Title

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Journal

Pediatric Annals, 52(8)

ISSN

0090-4481

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Publication Date

2023-08-01

DOI

10.3928/19382359-20230613-02

Peer reviewed

HHS Public Access

Author manuscript

Pediatr Ann. Author manuscript; available in PMC 2024 February 20.

Published in final edited form as:

Pediatr Ann. 2023 August ; 52(8): e283–e291. doi:10.3928/19382359-20230613-02.

Acute Bowel Ischemia in a Premature Neonate with Miller-Dieker Syndrome and Anomalous Right Coronary Artery From the Pulmonary Artery

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Abstract

Miller-Dieker syndrome (MDS) is a rare disease characterized by type I lissencephaly, craniofacial dysmorphisms, intellectual disability, seizures, and death in early childhood. We report a case of a premature infant with MDS with an anomalous right coronary artery from the pulmonary artery who developed sudden bowel ischemia. This case prompts the reconsideration of cardiovascular involvement in patients with MDS. In addition, this review highlights key clinical features and reviews the critical manifestations of MDS that persist into childhood.

Miller-Dieker syndrome (MDS) is a rare genetic disorder characterized by lissencephaly ("smooth brain"), distinct craniofacial features, seizures, and early childhood death.[1] Approximately 90% of MDS cases involve a de novo microdeletion on chromosome 17p13.3 that spans several genes, contributing to the variability in associated extracranial anomalies. MDS has reported associations with congenital heart defects (CHDs) including atrial septal defects, ventricular septal defects, Tetralogy of Fallot, and double outlet right ventricle[2,3] as well as abdominal wall defects, specifically omphaloceles[4-6] (Figure 1). We

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Disclaimer: The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Disclosure: The authors have no relevant financial relationships to disclose.

report a unique case of MDS in a premature infant found to have anomalous right coronary artery from the pulmonary artery (ARCAPA) who acutely developed total bowel ischemia leading to early death. This case suggests a possible cardiovascular component of MDS that may have been previously underrecognized, prompting an updated, critical review of the literature focusing on the careful assessment of clinical features that may contribute to the early demise of these patients. This review highlights the key clinical manifestations of MDS and underlying etiologies to aid the general practitioner in managing these patients.

CASE PRESENTATION AND NEONATAL INTENSIVE CARE UNIT COURSE

A 31-week gestational age female infant was delivered via emergent cesarean delivery to a 26-year-old Gravida 2 Para 1 mother with *Escherichia coli* urosepsis who had limited prenatal care. Delivery was indicated due to fetal bradycardia with the mother receiving only one dose of betamethasone prior to delivery. A vigorous female infant was born with APGAR (appearance, pulse, grimace, activity, and respiration) scores of 8 and 8 at 1 and 5 minutes, respectively. The infant initially required continuous positive airway pressure, which was quickly weaned to high-flow nasal cannula. Her birth weight was 1,730 grams (77th percentile), length was 42 cm (79th percentile), and head circumference was 28.5 cm (66th percentile). Physical examination was notable for a small midface, thick upper lip, thin vermillion border, low set, posteriorly rotated ears, nuchal redundancy, overlapping fourth and fifth digits, anterior anus, and sacral dimple with a visible base, prompting further work-up.

Head ultrasound (US) at 31 weeks showed a nonspecific finding of lenticulostriate vasculopathy (Figure 2A). A subsequent brain magnetic resonance imaging (MRI) scan demonstrated lissencephaly and subcortical band heterotopia (Figure 2B and 2C). Video electroencephalography was without evidence of seizures. Ophthalmologic evaluation was notable for right partial and left complete retinal detachment (Figure 2D), which was surgically repaired. A sacral US revealed a tethered cord and filar cyst. The abdominal US showed bilateral small cystic kidneys and left grade 1 hydronephrosis with no other significant findings.

An echocardiogram revealed ARCAPA, which was later confirmed on a computed tomography (CT) angiogram (Figure 3A and B). Troponins were initially elevated, prompting the initiation of a prostaglandin E1 (PGE) infusion to increase the pulmonary arterial diastolic pressure by maintaining the patent ductus arteriosus (PDA) to avoid coronary steal phenomenon. However, given that the initial troponin levels were decreasing and there was no clear evidence of ischemia or myocardial dysfunction on serial electrocardiograms (ECGs) and echocardiograms, the elevated troponin levels were attributed to prenatal exposure to maternal urosepsis. Therefore, the decision was made to discontinue the PGE infusion and delay cardiac catheterization as well as surgical planning due to the infant's prematurity, small size, and overall clinical stability.

