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Case Report

Paediatrics Section

Dandy-Walker Malformation in an Infant with Lambotte Syndrome: A Rare Case Report

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ABSTRACT

Lambotte Syndrome (LS) comprises Intrauterine Growth Retardation (IUGR), cerebral dysgenesis, microcephaly, and early mortality. Dandy-Walker Syndrome (DWS) is characterised by a triad of hypoplastic cerebellar vermis, cystic dilatation of the fourth ventricle, and enlargement of the posterior fossa with torcular-lambdoid inversion. The index case was delivered late preterm at 36 weeks of gestational age and exhibited evidence of IUGR and postnatal failure to thrive. A male infant was admitted at 1.5 months of age due to recurrent unprovoked seizures, which were controlled with phenobarbitone and phenytoin injections. He displayed grade I hypertelorism, fixed flexion deformities of the fingers and toes, and generalised hypotonia. Brain Magnetic Resonance Imaging (MRI) revealed severe semilobar holoprosencephaly, a polymicrogyria-pachygyria complex, multiple heterotopias, DWS, and brainstem malformations. Sudden infant death occurred on the third day after admission. He fulfilled the tetrad of LS. Hereby, the authors present the first case of LS outside an Arab sibship, the eighth case worldwide, and present the radiological details of DWS and complex brainstem malformations, which were previously unreported in LS.

Keywords: Brainstem, Cerebral dysgenesis, Intrauterine growth retardation, Microcephaly, Semilobar holoprosencephaly

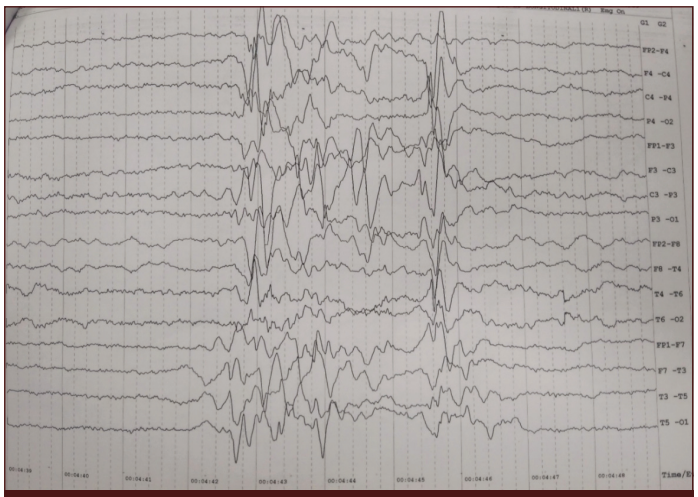
CASE REPORT

A 1.5-month-old male infant presented at the Paediatric Emergency Department with complaints of unprovoked abnormal limb movements accompanied by behavioural arrest, suggestive of pleomorphic seizures. The seizures occurred recurrently over one day, each episode lasting for 0.5 to 1 minute. His mother, a primigravida, was a non smoker and non alcoholic who had availed herself of incomplete antenatal visits. She was euglycemic, seronegative for syphilis, hepatitis, and Human Immunodeficiency Virus (HIV), and had no exposure to teratogens or exanthema during pregnancy. At 36 weeks of gestation, she had an unassisted vaginal delivery at an institution.

At birth, the baby had a New Ballard score of 30 and suffered from hypoxic-ischaemic encephalopathy (Sarnat stage I). The birth weight and Occipitofrontal Circumference (OFC) were 1.8 kg and 30 cm, respectively (below the 10th percentile of Lubchenko's chart [1], signifying IUGR. Despite exclusive breastfeeding, postnatal growth was suboptimal. At admission (42 weeks postmenstrual age), the weight, OFC, and length were recorded as 2.5 kg, 32 cm, and 48 cm (below the 3rd percentile of the Fenton chart). The inner and outer canthal distances were 3 cm and 8 cm, respectively, compared to the normal ranges of 1.5-2.33 cm and 6.26-7.74 cm (indicative of grade I hypertelorism) [2]. The fingers and great toes exhibited flexion deformities at the interphalangeal joints and hallux varus. Additionally, infant presented with generalised hypotonia and brisk tendon reflexes.

During active seizures at admission, the newborn showed signs of tachycardia (130/min) and tachypnoea (66/min) without circulatory shock.

