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Case Report

Cobblestone lissencephaly (Type II), clinical, and neuroimaging: A case report and literature review ☆,☆☆

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ABSTRACT

Cobblestone lissencephaly (C-LIS) (TYPE II) is a rare and severe neuronal migration disorder characterized by a smooth brain surface with overmigrated neurons and abnormal formation of cerebral convolutions or gyri during fetal development, resulting in a cobblestone appearance. C-LIS is associated with eye anomalies and muscular dystrophy. This case report presents a detailed clinical and neuroimaging analysis of a patient diagnosed with cobblestone lissencephaly (Type II). It reviews pertinent literature to enhance our understanding of this complex condition. We report a case of a 6-year-old female child with cobblestone lissencephaly (C-LIS) (Type II) severe developmental delays, hypotonia, and recurrent intractable seizures. Magnetic resonance imaging (MRI) revealed a characteristic cobblestone appearance on the brain surface, indicative of abnormal neuronal migration. In addition to the classic findings of Type II Cobblestone lissencephaly, the patient displayed ventriculomegaly and cerebellar hypoplasia, contributing to the overall neurological impairment observed. The literature review highlights the genetic basis of cobblestone lissencephaly, emphasizing the involvement of genes associated with glycosylation processes and basement membrane integrity. Neuroimaging findings, including MRI and computed tomography scans, are crucial for accurate diagnosis and prognostication. Early identification of cobblestone lissencephaly allows for appropriate counseling and management strategies. However, the prognosis remains guarded, and interventions primarily focus on supportive care and seizure management. This case report contributes to the knowledge of cobblestone lissencephaly, shedding light on the clinical spectrum and neuroimaging

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features associated with this rare disorder. To clarify the underlying genetic mechanisms and possible therapeutic pathways for better patient outcomes, more investigation is necessary.

Introduction

The term "LIS," coined by Owen Richard in 1868, is derived from the Greek words "lissos," meaning "smooth or soft," and "enkephalos," meaning "brain" [1]. The spectrum of LIS includes agyria (complete absence of cerebral convolutions), pachygyria (broad gyri), and subcortical band heterotopia (SBH), also known as double cortex, characterized by smooth gray matter layers following the cortex's curve. The LIS spectrum encompasses agyria, pachygyria, and SBH. Ross et al. identified 6 LIS subgroups, with cerebellar hypoplasia caused by mutations in LISencephaly 1 (LIS1), Double Cortin (DCX), and Reelin (RELN) genes [2]. LIS is divided into 2 types: classic LIS (Type I) and cobblestone LIS (Type II) [3]. Classic LIS (Type I) is associated with a lack of primitive neuronal migration, presenting as either isolated LIS or Miller-Dieker syndrome (MDS), linked to mutations in LISencephaly 1 (LIS1), Double Cortin (DCX), and Tubulin Alpha-1A (TUBA1A12) genes. Cobblestone LIS (Type II) is characterized by cortical dysplasia due to neuroglial over migration. This condition arises from disruptions in neuronal migration during embryonic development, particularly affecting glycosylation processes crucial for proper cortical formation [4].

Mutations in genes associated with glycosylation, particularly those involved in the O-linked glycosylation pathway, have been identified, providing critical insights into the disorder's pathophysiology [5]. Cobblestone LIS is indicative of a continuum of autosomal recessive disorders involving brain, eye, and muscular deficits, such as Walker-Warburg syndrome and Fukuyama muscular dystrophy. Reports of cobblestone lissencephaly (Type II) have been documented globally, highlighting the need for a deeper understanding of its clinical manifestations and diagnostic challenges. Understanding the genetic basis not only aids in accurate diagnosis but also holds promise for future therapeutic interventions. By integrating recent research and advancements, this study aims to contribute to the evolving understanding of this complex neurodevelopmental disorder, with potential implications for diagnosis, management, and future research endeavors.

Case presentation

Presenting Complaints: A 6-year-old female was referred to a neurology clinic due to severe developmental delays, hypotonia, and recurrent intractable seizures. The parents reported concerns about the child's inability to achieve developmental milestones, such as sitting and babbling, raising suspicions of an underlying neurological disorder.

Clinical History: The clinical history revealed a challenging course since infancy, with the child failing to attain developmental milestones appropriate for his age. Parents observed generalized hypotonia, feeding difficulties, and episodes of abnormal movements consistent with seizures. The family history was unremarkable for neurological disorders, developmental delays, or consanguinity.

Examination: Upon assessment, the patient showed evidence of global developmental delay, severe hypotonia, and microcephaly. Neurological examination revealed bilateral nystagmus and increased deep tendon reflexes. Additionally, the child displayed poor head control and lacked purposeful hand movements. These clinical features prompted a thorough investigation to uncover the underlying cause.

Laboratory Investigations: routine laboratory tests, such as a metabolic panel, urine analysis, and full blood count, were within normal limits. Genetic testing, specifically targeted sequencing for genes associated with neuronal migration disorders was confirmed. Pathogenic mutations in the genes related to glycosylation processes support the diagnosis of cobblestone lissencephaly (Type II).