Shortly after the initiation of enteral feeds, the infant developed marked abdominal distension and intolerance of feeds, prompting bowel rest and close monitoring. Serial X-rays and an upper gastrointestinal series with small bowel follow through were reassuring,

confirming the absence of malrotation or an obstructive process. Feeds were then resumed and slowly advanced without further incident, and the initial feeding intolerance was attributed to prematurity.

At age 4 weeks old (35 weeks corrected gestational age), after 2 days of tolerating full enteral feeds, the infant precipitously developed sinus bradycardia without hemodynamic instability. Bedside ECG showed sinus bradycardia with subtle abnormalities including notched QRS complexes in leads I, II, and aVF, and upright T waves in V1 (Figure 4). An echocardiogram confirmed bradycardia and demonstrated new, moderate dilation of the right atrium and left ventricle, a moderate PDA (left to right shunt), and normal ventricular systolic function. Given the ongoing sinus bradycardia, an isoproterenol drip was started due to its properties as a nonselective beta-adrenergic agonist allowing for increased heart rate, contractility, and vasodilation of the mesenteric and renal vasculature. The patient continued to decompensate, requiring intubation and initiation of other vasoactive medications. Her abdomen became increasingly distended with worsening perfusion of the lower extremities, concerning for compartment syndrome. A bedside exploratory laparotomy revealed a grossly pale and ischemic bowel, which was noted to quickly reperfuse once exteriorized. There was no evidence of volvulus or malrotation and no apparent obstruction. During the procedure, the infant developed peaked T waves on the ECG and subsequent ventricular tachycardia with hyperkalemia (K = 8.3 mmol/L) and worsening metabolic acidosis (pH = 6.83, lactic acid = 15 mmol/L). Cardiopulmonary resuscitation was started, and she received multiple rounds of epinephrine, atropine, calcium gluconate, insulin, dextrose, and bicarbonate. However, she remained profoundly bradycardic and was unable to be resuscitated.

The autopsy demonstrated a normally sized brain with a weight of 280 g (normal mean for age = 265 g [SD = 39g])[7] and gross lissencephaly (Figure 5A and 5B). Histological studies revealed a 4-layer cortex with a diffuse agyric cerebral hemisphere but an adequately developed cerebellum and brainstem, consistent with MDS. ARCAPA was confirmed on gross assessment of the heart and coronaries (Figure 3C). The bowel was noted to have diffuse submucosal edema with no pneumatosis or necrosis, with confirmed presence of submucosal and intramuscular ganglion cells. Genetic testing confirmed 46XX with a deletion in 17p13.3 obtained via fluorescence *in situ* hybridization (FISH).

KEY FEATURES OF MDS

Lissencephaly

The defining feature of MDS is type I or “classical” lissencephaly resulting from the global failure of neuronal migration during fetal brain development. This disruption results in a smooth cerebral surface, a thick and disorganized cortex with only four primitive layers (normally six), diffuse neuronal heterotopia, hypoplasia of the corpus callosum, and enlarged, dysmorphic ventricles.[8] This is distinct from type II lissencephaly, characterized by a “cobblestone” surface believed to be due to basement membrane interruptions at the pial surface, causing neurons to migrate beyond the cortex resulting in a nodular-appearing cortex.[9,10]

In type I lissencephaly, the cerebellum is typically preserved, whereas type II lissencephaly presents with a dysplastic cerebellum.[11] Type I lissencephaly can be further broken down into four distinct grades. Grade 1, the most severe, results in complete agyria and is characteristic of MDS. Grades 2 and 3, seen in isolated lissencephaly sequence (ILS), are characterized by agyria-pachygyria, and grade 4 is defined solely by pachygyria or incomplete formation of the gyri resulting in abnormal convolutions of the cortex.[12] Differentiating features of ILS and MDS are highlighted in Table 1.

