Case Report
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Lodder–Merla Syndrome, a Multisystemic Disorder: Perioperative Anesthetic Management of an Infant

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Abstract

Objective. This paper aims to present the perioperative anesthetic challenges in an infant with Lodder–Merla syndrome. **Case Report.** We present a case report of a 7-month-old infant with Lodder–Merla syndrome, a pacemaker, epileptic spasms, and severe reflux, who was scheduled for open gastrostomy and gastrojejunal tube insertion. Such an intervention would constitute a second consecutive procedure under general anesthesia, shortly after pacemaker implantation. Perioperatively, emphasis was given to maintaining respiratory and cardiac stability, avoiding drugs with parasympathomimetic effects, preventing aspiration, optimizing ventilation, and controlling seizures. **Conclusion.** Since Lodder–Merla syndrome affects many organs, perioperative multidisciplinary collaboration and optimization of the affected systems are fundamental.

Key Words: Lodder-Merla ▪ Sick Sinus Disease ▪ Child.

Introduction

Lodder-Merla syndrome type 1 (OMIM® genetic database 617173) is a very rare autosomal recessive multisystem disorder caused by mutations in the GNB5 gene (15q21.2). The first cases were described in 2016 (1), and only 41 cases have been reported until 2021 (2). The GNB5-related neurodevelopmental disorder (GNB5-NDD) is characterized by a spectrum of neurodevelopmental phenotypes. A specific feature is bradycardia caused by sinoatrial node dysfunction (sick sinus disease). Most individuals also present with profound cognitive disorders, epileptic encephalopathy, visual impairment, feeding difficulties, hypotonia, hyporeflexia, and gastroesophageal reflux disease. The risk of early mortality is higher. Management should be tailored to individual needs and requires a multidisciplinary team approach, including pediatricians, pediatric cardiologists, neurologists, speech therapists, orthopedists, and physical medicine and rehabilitation specialists (2).

We present the anesthetic management of an infant with Lodder-Merla syndrome type 1 undergoing open gastrostomy for impaired feeding (severe gastroesophageal reflux disease).

Case Description

The 7-month-old male infant (5 months corrected age), weighing 6 kg, was scheduled for gastrostomy because of poor thriving due to severe gastroesophageal reflux. The infant was born prematurely at 32 + 6 weeks of gestation (1670 g) from a primigravida mother after an emergency Caesarean section prompted by a pathological non-stress test. The Apgar score was 5 at 1 minute and 9 at 5 minutes. Immediately after birth, the neonate required respiratory support, initially with nasal continuous positive airway pressure, followed by high-flow nasal cannula oxygen therapy due to episodes

of apnea and desaturation. From day one of life, the infant presented with episodes of severe sinus bradycardia that were confirmed by Holter monitoring and cardiological consultation. From the first month of life, the child also developed epileptic seizures that initially required antiepileptic treatment with oral levetiracetam. However, due to poor control, oral valproic acid and vigabatrin had to be added. Oral prednisolone was also administered to treat possible neuroinflammation of the brain. Genetic testing revealed a mutation in the GNB5 gene, and a diagnosis of Lodder–Merla syndrome was confirmed at 2 months of age. Due to the progression of bradycardia (Figure 1), a permanent epicardial pacemaker was placed on the right ventricle at three months of age (41 days corrected age).

The procedure involved a partial median sternotomy and was performed by a specialized team of cardiac surgeons and anesthesiologists. The body weight at that time was 3.7 kg. On arrival to the theatre, the infant was stable with good vitals and breathing spontaneously with a face mask (oxygen, 4 L/min). Prior to induction, intravenous (IV) atropine (0.02 mg/kg) was administered, followed by IV propofol (3 mg/kg), cisatracurium (0.2 mg/kg), and fentanyl (1.5 microg/kg). After ventilation with a mask, orotracheal intubation (with an endotracheal tube (ETT) of 4 internal diameter (ID), uncuffed, Portex®) was successful. Two 24G iv peripheral veins and a right radial arterial catheter were secured. Sevoflurane was used for maintenance, while higher doses of fentanyl (10 microg/kg) were required for analgesia. For ventilation, volume control mode was preferred with tidal volumes of 7 ml/kg, with positive end–expiratory pressure (PEEP) of 4 cmH2O and FiO_2 titrated accordingly, aiming for SpO_2 values above 98%. A total of 20 ml/kg of balanced crystalloids with 1.5% dextrose was administered. No inotropic agents were required. The procedure was uneventful and lasted for one hour and twenty-five minutes. The infant was hemodynamically stable and transferred to the cardiac intensive care unit (ICU). The following day, the infant was extubated, and the chest drain was removed. After a brief stay, the patient was transferred back to the neonatal high-dependency unit and received oxygen via a high-flow nasal cannula (25%, 5 L/min).