Imaging Findings: *Magnetic resonance imaging (MRI) of the brain: T1-weighted (T1W) and T2-weighted (T2W)* shows thick cortices in the bilateral high frontoparietal lobes (predominantly in bilateral high frontal lobes) with microlobulated/multi-nodular gyri/surface of "Pebbly/cobblestone complex" with sparse cortical sulci {*Fluid attenuation inversion recovery (FLAIR):* isointense to gray matter, *Diffusion-weighted image (DWI):* no reduced diffusivity, *Apparent diffusion coefficient (ADC):* no signal change; gradient (GRE): no blooming}. [(Figs. 1A-D), (Figs. 2A-D), Figs. 3A-D), Figs. 4A-C).

T2W shows that the ventricular system (bilateral lateral ventricles, third ventricle, and fourth ventricle) appears prominent (Figs. 5A-D).

FLAIR shows asymmetrical few smooth hyperintensities in the periventricular white matter of the bilateral corona radiata, frontal lobes, and parietooccipital lobes, and asymmetrical few small confluent hyperintensities in the deep white matter of the bilateral corona radiata, centrum semiovale, frontal lobes, and parietooccipital lobes—*Small* vesselischemia (ischemic microangiopathy)—Fazeka's type 2 (Figs. 6A-D).

Based on the clinical and imaging findings, *congenital etiology or malformation (abnormal neuronalmigration: Group II.B.; Agyria-Pachygyria Complex; cobblestone Lissencephaly (or Type II Lissencephaly)* was considered.

Treatment: Given the seriousness of the illness and the lack of effective therapies, the treatment approach primarily focused on supportive care. Antiepileptic medication was prescribed to manage seizures, and physiotherapy was initiated. To address hypotonia and promote motor development.

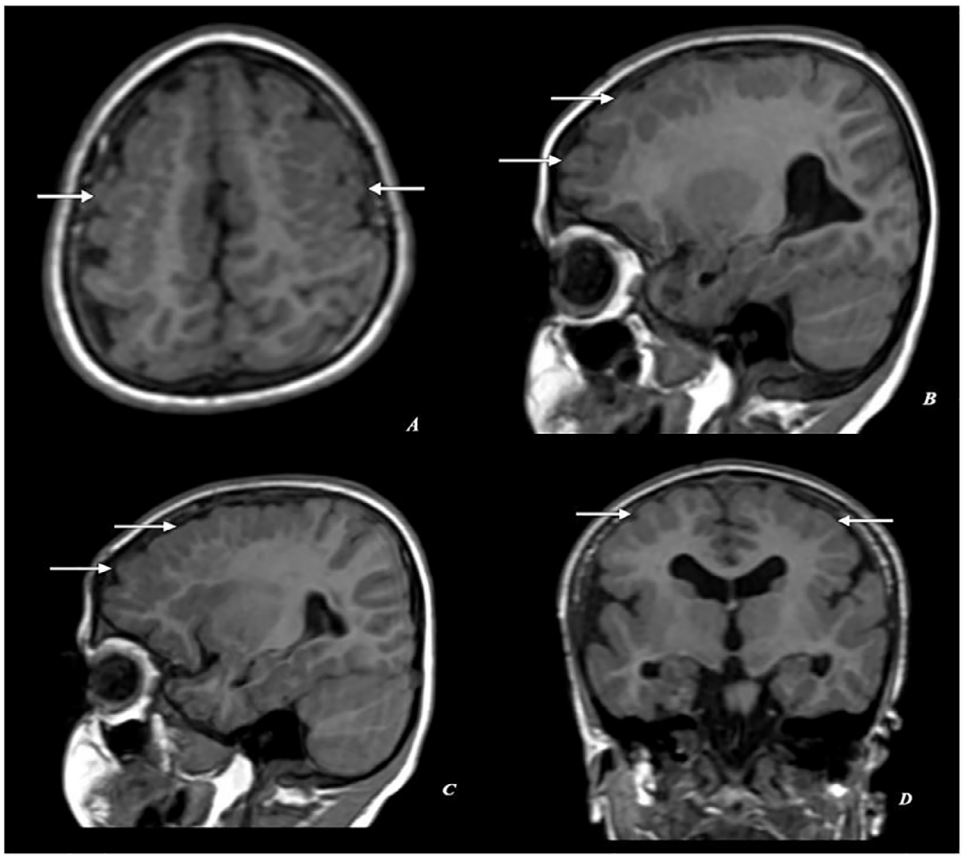

Fig. 1 – (A-D): A 6-year-old female was referred to a neurology clinic due to severe developmental delays, hypotonia, and recurrent intractable seizures. *Magnetic resonance imaging (MRI) of the brain: T1-weighted (T1W)* shows thick cortices in the bilateral high frontoparietal lobes (predominantly in bilateral high frontal lobes) with micro-lobulated or multi-nodular gyri/surface of the "Pebbly/Cobblestone complex" with sparse cortical sulci *(arrows)*.

A multidisciplinary team, including neurologists, physiotherapists, and genetic counselors, collaborated to provide comprehensive care.