Neurodevelopment and Seizures

Patients with MDS are typically hypotonic in the neonatal period but often go on to develop hypertonicity. By age 1 year, 90% of patients with MDS have seizures.[13] Despite treatment with multiple antiepileptics, up to two-thirds of children will continue to have daily seizures.[14] For infants with the broader category of *LIS1*-related disorders, which include MDS, developmental milestones between ages 6 and 12 months are rarely achieved.[14]

Ocular Manifestations

Retinal abnormalities have traditionally been associated with type II lissencephaly, which tends to have more severe ocular abnormalities. Nonetheless, there have been several case series reported that suggest that ocular findings may be more common in type I lissencephaly than previously described.[15,16] Our patient was diagnosed with bilateral retinal detachment, which has not been reported in association with Miller-Dieker syndrome. Notably, several cases have been reported describing associations of type I lissencephaly and retinal dysplasia, peripheral proliferative retinopathy, and tortuous retinal vessels, which suggests there may be greater retinal and ocular manifestations in type 1 lissencephaly than previously understood.[16,17]

Feeding Difficulties

Neonates with MDS have generalized hypotonia with poor head control, impacting the coordination of suck-swallow-breathe capabilities. The spasticity and intractable seizures that develop within the first year of life further compound already disorganized eating patterns and a limited ability to protect the airway, leading to an overall increase in aspiration events, apneas, bradycardic events, oxygen desaturations, and failure to thrive. Babies with MDS often require gastrostomy tube placement to provide adequate nutrition and decrease aspiration risk, a common cause of early childhood death in MDS.[12] A previous report of an extremely low birth weight premature infant with MDS described the development of intestinal pseudoobstruction that required surgical intervention after periods of intermittent abdominal distension and intolerance to feeds.[18]

Gastrointestinal Manifestations of MDS

Omphaloceles are abdominal wall defects that have previously been reported in several cases of MDS. Omphaloceles occur when there is a persistent herniation of the fetal intestines into the umbilicus beyond the 6 to 10 weeks gestation, when this normally occurs. This period has some overlap with postmitotic neuronal cell migration (beginning at 8 weeks gestational age and continuing through 20 weeks[9]) that is impaired in MDS, suggesting the possibility

of a gene or multiple genes within the 17p13.3 chromosome involved in the regulation and/or coordination of the closure of the lateral folds or the return of the midgut back into the abdomen.[4] In addition, omphaloceles are highly associated with CHDs, occurring in approximately 32% of patients with omphalocele.[19] This association may be due to the parallel development of the fetal heart and gut and the possibility of regulatory signaling genes present within the 17p13.3 chromosome.

Cardiovascular Considerations

MDS has been associated with several CHDs, including atrial septal defects, ventricular septal defects, double outlet right ventricle, and Tetralogy of Fallot.[2] However, coronary anomalies have not been previously reported. ARCAPA is an extremely rare CHD, occurring in 1 to 2 in 1,000 live births.[20] This number, however, may be underestimated given that many patients remain asymptomatic, delaying diagnosis.[21] Approximately 40% of patients with ARCAPA have myocardial ischemia[22] and an increased risk of sudden cardiac death. The exact mechanism by which ARCAPA becomes symptomatic or leads to sudden death remains unclear but is believed to be driven by the direction of the flow in the anomalous coronary artery, the extent of coronary artery collateralization, coronary arterial dominance, and vasospasm activity.[23] Furthermore, the right coronary artery (RCA) supplies the atrioventricular and sinus nodes. Thus, the presence of ARCAPA can impair adequate blood flow and the function of these pacemaker nodes, potentially resulting in bradycardia, sudden cardiac death, or both.[24]

ETIOLOGY AND PATHOGENESIS OF MDS

Approximately 90% of MDS cases are caused by a de novo contiguous gene deletion of chromosome 17p13.3,[25] typically greater than 250 kilobases,[26] and involving *PAFAH1B1* (*LIS1*) and *YWHAE*. Other causes of MDS include a ring chromosome and inheritance of an unbalanced parental translocation. Chromosome 17 has the second highest gene density among humans and has many low-copy repeats on the short arm, making it ripe for genomic instability.[25] The *PAFAH1B1* and *YWHAE* genes play essential roles in regulating neuronal migration. *PAFAH1B1* encodes platelet-activating factor acetyl-hydrolase, which is thought to play a vital role in coordinating brain development. *YWHAE* encodes a microtubule-associated protein and is located 1 megabase away from *PAFAH1B1*.[27] The additional deletion of *YWHAE* is believed to add to the severity of the lissencephaly in MDS, differentiating it from ILS.[28] In addition, microdeletions in *YWHAE* are associated with facial dysmorphisms and growth restriction.[29] Several other genes in an MDS critical telomeric region are implicated in the phenotype, including *CRK*.[26,30] *CRK* is involved in cytoskeletal organization during cell migration and may also play a role in modulating both the severity of craniofacial dysmorphisms and lissencephaly in MDS.[26]

