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CLINICAL SERIES

Prenatal diagnosis and early neonatal management of patients with hypoplastic left heart syndrome: experience of a perinatal center

Diagnóstico prenatal y manejo neonatal precoz de pacientes con Síndrome de corazón izquierdo hipoplásico: experiencia de un centro perinatal

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What do we know about the subject matter of this study?

HLHS represents 2-3% of all congenital heart diseases and, without surgical treatment, it has a fatal outcome. Morbidity and mortality are high, with a 50-57% survival rate at 5 years of age. There are few national reports on neonatal management.

What does this study contribute to what is already known?

This study shows our experience in the prenatal and neonatal management of patients with HLHS, who require hemodynamic and ventilatory support to maintain adequate conditions for surgery.

Abstract

Hypoplastic Left Heart Syndrome (HLHS) is the most common form of functional single-ventricle heart disease. Despite improvements in medical and surgical care, morbidity and mortality remain high, especially around the first surgical stage. **Objective:** To describe the clinical characteristics of newborns with HLHS, seen at a perinatal referral center. **Patients and Method:** Retrospective descriptive study of all newborns with pre and/or postnatal diagnosis of HLHS between 2014 and 2019 in the *Complejo Asistencial Dr. Sótero del Rio*. Medical records were reviewed collecting demographic and perinatal variables, clinical evolution, mortality associated with the first surgery, and survival at

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one year. **Results:** Nineteen patients were included. Most were term newborns and 13/19 were female. All had a prenatal diagnosis. Five patients had associated extracardiac anomalies. 16/19 required vasoactive drugs and 17/19 used invasive mechanical ventilation. Seven patients received enteral feeding, without episodes of enterocolitis. The median age at transfer for surgery was 8 days. Thirteen patients underwent the Norwood procedure, with 31% of mortality, and 47% of survival at one year. **Conclusions:** Neonatal management of patients with HLHS is complex and the multidisciplinary approach is fundamental. Mortality around the first surgical stage of our cohort is greater than the international reports which could be influenced by the absence of fetal therapy and the higher incidence of extracardiac malformations.

Introduction

Heart defects are the most frequent congenital anomalies, with an incidence of 4-10 per 1,000 live births[1,2]. In Chile, mortality due to congenital heart disease is the second leading cause of death in children under 1 year of age and accounts for one-third of deaths due to congenital anomalies[2]. The prenatal diagnosis of complex heart malformations has significantly modified their prognosis.

Hypoplastic left heart syndrome (HLHS) is composed of a spectrum of complex congenital heart diseases characterized by abnormal development of the left heart structures, presenting as a common factor the left ventricle unable to sustain the systemic circulation[4-7]. They maintain an adequate atrioventricular and ventriculoarterial concordance, as well as an intact ventricular septum. It is frequently accompanied by different degrees of hypoplasia of the mitral and aortic valves and aortic arch[4-7]. It is the most common form of single ventricle, accounting for 2-3% of all congenital heart disease[2,7]. Without a surgical correction, its course is fatal, with a 95% of mortality rate before one month of life[7,8].

During the last 40 years, there have been multiple medical and surgical advances that have significantly improved the survival of these patients[7]. Since 1983, 3 surgical stages have been described. The first one is carried out during the neonatal period, and it is the most lethal (10-30%) and has three alternatives: 1) Norwood procedure with modified Blalock-Taussig Shunt, 2) Norwood procedure with Sano conduit or 3) a hybrid procedure (pulmonary artery cerclage and ductal stenting)[7,8,9]. The second stage corresponds to Glenn anastomosis, which is performed at 4-6 months of life and has a perioperative mortality rate between 2 and 5%[7,8,9]. The last stage is the Fontan procedure, where the cavopulmonary anastomosis is completed and is performed around 3-4 years of age, with a mortality rate of 3-5%[7,8,9]. Despite these advances, survival of these patients does not exceed 50-57% at 5 years of age[9,10].

In their first days of life, patients require strict monitoring of the delicate balance between pulmonary and systemic flow[7,8]. After the physiological decrease in pulmonary vascular resistance, pulmonary flow increases, which, depending on its level, can cause permanent damage to the vasculature and secondary systemic hypoperfusion[7,8]. Neonatal management before the first surgical stage is based on the maintenance of ductal patency using prostaglandin E1 (PGE1) and early recognition of signs of pulmonary hyperflow with systemic hypoperfusion[7,8].