Follow-up: Regular follow-up evaluations were planned to track the child's developmental progress, seizure control, and overall well-being. Despite therapeutic efforts, the patient's neurological deficits persisted, highlighting the challenges of managing Cobblestone lissencephaly. The family received ongoing support and counseling. To navigate the complex medical and emotional aspects associated with the disorder. Continued surveillance and adaptation of the management plan were emphasized to address evolving needs throughout the child's developmental journey.

Discussion

Incidence and Demographics: cobblestone lissencephaly (Type II) is an extremely rare malformation, with an estimated incidence of less than 1 in 100,000 live births [6]. Although it occurs globally, the limited number of reported cases makes it challenging to discern specific demographic patterns.

Age of Presentation: Typically, cobblestone lissencephaly (Type II) presents in early infancy or the neonatal period, with symptoms becoming evident as developmental delays, seizures, and hypotonia [7].

Pathophysiology and Causes: The pathophysiology involves disruptions in neuronal migration during embryonic brain development. Recent studies have identified gene mutations associated with glycosylation processes, particularly those involved in the O-linked glycosylation pathway, as critical contributors to cobblestone lissencephaly (Type II) [8]. The emergence of the cobblestone cortex can be attributed to irregularities resulting from defects in the limiting pial basement membrane. Consequently, an increased migration of neuroblasts occurs through these breaches, giving rise to atypical gray matter nodules, colloquially known as "cobblestones," on the brain's surface, located outside the cerebral cortex. Numerous genes are implicated in the disease process of cobblestone lissencephaly, of which the major is Protein O-Mannosyltransferase 1 (POMT1), Protein O-Mannosyltransferase 2 (POMT2), Protein O-Linked Mannose Beta-1,2-N-Acetylglucosaminyltransferase (POMGnT1), Fukutin, and Fukutin-Related Protein (FKRP) [9].

Clinical Features: Clinical features are characterized by profound neurodevelopmental impairment, hypotonia, microcephaly, and intractable seizures. The variability in clinical presentation underscores the complexity of the disorder. The confluence of central nervous system (CNS) involvement

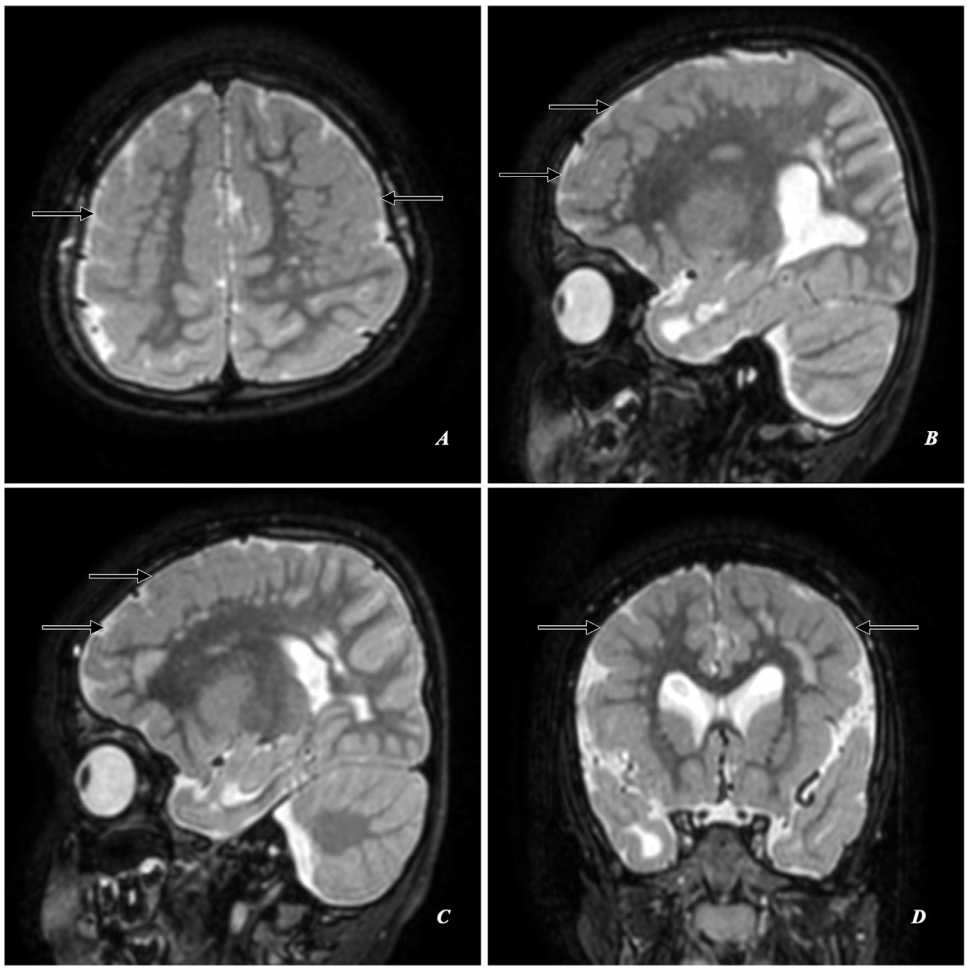

Fig. 2 – (A-D): A 6-year-old female was referred to a neurology clinic due to severe developmental delays, hypotonia, and recurrent intractable seizures. *Magnetic resonance imaging (MRI) of the brain: T2-weighted (T2W)* shows thick cortices in the bilateral high frontoparietal lobes (predominantly in bilateral high frontal lobes) with micro-lobulated or multi-nodular gyri/surface of the "Pebbly/Cobblestone complex" with sparse cortical sulci *(arrows)*.

with congenital muscular dystrophy (CMD) is a characteristic shared by all cases of type 2 lissencephaly. While most patients exhibit symptoms within the first year of life, the extent of muscle weakness can vary among individuals.