At 7 months of age (5 months corrected age), an open gastrostomy procedure (Open Stamm gastrostomy modification) was scheduled for nutritional support because of poor weight gain and impaired feeding despite nasogastric tube (NGT) feeding with a special formula at a rate of 80 ml per 24 hours. Preoperatively, a meeting that involved all relevant specialists was organized, with emphasis placed on the potential risks arising from airway management, aspiration, pacemaker dysfunction, difficult ventilation, cardiac instability, uncontrolled seizures, and prolonged postoperative mechanical ventilation. It was decided to insert a gastrojejunal feeding tube through the gastrostomy site to temporarily bypass the stomach and manage reflux without performing a more invasive antireflux procedure.

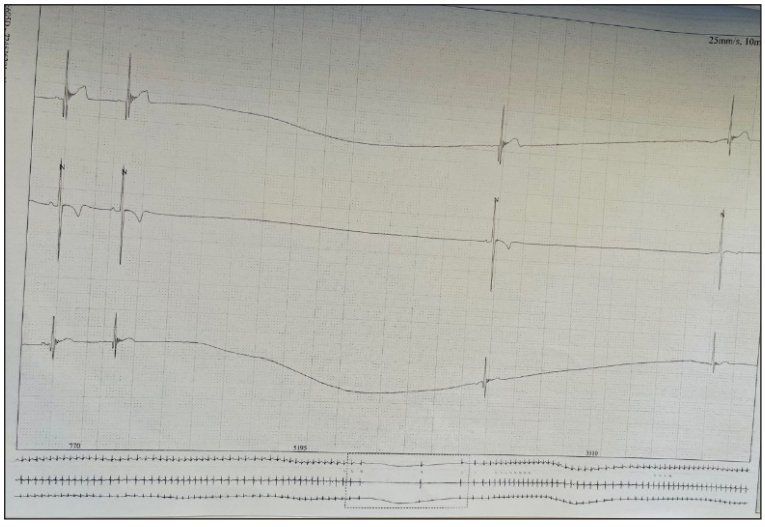

Figure 1. The last 24-hour Holter before pacemaker implantation: Detection of three sinus pauses lasting more than 3 seconds.

Medical treatment included vitamin D, omeprazole, levetiracetam, valproic acid, vigabatrin, and carnitine. Examination of the pacemaker showed good function, in VVI mode with an HR of 100 bpm. IV

hydrocortisone was also administered as a tapering scheme for previous prednisolone therapy.

Prior to surgery, the infant was in the neonatal high-dependency unit, spontaneously breathing on a simple O2 face mask (4 L/min), with a SpO2 of 96 – 97% and an HR of 100 – 120 bpm. Laboratory test results were within the normal range for age. NGT feeding was stopped 6 hours prior to surgery, and IV maintenance fluid administration was initiated. Antiepileptics were continued via the intravenous route (except Sabril, which is only available in oral form; therefore, it was stopped perioperatively).