There are several strategies to increase pulmonary vascular resistance and thus regulate the amount of pulmonary circulation, including sedation, invasive mechanical ventilation (IMV) with high positive end-expiratory pressure (PEEP), low respiratory rates, and eventual use of gas mixing to decrease the fraction of inspired oxygen below 21%[7,8]. To maintain adequate oxygen delivery to the tissues, it is necessary to optimize blood volume and maintain a high hematocrit[7,8]. These patients may also require inotropic support[7,8].

Since 1991, the *Complejo Asistencial Dr. Sótero del Río* (CASR) has developed a congenital heart disease management program[11]. It is a perinatal referral center for patients with congenital heart defects (CHD) diagnosed in the fetal and/or neonatal period from the Health Services of Iquique, Maule, Reloncaví, Chiloé and the Southeast Metropolitan Health Service. The patients have several prenatal evaluations at CASR, diagnosis is confirm and complete prenatal studies when is needed. The patients are born in our center, where the neonate is studied and stabilized, and then referred to the *Hospital Clínico de la Pontificia Universidad Católica* (HCUC) for the first stage of surgery. Subsequently, follow-up continues at their respective hospital and the remaining surgical stages are evaluated and performed at the HCUC.

Considering the medical and surgical management complexity of patients with this heart disease, it is important to know the characteristics of the patients from the moment of prenatal diagnosis, the neonatal and postoperative evolution of the first surgery, in order to

evaluate, as a whole, possible aspects to improve the quality of care and to provide parents with more information about this pathology.

The objective of this study is to describe the perinatal and demographic characteristics, preoperative neonatal evolution, mortality of the first surgery and survival at one year of life of patients with HLHS treated in the Obstetrics-Gynecology and Neonatology Unit of the CASR during the last 5 years. The focus of this study is on fetal diagnosis and evaluation, obstetric aspects and management only during the neonatal period until the first surgery.

Patients and Method

Descriptive study of a retrospective cohort of patients diagnosed with HLHS born at CASR between January 2014 and January 2019. We included all carriers of hypoplastic left ventricle with atrioventricular and ventriculoarterial concordance and intact septum, with prenatal diagnosis of HLHS and postnatal confirmation, and those who only had postnatal diagnosis, without exclusions.

To obtain prenatal data, the electronic record of ultrasound scans (Viewpoint software) and the genetic database (CytoGenetics Laboratory) were reviewed. The clinical records of the mothers were reviewed to obtain data on delivery, invasive studies, or procedures performed during pregnancy. In the case of newborns (NB, sacar), data were obtained from the clinical record during hospitalization and outpatient records, as well as demographic data, echocardiographic records, brain ultrasound, the study of associated malformations and pre-surgical neonatal hospital evolution, age at referral to the HCUC for surgery, type of surgery, and associated mortality.

Numerical variables were described as median, interquartile range (IQR), and categorical variables were expressed as fractions.

The study was approved by the Research Ethics Committee of the Southeast Metropolitan Health Service.

Results

Nineteen patients with HLHS were included. Table 1 describes demographic data. From a total of 9 cesarean births, 7/9 patients were elective C-sections due to maternal or fetal obstetric indication (3 previous cesarean scar, 2 fetal dystocia, 1 presence of fetal heart disease and 1 severe IUGR plus oligohydramnios), and 2/9 corresponded to an emergency cesarean. Two patients had a birth weight below 2,500 grams.

Out of a total number of newborns, 15/19 had a normal karyotype test (pre and/or postnatal), and in 4 no test was performed. The FISH or MLPA study of chromosome 22q11 was performed postnatally in 11/19 patients and 1 prenatally, none of them presented microdeletion. Within the study of other malformations, only one case presented central nervous system alteration (corpus callosum agenesis) in the brain ultrasound. Abdominal ultrasound was performed in 7 patients, of which 6 were normal and 1 case presented right pelvic kidney dysplasia. As a resume 5/19 (26%) of the newborns presented extracardiac malformations. Table 1 describes the associated extracardiac malformations in this 5 cases. SACAR and the cardiac variants. Two patients had clinical and echocardiographic signs of anomalous pulmonary venous return obstruction secondary to a restrictive atrial septal defect. Six patients had a diminutive ascending aorta defined by a diameter equal to or less than 2 mm.