DIAGNOSIS OF MDS

Prenatal Diagnosis

The most common prenatal US findings in MDS are polyhydramnios, symmetric intrauterine growth restriction, and mild ventriculomegaly.[31] Isolated mild ventriculomegaly

can be the first sign of abnormal brain maturation. A targeted US evaluating fetal sulcal development, with close attention to the Sylvian fissure, can aid in diagnosing lissencephaly as early as 23 weeks gestation.[32] It is crucial to remember that examination of the fetal cerebral cortex is not part of routine anatomic surveys and often may be missed if not explicitly assessed.[32] Based on prenatal findings, a concern for MDS should prompt a fetal MRI in the third trimester, which can aid in detecting lissencephaly. Genetic evaluation with amniocentesis or chorionic villus sampling can also provide confirmatory diagnosis of MDS prenatally, but is not without risk.

Postnatal Diagnosis

MDS should remain on the differential for any infant with craniofacial anomalies, an abnormal head US, or seizures of unclear etiology. In a premature neonate, lissencephaly can only be reliably diagnosed postnatally on MRI.[33] Other nonspecific symptoms of MDS in the neonatal period include hypotonia and feeding difficulties. Diagnosing MDS in a premature neonate can be challenging, as craniofacial anomalies may be subtle and complex. Furthermore, feeding difficulties are nonspecific and frequently encountered in the premature population.

Genetics

Although 90% of cases of MDS are attributable to de novo microdeletions on chromosome 17p13.3, MDS can also rarely be the result of a ring chromosome (1 in 50-100,000 patients with MDS) or can be inherited from a parent with an unbalanced translocation.[34] Thus, after the diagnosis of MDS is confirmed, both parents of an affected person should have a karyotype and FISH analysis sent. If it is inherited because of an unbalanced translocation, the risk of recurrence is approximately 25%. If MDS occurs because of a de novo mutation, the risk of recurrence is <1%.[35]

In our patient, genetic testing via FISH confirmed MDS. However, there are reports in the literature of small deletions on *LIS1* that have been missed on FISH.[36] Therefore, in a patient presenting with lissencephaly, in the absence of a high suspicion for a single gene disorder, a chromosomal microarray is the initial recommended genetic test of choice.[33,37]

PROGNOSIS AND MANAGEMENT CONSIDERATIONS

Few patients with MDS survive beyond the first decade of life. Life expectancy is correlated to the severity of lissencephaly.[38] Improvements in supportive care (eg, the ability to place gastronomy tubes and new antiepileptics) may modulate the life expectancy of patients with MDS over time.[12,38] Potential gene therapies are currently being studied but are far from clinical translatability.[39]

Current MDS therapies focus on managing symptoms, particularly intractable seizures, feeding difficulties, and developmental delays. The close monitoring of seizures and effective antiepileptic treatment is essential in allowing patients with MDS to reach their developmental potential and improve their quality of life. Early in the disease course, some evidence suggests seizures are best managed similarly to infantile spasms with vigabatrin, adrenocorticotropic hormone, and steroids.[14] As the seizure type evolves, lamotrigine and

valproic acid used together for synergy may be beneficial.[14] Aspiration risk should also be routinely assessed, and growth closely monitored.