Walker-Warburg syndrome (WWS) is distinguished by a triad of clinical features, including congenital muscular dystrophy (CMD), brain anomalies (with a primary occurrence of the cobblestone cortex), and ocular abnormalities [10]. Infants with WWS typically display profound hypotonia, ocular anomalies like colobomas and persistent hypoplastic primary vitreous, severe developmental delays, and frequent seizures. Unfortunately, the prognosis is often grave, with the majority of affected individuals not surviving beyond the age of 1 or 2 years. Patients with muscle-eye-brain disease (MEB) experience hypotonia, visual impairment, seizures, and intellectual disabilities. Ocular abnormalities are typically evident from birth, and motor delays often manifest earlier than symptoms related to brain involvement [11]. Infants affected by Fukuyama congenital muscular dystrophy (FCMD) exhibit manifestations including reduced muscle tone, delays in development, and epileptic seizures. However, the ocular abnormalities observed in FCMD are milder than in WWS or MEB [12].

Associated Abnormalities: Cobblestone lissencephaly (Type II) may be associated with additional structural brain abnormalities such as ventriculomegaly and cerebellar hypoplasia, highlighting the need for a comprehensive evaluation of associated features [13].

Location: The characteristic cobblestone appearance is observed predominantly in the cerebral cortex, disrupting standard cortical architecture [14].

Imaging Findings: Advanced neuroimaging techniques, particularly magnetic resonance imaging (MRI), remain crucial for diagnosing cobblestone lissencephaly (Type II). The hallmark smooth brain surface resembling a cobblestone pavement, along with additional features like ventriculomegaly and cerebellar hypoplasia, aid in accurate diagnosis [15].

Walker-Warburg Syndrome (WWS) presents distinct MRI characteristics. The cortex, in part or entirety, exhibits noticeable thickening, with disorganized neuronal nodules on the brain's surface, resulting in the characteristic cobblestone ap-