His seizures were controlled with phenobarbitone and phenytoin injections (20 mg/kg loading doses followed by maintenance doses of 5 mg/kg/day). Soon after, an episode of apnoea with bradycardia occurred, during which he was unresponsive to tactile stimulation, necessitating continuous positive airway pressure. A burst-suppression pattern was observed in his electroencephalogram [Table/Fig-1]. The sepsis and metabolic screens, echocardiogram, and electrocardiogram were normal. The Toxoplasmosis, Other infections, Rubella, Cytomegalovirus, and Herpes simplex (TORCH) Immunoglobulin M (IgM) titers were negative.

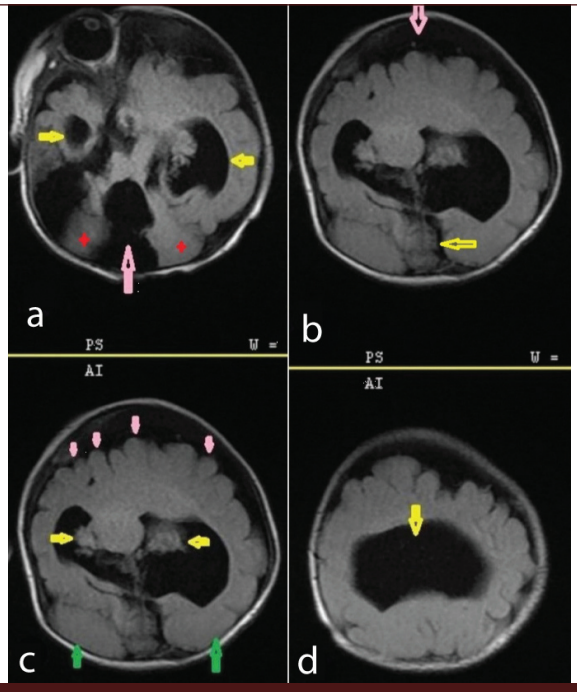


[Table/Fig-1]: A 10 second epoch in the bipolar longitudinal montage of his electroencephalogram shows burst-suppression activity, with bursts occurring over 3.5 seconds, preceded and followed by suppression of the background activity. (EEG settings: Low Frequency Filter: 1Hz- High Frequency Filter: 70 Hz, Sensitivity: 10 µV/mm, Speed 30 mm/sec, Notch filter: 50 Hz).

The brain Magnetic Resonance Imaging (MRI) revealed a single large horseshoe-shaped ventricle with some differentiation of the temporal lobes and the temporal horns of the lateral ventricles, indicating severe semilobar holoprosencephaly. The basal ganglia and thalami were fused anteriorly, with a cleft in the dorsal aspect. There was frontal polymicrogyria, occipital pachygyria,

and frontotemporal atrophy. Heterotopic gray and white matter projected into the ventricular cavity.

Additional findings included cystic dilatation of the fourth ventricle, hypoplastic vermis, and superiorly displaced cerebellar hemispheres, with the torcula situated above the lambdoid suture, suggesting Dandy-Walker Syndrome (DWS) [3]. The hypoplastic midbrain and pons exhibited concavities on their dorsal surfaces, a cleft at the ponto-mesencephalic junction, and kinking at the ponto-medullary junctions [Table/Fig-2a-d, 3a-d].