MDS patients should be cared for by a multidisciplinary team composed of neurologists, geneticists, developmental and general pediatricians, dieticians, physical and occupational therapists, ophthalmologists, and audiologists, with prompt referral to early intervention services.[33] Families should be referred to community resources as well as palliative and respite care if desired.[40] In addition, families should consider an individualized educational plan, enrollment in the developmental disabilities administration, and application for supplemental security income.[40]

Causes of Death

Among patients with MDS, the most frequent cause of death is sepsis secondary to aspiration pneumonia.[41] Our patient, however, developed acute bowel ischemia resulting in reperfusion injury with subsequent hyperkalemia causing dysrhythmias leading to her death. This event occurred quickly and was preceded by the sudden onset of sinus bradycardia with normal perfusion and blood pressures. Given the incidental finding of ARCAPA, we hypothesized that the bradycardia may have been a manifestation of several factors including a potentially malperfused sinus node and a chronic but subtle myocardial ischemia.

ARCAPA: IT'S ALL IN THE DETAILS

Anomalous left coronary artery from the pulmonary artery, as opposed to ARCAPA, frequently presents with ischemia and heart failure and has a 90% mortality rate if left untreated in the first year of life.[42] ARCAPA may remain asymptomatic in childhood because of the RCA's relatively smaller perfusion area, which includes the right side of the heart (including the sinoatrial node), left atrium, and posterior portion of the left ventricle.[43] The presentation of ARCAPA depends on many factors, the most important of which is the degree of collateral blood flow between the RCA and left coronary artery. If the RCA has its origin in the pulmonary artery, as the transition from fetal to neonatal circulation occurs the pressure in the pulmonary artery drops, causing hypoperfusion of the RCA, leading to the development of collaterals between the high-pressure left coronary artery and the low-pressure RCA. Coronary steal can lead to left ventricular ischemia and signs of left heart failure on echocardiogram, including left ventricular hypertrophy.[44] This coronary steal phenomenon would likely be blunted in the setting of a PDA. A review of the literature suggests that infants with ARCAPA can have subtle ischemic changes detected on ECG,[45] ischemic changes detected only on exertion (ie, crying) as opposed to at rest,[46] as well as echocardiographic findings consistent with left ventricular posterior wall ischemia[22] and left ventricular dilatation and wall motion abnormalities.[47]

Our patient's ECG on the day of her death (Figure 4) shows several abnormalities, including QRS notching in leads I, II, and aVF, and upright T waves in V1. QRS notching, or a fragmented QRS, is associated with developing myocardial scar.[48] In a neonate in the first 2 to 3 days after birth, T waves in the right precordial leads are typically upright, and then transition to becoming inverted within the first week of life.[49] Our patient's upright T waves at age 5 weeks, although nonspecific, are certainly abnormal. Finally, the echocardiogram on

the day of her death demonstrated new dilatation of the left atrium and left ventricle, which may suggest a developing scar from an ischemic process related to her underlying ARCAPA.

Her prolonged bradycardia likely resulted in inadequate perfusion of the gut, causing ischemia. During the exploratory laparotomy, as the bowel was exteriorized and reperfused, there was likely significant washout of lactic acid and potassium, contributing to her worsening acidosis and ultimately causing an unstable dysrhythmia. This reperfusion injury and resulting hyperkalemia in the setting of her MDS and ARCAPA potentially causing subclinical manifestations of myocardial and nodal injury likely led to the sudden cardiopulmonary failure from which she was unable to be resuscitated.

CONCLUSION

This case highlights an unusual presentation of MDS in a premature infant. MDS is an extremely rare disease with an overall poor prognosis associated with intractable seizures and early childhood death. Therefore, timely diagnosis driven by clinical suspicion is crucial to providing appropriate counseling, involving key subspecialties, and initiating critical services and therapies.

Unfortunately, diagnosis is often delayed and does not occur until patients present with developmental delays and seizures between the ages of 3 and 12 months. Diagnosis in premature infants can be particularly challenging, given that hypotonia and feedign difficulties are common in prematurity, which may lower the level of suspicion for disorders such as MDS, and may delay further evaluation.

Finally, this is the first reported association of ARCAPA and MDS in the literature. The diagnosis of ARCAPA can be difficult to make and often requires repeat imaging with multiple modalities. Patients with MDS should be screened carefully for CHD, and if there is any suspicion for ARCAPA a CT angiogram or MRI angiogram should be considered.