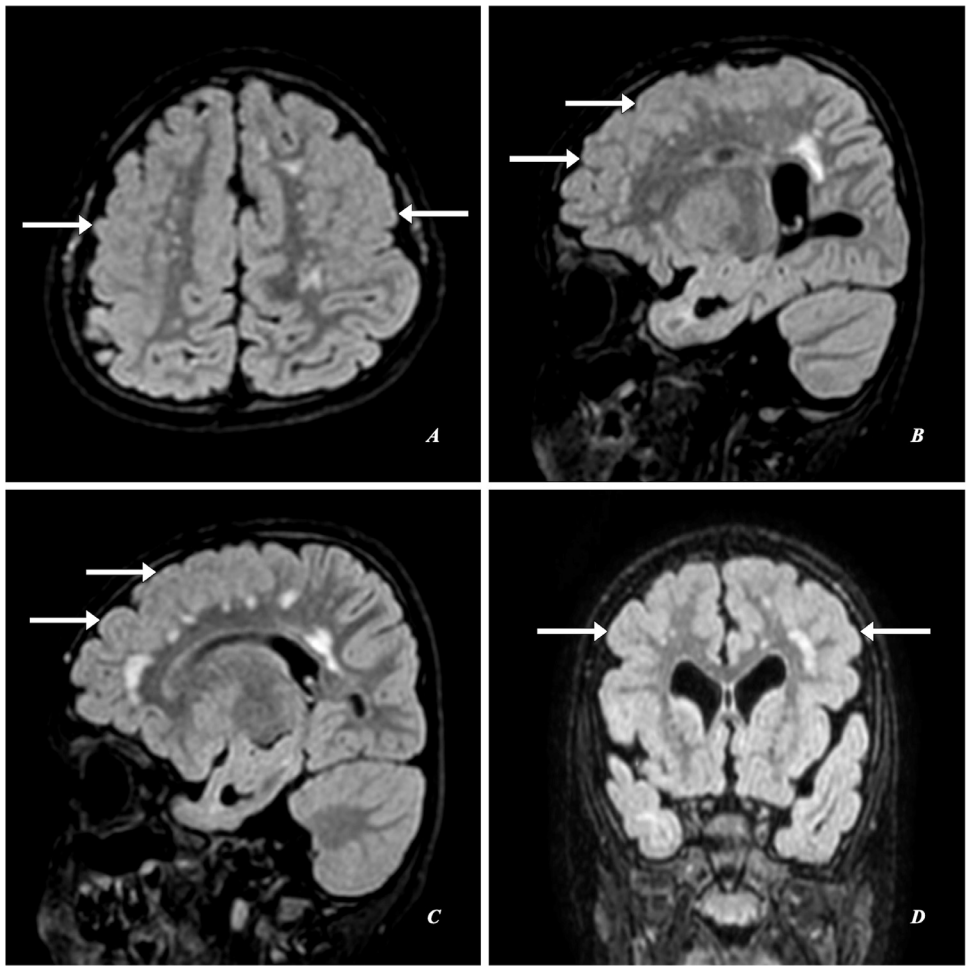

Fig. 3 – (A-D): A 6-year-old female was referred to a neurology clinic due to severe developmental delays, hypotonia, and recurrent intractable seizures. *Magnetic resonance imaging (MRI) of the brain: Fluid attenuation inversion recovery (FLAIR)* shows thick cortices in the bilateral high frontoparietal lobes (predominantly in bilateral high frontal lobes) with micro-lobulated or multi-nodular gyri/surface of the "Pebbly/Cobblestone complex" with sparse cortical sulci *(arrows)*.

pearance. Moreover, gray matter (GM) forms linear bundles that extend into the underlying white matter (WM). Hydrocephalus is a common finding [16]. The brainstem often shows underdevelopment and a "kinked" appearance, while the tectum appears enlarged. There might be pontine hypoplasia and the cerebellum is frequently small and shows malformation with abnormal folding [17]. Multiple small cerebellar cysts are a typical feature of WWS, optimally visualized using thin-section, high-resolution T2-weighted imaging. These cysts can be fully suppressed with FLAIR imaging.

In individuals with Muscle-Eye-Brain Disease (MEB), it is common to observe retinal detachment along with microphthalmia [18]. Additionally, typical imaging findings include cortical dysplasia, polymicrogyria, and inferior vermis hypoplasia. However, it's important to note that cortical dysplasia may not be immediately evident on magnetic resonance (MR) imaging until several months after birth.

Fukuyama Congenital Muscular Dystrophy (FCMD) exhibits distinctive characteristics in brain imaging studies. Affected individuals typically exhibit cobblestone cortex in the temporooccipital region [19]. The brainstem appears small, and the collicular plate is enlarged and fused. Moreover, the cerebellum displays gross dysmorphia with disorganized folia and the presence of subcortical T2/FLAIR hyperintense cysts.

In contrast to Walker-Warburg syndrome, a primary distinguishing feature of FCMD is the relative rarity of cerebellar dysplasia, retinal dysplasia, and gyral malformations.

Treatments: As of now, there is no curative treatment for cobblestone lissencephaly (Type II). Current management primarily involves supportive care, including antiepileptic medications for seizure control and physiotherapy to address developmental challenges. A multidisciplinary approach is essential for comprehensive patient care [20,21].

Encounter of this case, provided valuable insights into the diagnosis, management, and outcome of patients with this complex condition. Given the severity of the neurological deficits and the absence of curative treatments for cobblestone lissencephaly, a multidisciplinary approach was initiated. The management plan included early intervention therapies, physiotherapy, occupational therapy, and speech

