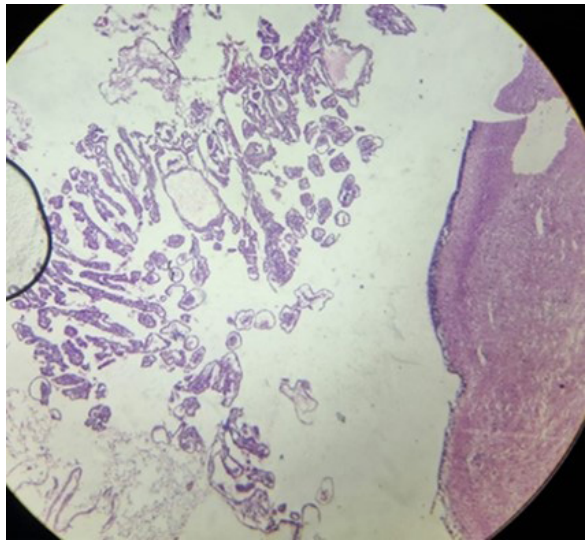


Figure 7. *Choroid plexus in the area of the fourth ventricle with cerebellum on the right side.*

3. DISCUSSION

A surgeon named John Sutton discovered Dandy-Walker malformation in 1887. Walter Dandy, a neurosurgeon, studied this anomaly in a 13-month-old infant in 1910. In 1942, two scientists, Taggart and Walker, conducted further research. Finally, in 1954, Clemens, a psychiatrist, penned the term 'Dandy-Walker malformation' for this anomaly [1]. It is a malformation of the cerebellum and posterior fossa of the brain characterized by a dilated fourth ventricular cavity, agenesis or hypoplasia of the vermis, and an enlarged posterior fossa of the cranium, as observed in our case. Statistics suggest that females are more affected than males [2]. Our patient was a male fetus.

Dandy-Walker malformation is also associated with a few variants known as Dandy-Walker variants. These variants are comprised of diagnostic elements of Dandy-Walker malformation in varying proportions but differ from it by having a normal-sized posterior fossa. These variants present as a less severe form of the disease; hence, they are usually diagnosed in adulthood with a better prognosis [3].

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The etiopathogenesis of Dandy-Walker malformation is complicated and depends on numerous factors. The environmental risk factors include exposure to infections, teratogens during pregnancy and gestational diabetes mellitus. Several genes have been implicated in the pathogenesis of this malformation. These include forkhead box C1 (FOXC1), laminin subunit gamma 1 (LAMC1), zinc finger protein of the cerebellum 1 (ZIC1) and zinc finger protein of the cerebellum 4 (ZIC4) genes. It can also be associated with chromosomal trisomies of 13,21 and 9 [4]. Studies have shown that ZIC1 and ZIC4 mutations lead to decreased proliferation of granular cell precursors (GCPs) in the external granular layer (EGL), which further affects the development of the vermis [4].

Some studies have suggested that the FOXC1 gene contributes to the pathogenesis of malformation. The expression of this gene is observed in different areas of the brain, including mesenchymal tissue, which surrounds the developing cerebellum. It encodes the FOXC1 protein, which helps in the normal development of the cerebellum. Aldinger et al., found that FOXC1 regulates the expression of bone morphogenetic protein (BMP) and transforming growth factor beta (TGF β) which activate the atonal BHLH transcription factor 1 (ATOH1) gene, which is crucial for the growth of GCPs. According to the study, gross defects found in FOXC1-null mouse embryos included an enlarged fourth ventricle roof plate, lack of posterior foliation of the cerebellum, vermian hypoplasia, deficient midline vermian fusion, and increased choroid plexus epithelium in the walls of the fourth ventricle cavity, which was also observed in our case [5,6]. Microscopically, there was migration of GCPs from the EGL into the cerebellar core. GCPs usually secrete a chemical called reelin, which attracts Purkinje cells. As a result, there was a disruption of the Purkinje cell layer under the EGL during the migration of GCPs; thus, ectopic clusters of Purkinje cells were found in the cerebellar core [5,6]. Microscopically, our case showed clusters of multiple large neurons with prominent nucleoli and abundant eosinophilic cytoplasm within the cerebellar white matter and internal granular layer, consistent with ectopic Purkinje cells. These were not aligned in the typical linear Purkinje cell layer. The surrounding cortex showed disorganization of the normal laminar pattern and focal gliosis. Also seen was expanded choroid plexus in the area of the fourth ventricle, indicating that this could be a possible mechanism based on previous research. To our knowledge, detailed histopathologic illustration of ectopic Purkinje neurons within the cerebellar parenchyma in a fetal Dandy–Walker malformation has been rarely reported in human autopsy studies. This observation provides morphologic evidence of abnormal neuronal migration possibly related to FOXC1-mediated mesenchymal signaling defects described in experimental models. This misplacement of Purkinje cells can disrupt the formation of synaptic connections with other cerebellar neurons, which may lead to deficits in motor control and coordination [5]. Recent experimental and human studies have demonstrated that FOXC1, expressed in the mesenchyme adjacent to the developing cerebellum, regulates signaling pathways (BMP/TGFβ) essential for migration of ATOH1-positive granule cell precursors and alignment of Purkinje neurons [5,6]. FOXC1 deficiency results in expanded choroid plexus and ectopic Purkinje cells, features mirrored in our case. Although molecular confirmation was not possible, the histologic parallels suggest that similar mechanisms may underlie our findings.