Acknowledgment:

The authors thank the following people from the University of California Davis Children’s Hospital: Dr. Arzu Ozturk for assistance in analyzing the neuroradiology imaging and putting together the figures; Dr. Jason Tovar and Dr. Jiejun Wu for assistance with obtaining and analyzing the pathology specimens; Dr. Kristin Herman for input on her experience with patients with Miller-Dieker syndrome; and neonatologists Dr. Lee Donohue and Dr. Lida Zenali, pediatric surgeon Dr. Jonathan Kohler, and cardiologist Dr. Jay Yeh for their excellent clinical care of the patient.

Grant

This work was supported by the National Center for Advancing Translational Sciences of the National Institutes of Health (NIH) grant (UL1 TR001860, KL2 TR001859).

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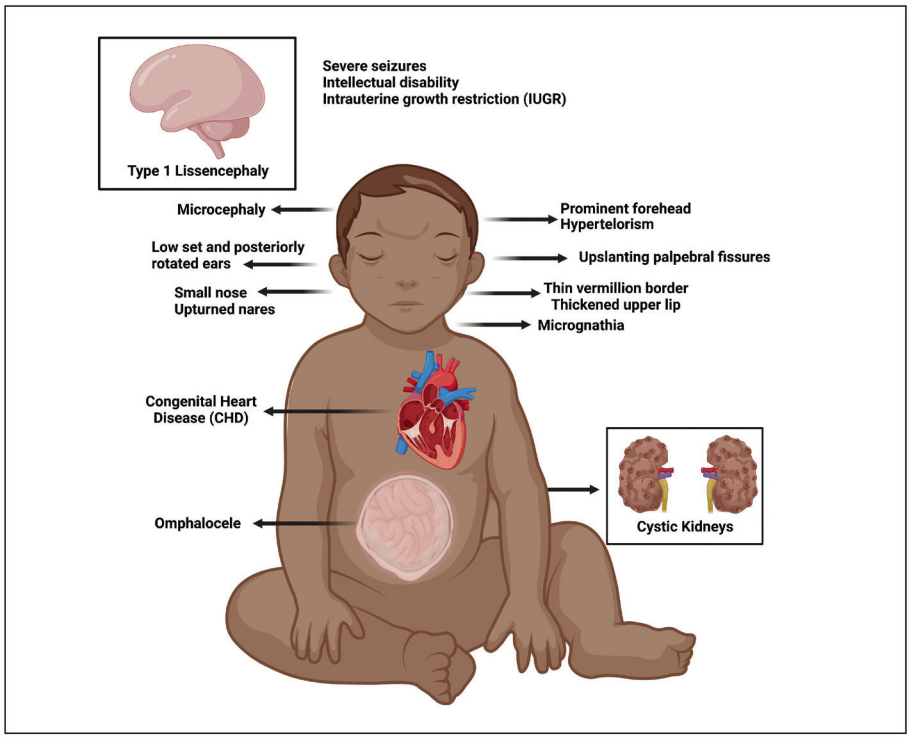

Figure 1.

Key physical features and findings associated with Miller-Dieker syndrome, which is primarily distinguished by type I lissencephaly and dysmorphic facies. Created with Biorender.com.