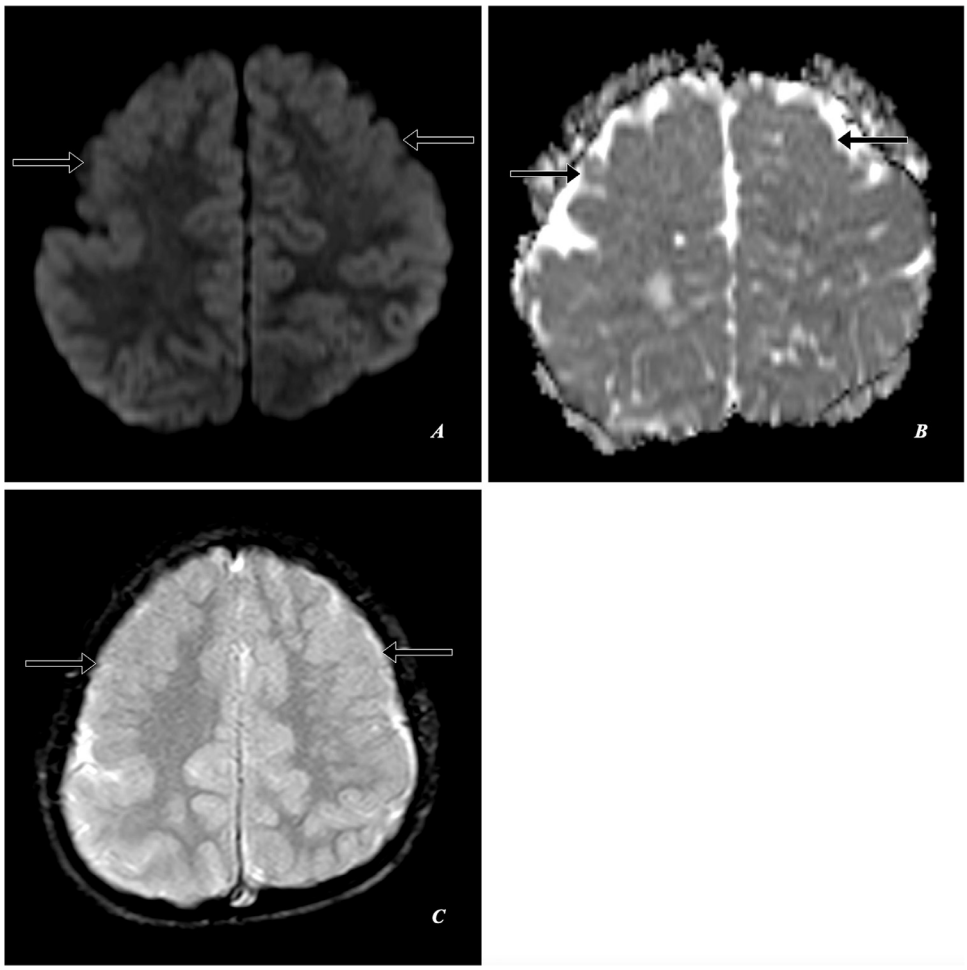

Fig. 4 – (A-C): A 6-year-old female was referred to a neurology clinic due to severe developmental delays, hypotonia, and recurrent intractable seizures. *Magnetic resonance imaging (MRI) of the brain* shows thick cortices in the bilateral high frontoparietal lobes (predominantly in bilateral high frontal lobes) with micro-lobulated or multi-nodular gyri/surface of the "Pebbly/Cobblestone complex" with sparse cortical sulci *(A)Diffusion-weighted image (DWI)* - no reduced diffusivity, *(B)Apparent diffusion coefficient (ADC)*-no signal change, *(C)Gradient (GRE)* - no blooming *(arrows)*.

therapy to optimize the child's developmental potential and enhance quality of life. Additionally, genetic counseling and support were provided to the family.

Literature review

Cobblestone lissencephaly (Type II) is a rare neuronal migration disorder characterized by a cobblestone-like appearance of the brain's surface. The disorder is associated with mutations in glycosylation pathway genes such as POMT1 and POMT2, which result in severe neurodevelopmental impairments, hypotonia, and intractable seizures. Accogli et al. (2020) reported on various ages of patients with these clinical features, noting the presence of cobblestone cortex, ventriculomegaly, and cerebellar hypoplasia on MRI, leading to severe neurodevelopmental impairment [22]. Similarly, Beltrán-Valero De Bernabé et al. (2002) identified POMT1 mutations in patients presenting with muscular dystrophy and ocular anomalies, with imaging revealing a smooth brain surface and cobblestone cortex, often resulting in severe impairment and early death [23].

Juric-Sekhar et al. (2019) discussed the variability of neurological impairments associated with multiple glycosylation-related gene mutations, highlighting the disorganized cortical structure seen in affected individuals [24]. Vasung et al. (2019) also detailed similar findings in their study, noting severe developmental delays and seizures in patients with glycosylation gene mutations [25]. Van Maldergem et al. (2008) reported on patients with hypotonia and ocular anomalies due to POMT1 and POMT2 mutations, showing cobblestone cortex and cerebellar hypoplasia on MRI, often leading to early death [26].

In prenatal diagnoses, Tonni et al. (2016) identified severe brain anomalies detectable in utero, including cobblestone cortex and ventriculomegaly, often leading to early termination of pregnancy [15]. Lapo-Córdova et al. (2021) highlighted the persistent and severe neurological issues in patients with various glycosylation gene mutations, with MRI showing