Children with Dandy-Walker malformation may clinically present with hydrocephalus, seizures, drowsiness, irritability, developmental delay, muscle weakness, ataxia, psychomotor retardation, and motor and coordination impairments. Hydrocephalus is a complication of this disease [7]. Approximately 75–80% of cases are diagnosed during the prenatal period or infancy with the help of neuroimaging modalities such as ultrasonography, computed tomography, and magnetic resonance imaging, while long-term neurological outcome depends on vermian development and associated anomalies [8]. The prognosis of this condition depends on the severity of the defects, degree of hydrocephalus, presence of other associated anomalies and malformations, and treatment given to the patient. Studies have suggested that half of patients with untreated hydrocephalus die before the age of 3 years. Approximately 30 – 35% of affected children develop normally [9].

The management of Dandy-Walker malformation includes a combination of different approaches. Surgeries such as ventriculoperitoneal shunt, cystoperitoneal shunt, or combined ventriculo-cystoperitoneal shunt help to drain excess fluid and relieve the pressure symptoms of hydrocephalus. Other strategies include physical and occupational therapies, antiseizure medications, and special education [10,11].

Previous human studies on Dandy–Walker malformation have primarily emphasized either gross neuropathologic features or genetic associations, with variable attention to detailed cerebellar histology. Phillips et al., correlated prenatal ultrasonographic findings with postmortem examination and documented macroscopic abnormalities, including vermian absence and cystic dilatation of the fourth ventricle with associated choroid plexus changes [12]. In the setting of these classical gross features, examination of the cerebellar cortex may also reveal subtle histologic alterations, such as ectopic localization of Purkinje neurons and disorganization of cortical lamination, which were observed in the present fetal specimen. Similarly, Pasquier et al., described the association of Dandy–Walker malformation with chromosome 13q deletion, underscoring the genetic basis of the disorder [13]. When considered alongside such genetic insights, the presence of Purkinje cell heterotopia, focal gliosis, and expanded choroid plexus provides morphologic support for disrupted neuronal migration in the developing cerebellum.

Conclusion

Dandy-Walker malformation is an inevitable anomaly of the brain and timely diagnosis and appropriate management of this condition can improve the quality of life of the patient. Further research on the genetic basis of Dandy-Walker malformation and cellular migration defects could pave the way for improved diagnostic markers and potential targeted gene therapies for Dandy-Walker malformation. By integrating histopathological findings and

genetic studies, timely diagnosis and intervention can be made possible in these cases. Autopsy is considered the gold standard for confirming Dandy-Walker malformation. Autopsy studies can also help discover any additional findings or anomalies associated with it and further guide genetic studies. Beyond classical anatomic findings, our case highlights distinct histologic abnormalities—ectopic Purkinje clusters and choroid plexus expansion—that parallel changes described in FOXC1-related Dandy–Walker models. These observations strengthen the concept that impaired cerebellar neuronal migration may contribute to the morphologic spectrum of Dandy–Walker malformation, even in the absence of demonstrable genetic testing.

Compliance with Ethical Standards

This research was conducted ethically by following per under Helsinki World Medical Association Declaration.

Patient consent: The patient gave her consent for images and other clinical information relating to her case to be reported in a medical publication.

Conflict of interest statement: The authors have no conflicts of interest to declare.

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Author contributions: NP: Conceptualization of the study; complete gross examination and documentation; histopathological evaluation and interpretation; literature review; drafting and revision of the manuscript, MG: Supervision of the autopsy and histopathological assessment and interpretation of findings, and provided revision of the manuscript for important content. AR: Provided overall academic guidance, oversight of the study, and final review and approval of the manuscript prior to submission. All authors approved the final version of the manuscript.

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