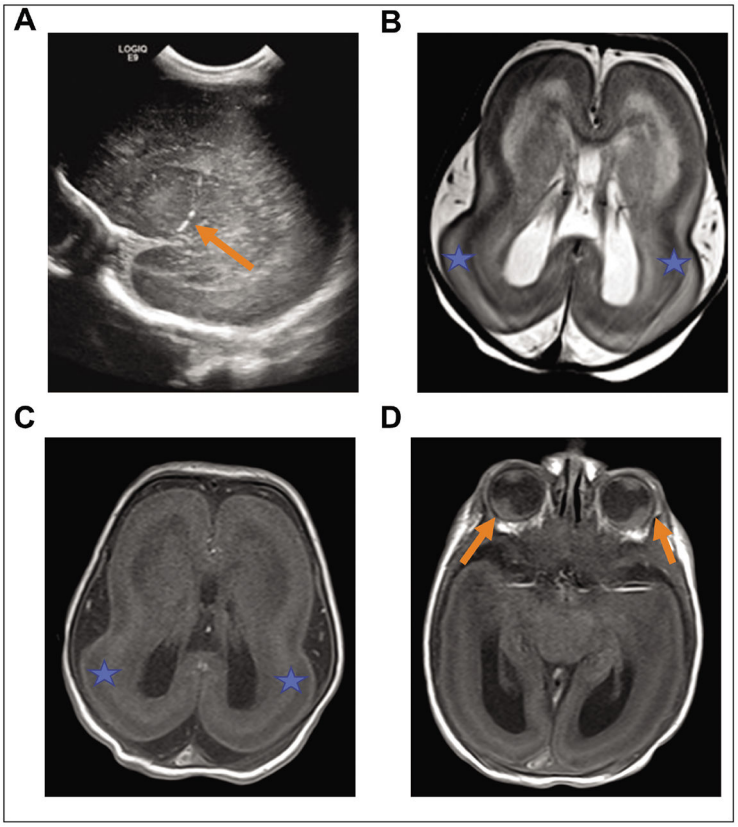

Figure 2.

Neuroradiographic anomalies. (A) Left sagittal head ultrasound demonstrating nonspecific lenticulostriate vasculopathy (arrow). (B) Axial T1-weighted and (C)T2-weighted MRI of brain show lissencephaly, a few shallow sulci, (B and C) shallow Sylvian fissures with hourglass appearance and subcortical band heterotopia (stars). (D) Retinal detachments bilaterally also noted (arrows).

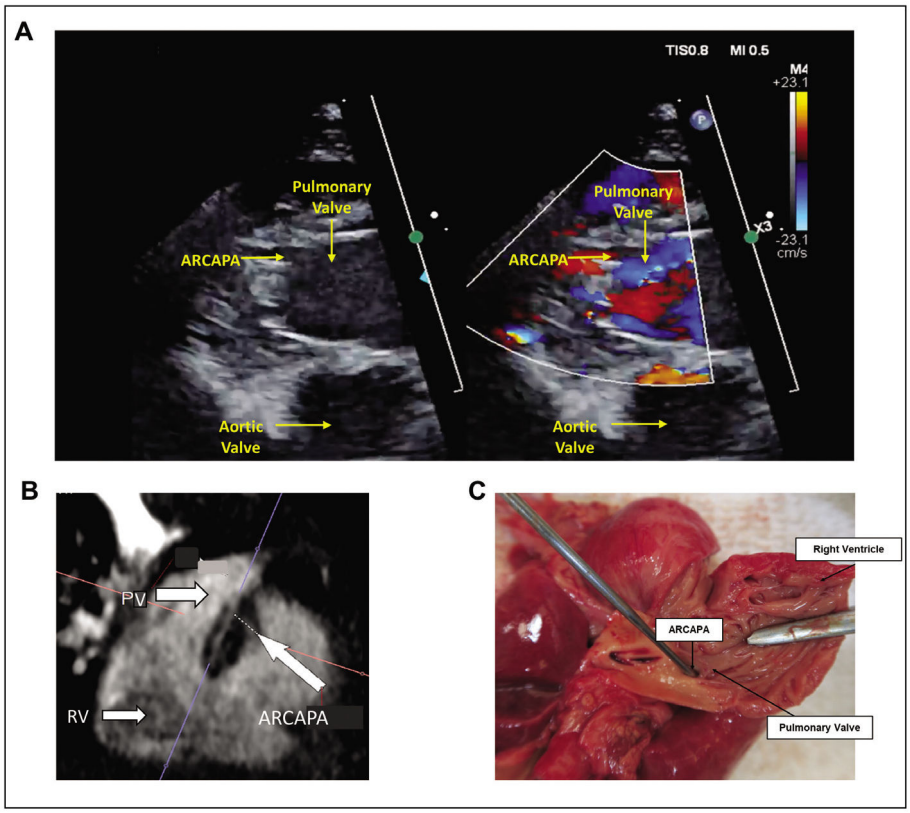

Figure 3.

ARCAPA (anomalous right coronary artery from the pulmonary artery) identified on multiple imaging modalities. (A) Short axis echocardiographic images of the pulmonary and aortic valve en face demonstrating ARCAPA arising from the right sinus of the pulmonary valve. (B) Coronal computed tomography image with the RV and PV with the ARCAPA (arrows) and (C) autopsy image with the RV, PV, and a probe in the ARCAPA (arrows). ARCAPA, anomalous right coronary artery from the pulmonary artery; PV, pulmonary valve; RV, right ventricle.