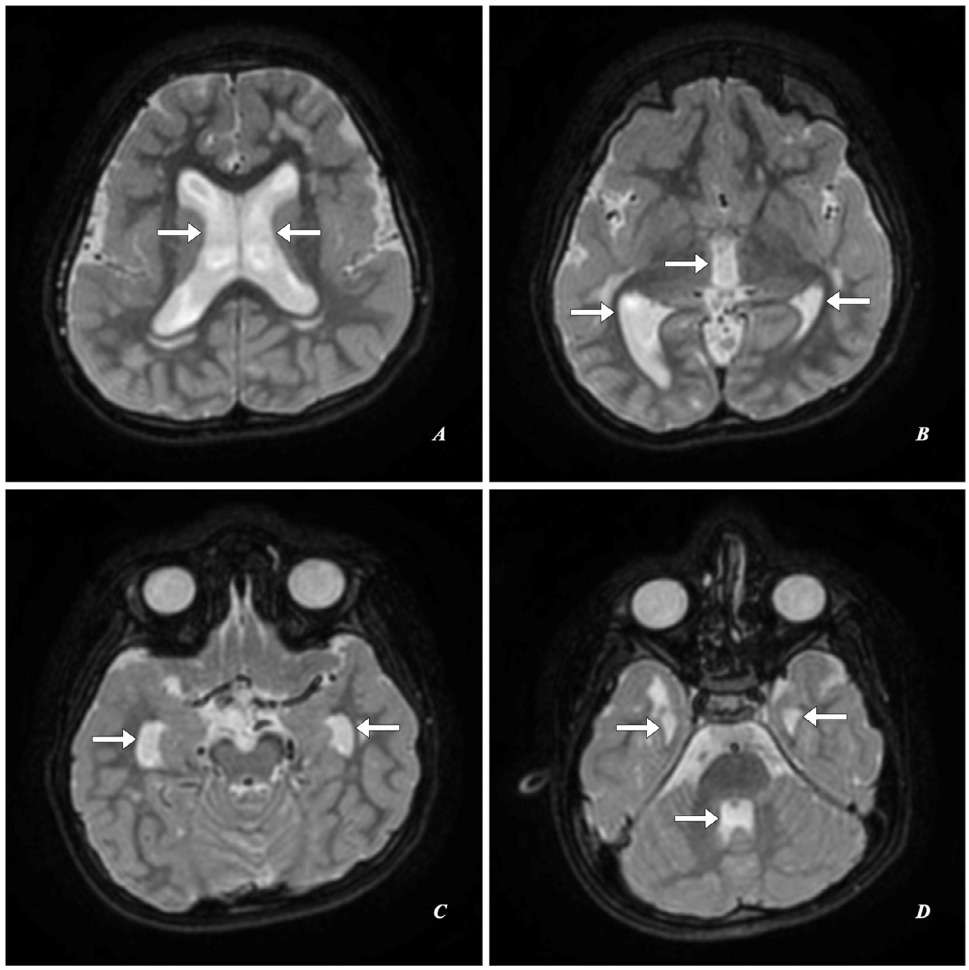

Fig. 5 – (A-D): A 6-year-old female was referred to a neurology clinic due to severe developmental delays, hypotonia, and recurrent intractable seizures. *Magnetic resonance imaging (MRI) of the brain: T2-weighted (T2W)* shows that the ventricular system (bilateral lateral ventricles, third ventricle, and fourth ventricle) appears prominent *(arrows)*.

cobblestone cortex and brainstem abnormalities [6]. Yiş et al. (2014) discussed the severe hypotonia and ocular anomalies in infants with POMGNT1 mutations, with MRI revealing cobblestone cortex and cerebellar cysts, often resulting in early childhood fatalities [27].

Ikemoto et al. (2019) reported on pediatric patients with seizures and developmental delays, noting glycosylation-related gene mutations and chronic management challenges due to the cobblestone cortex and brainstem hypoplasia [20]. Severino et al. (2020) emphasized the severe prognosis and need for supportive care in patients with developmental delays and muscular dystrophy associated with POMT1 and POMT2 mutations, highlighting the white matter abnormalities seen on MRI [13]. Iman Saadallah (2023) discussed a case of a pediatric patient with developmental delays and seizures, showing a smooth brain surface and thick cortex on imaging, leading to persistent developmental challenges [28]. Tonni et al. (2016) again highlighted severe brain anomalies in fetal diagnoses, noting the presence of cobblestone cortex, ventriculomegaly, and cerebellar hypoplasia, often leading to early termination [29]. Lastly, BMJ case reports (2022) documented severe neurological deficits in patients with multiple glycosylation gene mutations, with MRI showing cobblestone cortex and cerebellar hypoplasia, leading to severe prognosis and the need for supportive care [30].

Differential Diagnosis: Differentiating cobblestone lissencephaly from other neuronal migration disorders is crucial for accurate diagnosis and management. Classic lissencephaly (Type I) presents with a smooth brain surface without the cobblestone appearance and is associated with mutations in LISencephaly 1 (LIS1), Double Cortin (DCX), and Tubulin Alpha-1A (TUBA1A) genes. Polymicrogyria, another differential diagnosis, features multiple small gyri, and genetic testing often reveals mutations in genes such as Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit R2 (PIK3R2) and Tubulin Beta-2B (TUBB2B). Walker-Warburg syndrome (WWS) presents with severe hypotonia, ocular anomalies, and congenital muscular dystrophy, and is associated with mutations in Protein O-Mannosyltransferase 1 (POMT1), Protein O-Mannosyltransferase 2 (POMT2), and other glycosylation-related genes. Similarly, Fukuyama congenital muscular dystrophy (FCMD) and muscle-eye-brain disease (MEB) present with muscular dystrophy, developmental delays, and ocular anomalies, and are linked to