After preoxygenation, rapid sequence induction with IV propofol (3 mg/kg), fentanyl (1.5 microg/kg), and rocuronium (1 mg/kg) was followed by orotracheal intubation (with an ETT of 4 ID, uncuffed, Portex®). Two IV peripheral lines were secured. In addition to standard monitoring, we added Pulse CO-Oximetry to noninvasively monitor Hb continuously (Masimo®) and a Train of Four (TOF) monitor (NMT Pediatric Mechanosensor, General Electric®). Sevoflurane and remifentanil infusion (0.1μg/kg/min) were used for maintenance. For ventilation, pressure control mode was preferred, aiming at tidal volumes of 6 – 8 ml/kg, with PEEP of 4 cmH2O and FiO2 titrated accordingly, aiming for SpO2 values above 98%. The surgical wound was infiltrated with ropivacaine 0.1% (1 mg/kg), and IV dexamethasone (0.15 mg/kg) and IV paracetamol (10 mg/kg) were also administered. Bipolar cauterization was preferred for surgical electrocautery. The procedure was uneventful and lasted for 40 minutes. After the completion of surgery, the TOF ratio was 0.7, and sugammadex (2mg/kg) was administered. Extubation was successful when TOF was >0.9. After completing the required time in a post-anesthesia care unit, the infant was transferred to a neonatal ICU with O2 by face mask (4L/min). Enteral feeding was initiated on the fourth postoperative day. Overall, the postoperative period was stable, with gradual weaning from oxygen. After forty days, the child was discharged home. Six months after pacemaker implantation, a routine follow-up confirmed proper function. However, readmissions due to poorly controlled seizures were noted.

Discussion

GNB5-NDD is a very rare multisystem disorder characterized by a spectrum of neurodevelopmental phenotypes (intellectual disability, language disorder, attention–deficit/hyperactivity disorder, and autism spectrum disorder) and bradycardia. Other features include epileptic encephalopathy with focal seizures or epileptic spasms, visual impairment (central or retinal) with nystagmus, difficulty in feeding, hypotonia, hyporeflexia, and gastroesophageal reflux disease (1, 2). In our case, the infant had symptomatic sinus bradycardia, poorly controlled epileptic seizures, and severe gastroesophageal reflux. Bradycardia due to sick sinus syndrome is the most common arrhythmia in Lodder-Merla syndrome, and it may be present with apnea and cyanosis or may be asymptomatic. In animal models, the GNB5 protein is crucial for the parasympathetic control of heart rate (3).

Parasympathomimetics should therefore be used with extreme caution because of the potential to cause asystole, at least until a pacemaker has been inserted, and access to emergent pacing is desirable. Drugs that can potentiate bradycardia, particularly beta-blockers, high-dose synthetic opioids, and alpha2 agonists, should be avoided (2). In our case, we preferred to use rocuronium to be able to administer sugammadex for the reversal of neuromuscular blockade instead of neostigmine (even if the latter is always administered in combination with atropine); therefore, TOF monitoring was mandatory.

Until 2021, only six children had been reported to have undergone pacemaker implantation, and only two cases required long-term gastrostomy (2, 4). An anesthetic plan was not documented in any of the reported cases. This is the first documented perioperative management of an infant who underwent two consequent operations (pacemaker insertion and gastrostomy). Regarding surgical electrocautery, due to the proximity of the surgical area and the heart, bipolar cauterization

was favored over monopolar to reduce the risk of interference with the pacemaker's function. Cardiologists had suggested that an isoprenaline infusion should be readily available at a dose of 0.1 – 0.5 microgram/kg/min, in case of pacemaker failure. In the case of uncontrolled seizures, IV midazolam was recommended.

Conclusion

Lodder–Merla syndrome presents significant perioperative challenges due to various associated risks. The involvement of multiple systems, along with the limited available literature, requires a comprehensive plan that includes the participation of all relevant specialties. Therefore, it is crucial to optimize all affected systems. Ensuring cardiorespiratory stability is essential, as is preventing aspiration, securing adequate ventilation, implementing multimodal analgesia, avoiding pharmacologic agents presenting parasympathomimetic effects, and controlling seizures.

What Is Already Known on This Topic:
Lodder-Merla syndrome is a very rare autosomal recessive multisystem disorder that was first described in 2016. Until 2021, only 41 cases have been reported. To the best of our knowledge, there is no documentation regarding the perioperative anesthetic management of such patients.

What This Study Adds:
This is the first case of an infant who underwent two surgeries under general anesthesia within a short time interval, with documented perioperative anesthetic management. The scarcity of data and multisystem presentation necessitate an organized perioperative anesthetic plan in which the collaboration of relevant specialties and optimization of the affected systems are essential.

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Authors' Contributions: Conception and design: EA, EG, SG, DT and EG; Acquisition, analysis and interpretation of data: EA and EG; Drafting the article: EA and EG; Revising it critically for important intellectual content: EA, EG, SG, DT and EG; Approved final version of the manuscript: EA, EG, SG, DT and EG.

Conflict of Interest: The authors declare no conflict of interest.

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