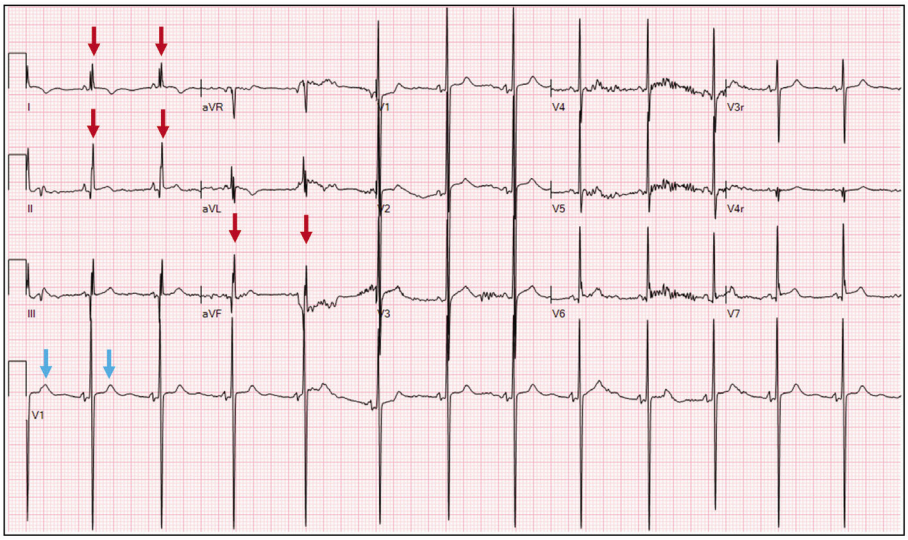

Figure 4.

Electrocardiogram on the day of death demonstrating sinus bradycardia with heart rate of 76 beats per minute. There are notched QRS complexes in leads I, II, and aVF (red arrows) and upright T waves in lead V1 (blue arrows). aVL, augmented vector left; aVR, augmented vector right; aVF, augmented vector foot.

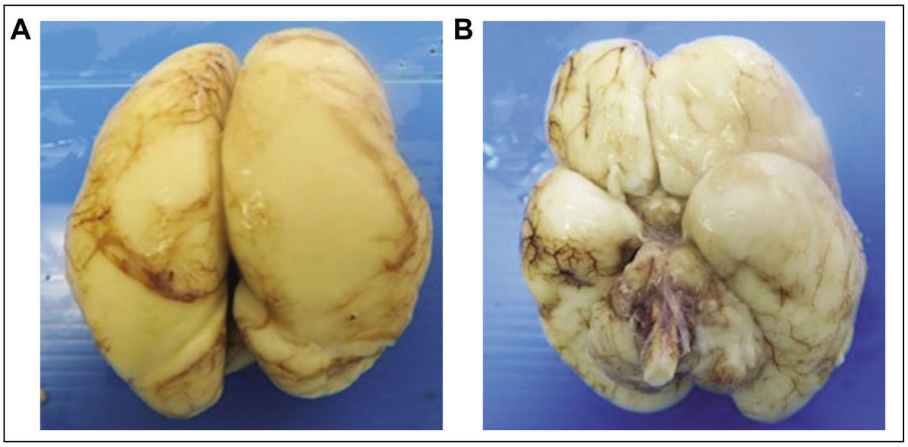

Figure 5.
Autopsy showing (A) superior and (B) inferior views of brain demonstrating gross lissencephaly.

TABLE 1

Variants of Type I Lissencephaly and Differentiating Features

Category	**Isolated lissencephaly sequence**	**Miller-Dieker syndrome**
Key features	Lissencephaly (grades 2-4) Developmental delay Intellectual disability Seizures	Lissencephaly (grade 1) Developmental delay Intellectual disability Seizures Microcephaly Micrognathia Craniofacial dysmorphisms Polyhydramnios
Distinguishing anomalies	Less severe form of classic lissencephaly (grades 2-4)	Abnormal tone Cardiac defects Omphalocele Cystic kidneys Polydactyly
Genetics	Smaller deletion in chromosome 17p13.3 (*LIS1*/polyhydroxyalkanoate) Heterozygous mutation or deletion of *PAFAH1B1*	Contiguous larger gene deletion of 17p13.3 Includes de novo microdeletions in *PAFAH1B1, YWHAE*, and *CRK*