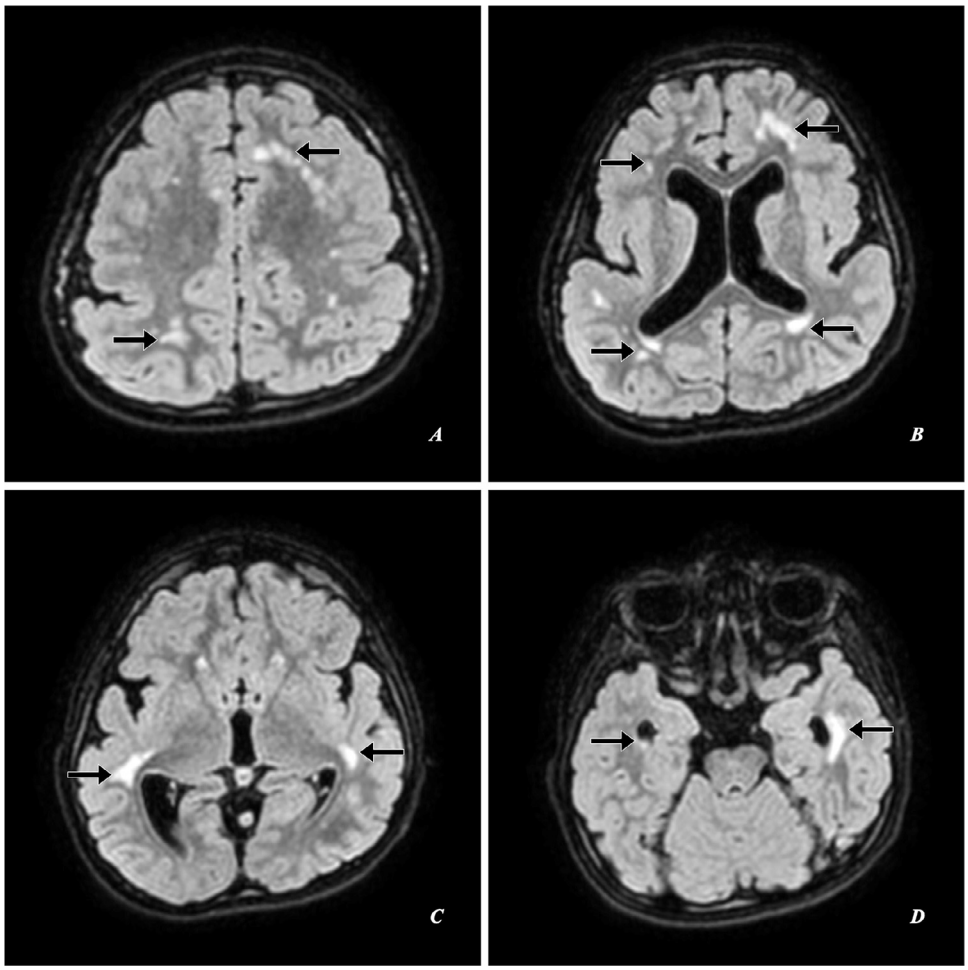

Fig. 6 – (A-D): A 6-year-old female was referred to a neurology clinic due to severe developmental delays, hypotonia, and recurrent intractable seizures. *Magnetic resonance imaging (MRI) of the brain: Fluid attenuation inversion recovery (FLAIR)* shows asymmetrical few smooth hyperintensities in the periventricular white matter of the bilateral corona radiata, frontal lobes, and parietooccipital lobes, and asymmetrical few small confluent hyperintensities in the deep white matter of the bilateral corona radiata, centrum semiovale, frontal lobes, and parietooccipital lobes—*Small vessel ischemia (ischemic microangiopathy)—Fazeka's type 2 (arrows)*.

mutations in Fukutin (FKTN) and Protein O-Linked Mannose Beta-1,2-N-Acetylglucosaminyltransferase (POMGNT1), respectively.

Genetic testing is essential in distinguishing these disorders. Targeted gene sequencing can identify specific mutations in known neuronal migration disorder genes, while whole exome sequencing (WES) can uncover mutations in less commonly implicated genes [22]. Chromosomal microarray analysis (CMA) is useful for detecting submicroscopic chromosomal deletions or duplications associated with these syndromes [22].

Advanced neuroimaging techniques, particularly magnetic resonance imaging (MRI), are crucial for diagnosing cobblestone lissencephaly. Key MRI sequences include T1-weighted, T2-weighted, and FLAIR images, which reveal the characteristic pebbly surface, ventriculomegaly, and cerebellar hypoplasia [22]. In contrast, classic lissencephaly (Type I) shows a smooth brain surface with thickened cortex and reduced sulci, while WWS exhibits brainstem hypoplasia and cerebellar cysts [4,5]. FCMD and MEB share a similar cobblestone appearance but with less severe cerebellar and retinal abnormalities compared to WWS [4,5].

Key diagnostic features include the clinical presentation of developmental delays, hypotonia, seizures, and associated systemic features such as ocular anomalies and muscular dystrophy [22]. Genetic mutations specific to each syndrome help confirm the diagnosis, and distinctive imaging findings, such as the cobblestone cortex and structural brain anomalies on MRI, are indicative of cobblestone lissencephaly [22].

Conclusion

This case report sheds light on the rare and challenging condition of type II lissencephaly (Cobblestone lissencephaly). Despite aggressive management, the prognosis for cobblestone lissencephaly remains guarded, and the child is likely to face

significant lifelong challenges associated with motor and cognitive impairments. Cobblestone lissencephaly is a rare and severe brain malformation associated with significant neurological disabilities. Early diagnosis through comprehensive radiological evaluation and clinical correlation is crucial for initiating appropriate management and providing support to affected individuals and their families. Improved understanding of the underlying genetic causes and advances in therapeutic approaches may 1 day offer hope for better outcomes for these patients.

Patient consent

We confirm that written consent has been obtained from the parents for the publication of the case report on Cobblestone lissencephaly (Type II), including clinical findings and neuroimaging. This consent encompasses the use of detailed medical information and any identifiable images for educational and scientific purposes. The parents were fully informed about the report's content, its publication in medical literature, and the potential benefits for medical research and education. They have agreed to this publication understanding the importance of sharing this information to advance knowledge in the field.

Consent for publication

All authors consent for publication.

Author contributions

All authors of the manuscript have read and agreed to its content.

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