Table 2 describes the neonatal evolution before the first surgery. All patients received PGE1, initiated during the first day of life. Vasoactive drug support (VAD) was required in 16/19 patients, determined by hypotension (9/16), signs of systemic hypoperfusion (4/16), persistent pulmonary hypertension secondary to congenital diaphragmatic hernia and sepsis (1/16), and congestive heart failure (1/16). Regarding ventilatory support, 17/19 required IMV, which was initiated from the first hours of life until 8 days of age. The causes of requirement IMV were persistent desaturation, apneas, respiratory distress, signs of heart failure, respiratory depression secondary to sedation and for managing pulmonary hyperflow.

All patients received parenteral nutrition. Before surgery, enteral stimulation was started in 7 patients, with a median start at 4 days of life (range 2-8 days). There were no cases of necrotizing enterocolitis.

The median age at referral for surgical correction was 8 days (range 4-8 days). Figure 1 shows the surgical evolution and mortality. 5/19 patients could not undergo the first surgery, 2 cases due to pulmonary venous return obstruction, one case due to kidney dysplasia, one due to right congenital diaphragmatic hernia, and the last one due to microcephaly and low birth weight. In addition, before the first surgical stage, one patient died due to refractory septic shock. There was a 32% rate of pre-surgical mortality.

Out of the 13 patients who underwent the first surgery (Norwood-Sano surgery), 1 died within the first 30 days after surgery (1 day after surgery while on ECMO) and 3 died after 30 days and before the second surgery. The first surgery presented 31% of mortality. After the first surgery, 2 patients could not undergo the next surgery, one patient due to septo-optic dysplasia that developed with significant neurological compro-

mise, who had not died at the time of the study, and a second patient with biliary atresia, who died 30 days after the Norwood-Sano surgery.

8 patients underwent Glenn surgery (42%) and 4 patients completed total cavopulmonary anastomosis (21%). In this series, there was 47% of survival at one year of life.

Discussion

HLHS represents a diagnostic and therapeutic challenge that requires specialists in Obstetrics (Maternal Fetal Medicine), neonatology, pediatric cardiology and heart surgery, highlighting the importance of multidisciplinary work and the coordination of the different specialties involved in the management of patients with this pathology. This clinical series reinforces the fact that patients diagnosed with HLHS continue to present high morbidity and mortality despite advances in surgical and medical techniques[10].

Prenatal detection depends on the availability of ultrasound equipment, training, and appropriate referral to specialists[12]. Currently, prenatal diagnosis of fetal congenital heart defects performed by an experienced specialist is 90-100%[3]. However, access to this test is limited in many countries, which decreases the screening range to 12-75% depending on the health characteristics of the country[1]. Today, most pregnant women have a general obstetric ultrasound that includes the evaluation of all four cardiac chambers[3]. In this retrospective cohort, all patients had a prenatal diagnosis, which may result from the fact that our institution is a referral center for congenital heart disease in the perinatal period for some regions of our country.

Prenatal detection of HLHS is important for eventual fetal management, family and genetic counseling, and optimizing postnatal management[5,8]. Currently, at the international level, there are fetal therapy alternatives (intrauterine Rashkind balloon atrial septostomy) with variable outcomes, which have not been developed in our country[5]. Prenatal diagnosis allows multidisciplinary coordination so that these patients are born in a center with experience in the management of this pathology, allowing optimization of the preoperative neonatal condition, reducing morbidity and mortality[5,8]. It has been reported that patients with a prenatal diagnosis of HLHS have a lower incidence of heart and other organ failures, less connection to IMV, use of antimicrobials, need for vasoactive support, and emergency surgery than postnatal diagnosis[12].

Approximately 20% of cases of congenital heart disease present chromosomal abnormalities[13]. Although most cases are sporadic, there are associations with some genetic syndromes such as Turner syndrome and

Table 1. Demographic, clinical characteristics and cardiac anatomical variants

Characteristics	n = 19
Male, n	6
Region of origin, n	
Metropolitana	12
X	3
VII	4
Prenatal diagnosis, n	19
Gestational age at prenatal diagnosis, weeks, median (IQR)	31 (27.7-34.5)
Gestational age at birth, weeks, median (IQR)	38 (37-38)
Birth weight, g, median (IQR)	2,925 (2,625-3,363)
Vaginal delivery, n	10
Apgar 1 min, median (IQR)	8 (2-9)
Apgar 5 min, median (IQR)	8 (4-9)
Extracardiac malformations, n	
Total	5
CDH	1
Neurologic	2
Microcephaly	1
Septo-optic displasia	1
Functional monorail	1
Bile duct atresia*	1
Cardiac anatomical variants, n	
Mitral Stenosis – Aortic Stenosis	6
Mitral Stenosis – Aortic Atresia	3
Mitral Atresia – Aortic Stenosis	1
Mitral Atresia – Aortic Atresia	9

IQR: interquartile range, CDH: congenital diaphragmatic hernia.
*Diagnosis made after Norwood-Sano surgery.