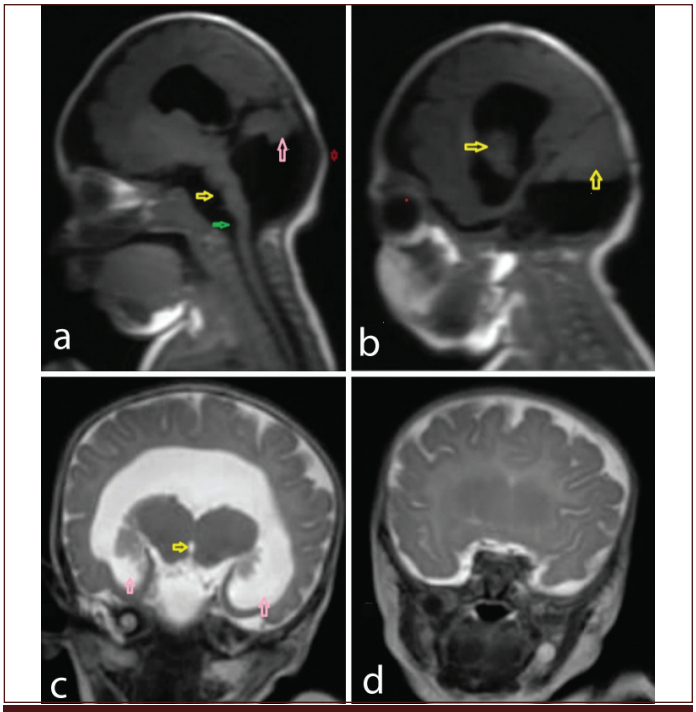


[Table/Fig-2]: Axial sections of T2FLAIR images of the MRI brain. a) It shows that the bilateral temporal horns of the ventricle are partially differentiated (marked with the horizontal yellow arrows). The posterior fossa cyst communicates with the fourth ventricle due to vermian hypoplasia, suggestive of Dandy-Walker malformation (marked with the vertical pink arrow). The cerebellar hemispheres are marked with red stars. b) Shows the single ventricular cavity with heterotopic tissues protruding into the ventricular cavity (marked with horizontal yellow arrows). Frontal polymicrogyria (marked by vertical pink arrows) and occipital pachygyria (marked with vertical green arrows) are noted. c) Shows the hypoplastic frontal areas of the brain with extra-axial fluid collection (marked with the vertical pink arrow). There is an ill-defined cleft separating the occipital lobes (marked with the horizontal yellow arrow). Grey-white differentiation is not well established. d) Shows a single horse-shaped ventricular cavity.

On the third day after admission, an episode of cardiac arrest necessitated cardiopulmonary resuscitation and mechanical ventilation; however, the subsequent arrest was fatal. The parents refused an autopsy. After excluding cardiac arrhythmias, sepsis, metabolic disorders, and toxin exposure, and ensuring a safe sleeping environment and normothermia in the intensive care unit, his early death was considered Sudden Infant Death Syndrome (SIDS). He fulfilled the tetrad of IUGR, cerebral dysgenesis, microcephaly, and early mortality [4], which constitutes Lambotte Syndrome (LS).

DISCUSSION

The index infant exhibited mild facial dysmorphism and skeletal deformities, intranatal and postnatal growth retardation, presenting with recurrent seizures due to severe semilobar holoprosencephaly, Dandy-Walker Syndrome (DWS), and complex brainstem malformations, ultimately suffering from SIDS. To date, only seven children with LS (OMIM 245552) from two Moroccan Arab families have been reported [4,5]. Verloes A et al., reported four siblings,



[Table/Fig-3]: Sagittal T1 (A and B) and coronal T2 (C and D) images of the MRI brain. a) Shows a superiorly displaced dysplastic cerebellum (marked by the vertical pink arrow). The torcula was placed above the level of the lambdoid suture (marked with a red star). There is a cleft at the ponto-mesencephalic junction (marked by the horizontal yellow arrow) and kinking at the cervico-medullary junction (marked by the horizontal green arrow). b. Shows the superiorly displaced cerebellar lobes (marked by the vertical yellow arrow) and heterotopic tissue jutting into the mono-ventricle (marked by the horizontal yellow arrow). c) Shows the partially developed temporal horns of the monoventricle (marked with the vertical pink arrows). The small cleft in the dorsal aspect of the fused basal ganglia and thalami is seen (marked with the horizontal yellow arrow). d) Shows the overmigration of white matter into gray matter, leaving a thin rim of gray mantle.

among whom one infant had semilobar holoprosencephaly [5]. An unaffected sister in this same family gave birth to a child with the disease, which was reported by Herens C et al., [6].

A translocation t(2;4)(q37.1;p16.2) was noted in the mother, suggesting a 2q/4p trisomy/monosomy in the affected children. The Deoxyribonucleic Acid (DNA) of the affected children was not available for analysis. Consanguineous mating and autosomal recessive inheritance were suspected [6]. Stillbirths or deaths within the second year following significant neurological impairments and failure to thrive have been reported in LS, as in present case.

Apart from hypertelorism, as in the index case, other dysmorphisms such as flat face, large soft pinnae, proptosis with lagophthalmos, telecanthus, squint, beaked or hooked nose, microstomia, deep grooved philtrum, and retrognathia; hypoplastic corpus callosum, external auditory meatus atresia, cardiac septal defects, radial aplasia, supernumerary vertebrae, hypoplastic ischiopubic rami, and polydactyly of the feet have also been described [5,6].