Table 2. Treatments received in the Neonatology Unit prior to transfer for surgery

Treatments	
Vasoactive drugs, n	16 (16/19)
Dopamine	8 (8/16)
Epinephrine	3 (3/16)
Dopamine + Epinephrine	3 (3/16)
Dobutamine	1 (1/16)
Epinephrine + Milrinone	1 (1/16)
Prostaglandin, n	19 (19/19)
Invasive Mechanical Ventilation, n	17 (17/19)
Median age at transfer to surgical correction (IQR)	8 (58-11)

IQR: interquartile range

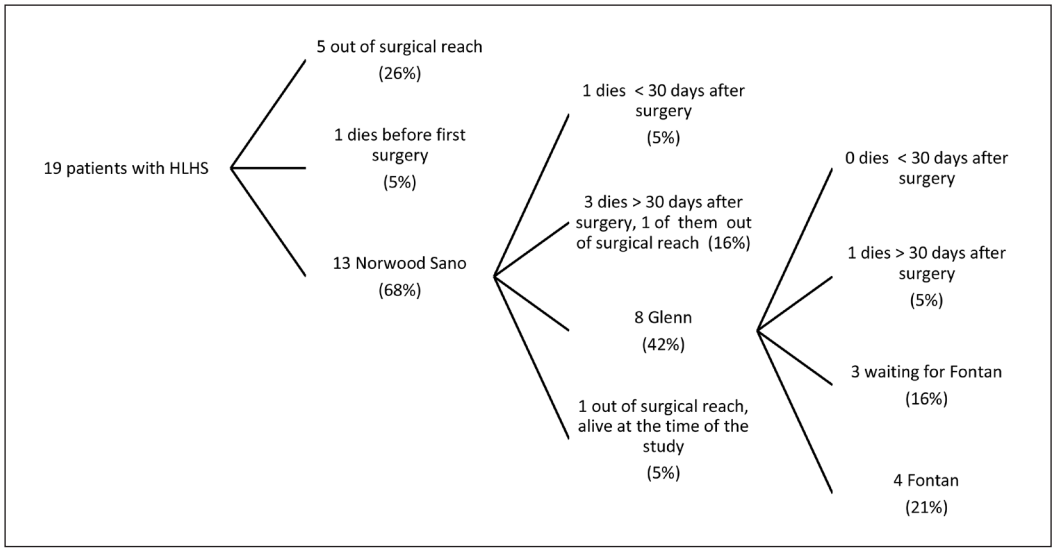

Figure 1. Surgical stages and associated fatality. Note: Percentage in relation to the total number of patients.

Trisomy 13 and 18[5]. Prenatal genetic evaluation is very important as it helps to determine prognosis and postnatal surgical possibility. In our hospital, prenatal genetic diagnosis is offered to all patients pregnant with fetuses with this pathology, but not all parents agree to it due to the risks of amniocentesis.

The association with extracardiac malformations in this cohort was higher than that published in the international literature (26% vs 6%)[14]. The reason for this observation may be that, in other countries, this pathology is a cause of voluntary termination of pregnancy, meaning that patients are born without other associated malformations.

Regarding the route of delivery, the data reported by large international series do not demonstrate benefits in patients born by elective cesarean section versus vaginal delivery[15]. Peterson et al.[15] reported a retrospective analysis of patients with a prenatal diagnosis of HLHS, comparing neonatal outcomes according to the route of delivery. They conclude that patients born by elective cesarean section have a lower gestational age and lower pH cord blood gas. It has been postulated that this is because the elective cesarean section has negative effects on extrauterine pulmonary adaptation, affecting cardiac output[15]. Analysis of this cohort regarding the route of delivery shows that the cesarean section rate was slightly higher compared with national data in public hospitals (47% vs. 37%)[16,17]. When analyzing the reasons for the indications for cesarean section, in only one of the mothers there was no justified obstetric cause. The protocol for delivery of fetuses with HLHS is ideally at 39 weeks of gestation, a gestational age associated with lower morbidity and better neonatal outcomes[18].