Combined prosencephalic and rhombencephalic dysgenesis is rare, as they are anatomically and developmentally distinct [3,4]. [Table/Fig-4] enumerates previously reported cases [7-11]. The present case was classified as severe semilobar holoprosencephaly, since the temporal lobes and temporal horns were somewhat differentiated, and a true interhemispheric fissure was not discernible [4]. The abnormal gyral patterns and heterotopias resulted from impaired telencephalic development following faulty

Authors name/Year of the study	Country	Sample size	Key findings
Shibuya K et al., (1991) Nayak R and Mohapatra S, (2014) [7,8]	Japan	11	3 and 8 cases with AHPC and SHPC, respectively. Co-existent anomalies: azygous anterior cerebral artery, polymicrogyria, aplastic olfactory bulb, and anterior displacement of both cerebellar hemispheres. Early deaths reported at 1.5 hours and 11 months.
McCormack WM Jr et al., (2003) [9]	America	2	One case each of AHPC and SHPC, having deletions of 13q21-q34 and 13q22-q33.
Nayak R and Mohapatra S, (2014) [8]	India	1	A nine-month-old boy with SHPC, microcephaly, generalised hypotonia, and global developmental delay.
Guvendag Guven ES (2019) [10]	Turkey	1	Antenatal diagnosis of foetus at 16 weeks six days with SHPC, asymmetric ventriculomegaly, right atrial isomerism and 69XXX.
Al-Sibahee E, (2019) [11]	Iraq	1	A 10-month-old boy having AHPC, macrocephaly, upbeating nystagmus, and generalised hypotonia.

[Table/Fig-4]: Enumeration of the 16 previously reported cases of the rare coexistence of non syndromic holoprosencephaly and DWS [7-11]. (AHPC, SHPC: Alobar and semilobar holoprosencephaly)

prosencephalic differentiation [7], leading to abnormal neuronal migration.

Patients with DWS exhibit two types of brainstem malformations; our patient displayed features of both: the mild variant, characterised by anteroposterior disproportions and hypoplasia of the brainstem structures, and the severe variant, featuring tegmental dysplasia with bumps, folds, and clefts. Patients with the severe variant had higher rates of interhemispheric cysts, massive hydrocephalus, corpus callosal dysgenesis, seizures, bulbar dysfunction, and suboptimal responses to hypoxia or hypercarbia, thereby triggering SIDS, as observed in our case [12]. In Dandy-Walker Syndrome (DWS), the cerebellar hemispheres are anterolaterally displaced, and 80-90% of cases develop hydrocephalus and macrocephaly [3]. However, the superiorly displaced cerebellum and microcephaly noted in our case are extremely rare [13]. Associations between DWS, microcephaly, and bilateral Wilms tumour have been reported in infants with variegated mosaic aneuploidy and premature centromeric division [14].

Defective common signaling molecules and regulatory genes can result in combined forebrain and hindbrain malformations [15]. Signaling molecules like Fibroblast Growth Factor (FGF)-8 and FGF-17 induce the expression of regulatory genes at two organising centres of the developing neural tube-BF1 at the anterior neural ridge and EN1 and EN2 at the isthmus rhombocephali. Ventral and dorsal patterning of the neural tube is controlled by Sonic Hedgehog (SHH), Bone Morphogenetic Protein (BMP) 4 and 7, respectively. The homeobox genes Empty Spiracles Homeobox 1 (EMX1), Empty Spiracles Homeobox 2 (EMX2), Orthodenticle Homeobox (OTX1) regulate the patterning of both the prosencephalon and mesencephalon. The deletion of a dosage-sensitive gene in the 13q22q33 region, essential for both prosencephalic and rhombencephalic development, resulted in holoprosencephaly with DWS [11].

From 35 gestational days onwards, the brain is vascularised by the proatlantic intersegmental, hypoglossal, ottic, and persistent trigeminal arteries. Although these arteries typically regress during embryonic development [15], their premature regression results in both prosencephalic and rhombencephalic vascular insufficiency, leading to their malformations [8].

CONCLUSION(S)

The present first case of Lambotte Syndrome (LS) outside an Arab sibling set exhibited mild skeletal and facial deformities in the presence of lethal prosencephalic and rhombencephalic malformations, which predisposed the infant to SIDS. If, the parents are willing, this insight will encourage clinicians to perform autopsies and genetic tests in suspected LS infants, as its morphological and genetic contexts remain unclear.

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