Regarding neonatal management before the first surgery, the current trend is to minimize invasive procedures. If the patient remains stable, a certain degree of pulmonary hyperflow should be tolerated as long as there are no signs of systemic hypoperfusion[7,8]. In this study, the rate of connection to IMV was high (89%) compared with that described in the literature (70%), and in only 41% of cases, the reason for connection to IMV was the management of pulmonary hyperflow with systemic hypoperfusion[19]. The use of VAD in our center was 84% which is comparable to that reported in the literature (30-88%)[19,20,21,22]. To initiate VAD in these patients, signs of inadequate systemic perfusion (such as oliguria, metabolic acidosis, hyperlactatemia, among others) should be considered in addition to the presence or absence of hypotension[22].

The initiation of enteral stimulation is highly variable between centers, ranging between 56% and 93% of patients[23]. There are few published reports on the safety and tolerance of enteral stimulation in patients with ductal-dependent heart disease. It is usually postponed mainly because of the risk of necrotizing enterocolitis (NEC), sacrificing the known benefits of breastfeeding (BF)[24]. Day et al.[24] evaluated patients with ductal-dependent congenital heart disease and the suspected NEC rate was 10% (n = 18) with only 2 confirmed cases[24]. Another retrospective study by Toms et al.[25] concluded that trophic stimulation can be safe, well-tolerated, and even have better postoperative outcomes, with fewer days of IMV and hospital stay[25]. At present, no evidence contraindicates the initiation of enteral feeding in patients with HLHS, especially if BF is available, although it seems safe to do so only in stable patients and with small volumes. In our institu-

tion, the initiation of trophic enteral feeding (prioritizing breast milk over formula) is performed only in patients without signs of systemic hypoperfusion. In this series, 6 patients received enteral stimulation, with no evidence of NEC episodes.

Although cardiac surgery has improved overall survival, neurodevelopmental sequelae are still prevalent[26], presenting around 30-60% of neurological alterations[26]. Factors contributing to this are the time of hypoxia since the fetal period, the use of extracorporeal circulation and hypothermic circulatory arrest during surgery, multiple surgeries, prolonged hospital stays, and genetic conditioning variables in addition to socioeconomic factors[26]. In our opinion, it is important to create a formal multidisciplinary follow-up program involving all subspecialties for the comprehensive management of the patient, with new strategies such as telemedicine. The latter considering that the patients are from different cities of the country and continue their follow-up in their respective hospitals, in order to know their long-term evolution.

In this series, survival at one year of life is lower than that described in the national literature, probably because we included those cases that did not qualify for surgery. The experience reported in the national literature is the result published in 2016 of 76 patients with HLHS treated at the HCUC between 2000 and 2010. In this report, they describe 64% of survival at one year and 57% at 5 years of life[9].

Regarding the mortality of the first surgical stage, our study shows a higher percentage than that described in the literature (31% v/s 16- 20%)[27,28]. This could be due to several factors, among which may be the lack of availability of fetal therapy, the higher incidence of extracardiac malformations than international series and the need for referral to another hospital center. Another factor to note is that isolated major congenital heart disease is not among the pathologies included in the law on voluntary termination of pregnancy in our country, in contrast to European data showing pregnancy termination rates due to prenatal congenital heart disease of 31-57%[29,30].

In recent years, there have been efforts to identify patients at higher risk of morbidity and mortality. Tabutt et al.[31] identified as high-risk factors those patients with low birth weight, carriers of genetic anomalies, and those who required ECMO or had a cardiorespiratory arrest before the first surgery[31]. In the national report of the HCUC, they established the presence of a diminutive ascending aorta and anomalous pulmonary venous return obstruction as a high-risk factor for mortality[9]. In our series, of all the patients who died during follow-up, only one did not have any of the risk factors described.

One of the main limitations of this report is the small sample size. However, we consider it important to know the local reality in order to improve the management and eventually the prognosis of our patients, in addition to describing the results of a center at the local level.

Conclusion

Multidisciplinary work and coordination of the different specialties (obstetrics, neonatology, pediatric cardiology and heart surgery) are essential in newborns with HLHS. Neonatal management is complex and should be focused on maintaining a balance between pulmonary and systemic circulation, in order to optimize the conditions in which patients reach their first surgical stage[32]. The mortality around the first surgical stage in our retrospective cohort is higher than international reports, which could be explained in part by the lack of availability of fetal therapy, the higher incidence of extracardiac malformations, and the need for referral to another hospital center.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: This study was approved by the respective Research Ethics Committee, which, according to the study's characteristics, has accepted the non-use of Informed Consent.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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