ORIGINAL ARTICLE

Clinical Presentation and Outcome of Right Isomerism

Presentación clínica y evolución del isomerismo derecho

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ABSTRACT

Background: Right isomerism is one of the most complex forms of congenital heart disease. Recent advances in medical treatment and surgical procedures have allowed addressing the management of these patients. Nevertheless, the prognosis remains uncertain or unsatisfactory.
Objective: The aim of this study was to report the clinical characteristics, management and outcomes of right isomerism in our hospital population.
Methods: This was a retrospective cohort design study conducted at Hospital Nacional de Pediatría "Prof. Dr. Juan P. Garrahan". Between 1997 and 2011, 72 patients with median follow-up of 5.1 years (1 and 26 years) were identified.
Results: In 91.7% of cases, patients were in the neonatal period, 66 patients with cyanosis and 6 patients with heart failure.
The most frequent anatomic lesions were: common AV valve (n=56), pulmonary obstruction (n=67), ventriculoarterial discordance (n=44) and double outlet right ventricle (n=27), commom atrium (n=25), bilateral superior vena cava without innominate vein (n=30), total anomalous pulmonary venous return (APVR) (n=43) and asplenia (n=53).
Extracardiac lesions were detected in 11 patients.
Cardiovascular surgery was indicated in 76.38% of cases: The maximum stage achieved was palliative surgery in 14 patients, Glenn procedure in 17 patients, subpulmonary ventricular bypass (PVBP) in 23 patients and one and a half ventricular correction in 1 patient.
Overall mortality was 39.45% (n=28). Mortality for the different palliative procedures was 29%, for the Glenn stage, 29% and for PVBP, 21.76%.
In the univariate analysis, a significant association was found between mortality and infradiaphragmatic APVR (p=0.02). Glenn stage mortality was related to bilateral Glenn procedure (p=0.04), whereas no related cause was identified for PVBP.
In the single ventricle stages of surgery, 3 patients developed pulmonary vein stenosis,4 patients developed aortopulmonary collaterals, and 2 patients progressed to AV regurgitation.
Conclusions: The majority of cases presented in the neonatal period and with cyanosis characteristics. In right isomerism, single ventricle physiology is predominant. Extracardiac anomalies were detected in 15% of cases. Mortality of non-surgical and palliative procedure cases was associated with infradiaphragmatic APVR. Glenn stage mortality was related to bilateral procedures. Only one third of patients could reach PVBP. Events in Glennand PVBP midterm follow-up are frequent.

Key words: Dextrocardia - Heterotaxy Syndrome - Heart Defects, Congenital

RESUMEN

Introducción: El dextroisomerismo es una de las formas más complejas de cardiopatías congénitas. Los avances en el tratamiento médico y en los procedimientos quirúrgicos de los últimos años han permitido encarar el manejo de estos pacientes, no obstante lo cual el pronóstico sigue siendo incierto o poco satisfactorio.
Objetivo: Comunicar las características clínicas, conductas y resultados del dextroisomerismo en nuestra población hospitalaria.
Material y métodos: Estudio de diseño de cohorte retrospectivo realizado en el Hospital Nacional de Pediatría "Prof. Dr. Juan P. Garrahan". Entre 1997 y 2011se identificaron 72 pacientes con una mediana de seguimiento de 5,1años (rango 1-26 años).
Resultados: En el 91,7%la presentación fue neonatal, 66 pacientes con cianosis y 6 con insuficiencia cardíaca.
Las características anatómicas más frecuentes fueron válvula AV común (n=56), obstrucción pulmonar (n=67), conexión ventriculoarterial discordante (n=44) y tipo doble salida (n=27), aurícula única (n=25), vena cava superior bilateral sin innominada (n=30), anomalía total del retorno venoso pulmonar (ARVP) (n=43), asplenia (n= 53).
Se detectaron anomalías extracardíacas en 11 pacientes.

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Hospital Nacional de Pediatría "Prof. Dr. Juan P. Garrahan"
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Al 76,38% se les indicó tratamiento quirúrgico, el estadio máximo alcanzado fue la cirugía paliativa en 14 pacientes, Glenn en 17, bypass de ventrículo subpulmonar (BPVP) en 23 y cirugía tipo ventrículo uno y medio en 1 paciente.
La mortalidad global fue del 39,45% (n=28); para los diferentes procedimientos paliativos fue del 29%, para el estadio de Glenn del 29% y para el BPVP, del 21,76%.
En el análisis univariado, la mortalidad asociada con ARVP infradiafragmática fue significativa (p = 0,02). Para el estadio de Glenn la mortalidad se relacionó con el Glenn bilateral (p = 0,04), mientras que para el BPVP no se identificó una causa determinada.
En los estadios de la cirugía univentricular desarrollaron estenosis de venas pulmonares 3 pacientes, colaterales aortopulmonares 4 pacientes y progresión a insuficiencia AV grave 2 pacientes.
Conclusiones: En la mayoría, la edad de presentación fue neonatal y con clínica de cianosis. En el dextroisomerismo, la fisiología univentricular es predominante. Se detectó un 15%de anomalías extracardíacas. La mortalidad de los pacientes no quirúrgicos y con cirugía paliativa estuvo asociada con ARVP infradiafragmática. En el estadio de Glenn, la mortalidad se relacionó con el tipo bilateral. Solamente un tercio de los pacientes pudieron alcanzar el estadio de BPVP. Los eventos en el seguimiento a mediano plazo en los pacientes en los estadios de Glenn y BPVP son frecuentes.

Palabras clave: Dextrocardia - Síndrome de heterotaxia - Cardiopatías congénitas

Abbreviations

APVR	Anomalous pulmonary venous return	**PVBP**	Pulmonary ventricular bypass
AV	Atrioventricular		

INTRODUCTION

Heterotaxy syndrome is considered one of the most complex heart diseases. Its incidence is of 1 in 5000/7000 live births with heart disease. (1)

Right and left isomerisms are characterized by a wide variety of cardiac and extracardiac malformations originating from an alteration of the left-right axial rotation during the early stage of embryonic development.

The anatomic features of dextroisomerism are the presence of situs ambiguous abdominal manifestations, complex heart diseases, atrioventricular (AV) defects such as single ventricle anomalies, and splenic anomalies, usually asplenia. Pulmonary venous return is usually abnormal and considered normal in cases where the pulmonary veins drain independently into the left atrium.

Recent advances in medical treatment and surgical procedures have allowed addressing the management of these complex patients. However, the prognosis still remains uncertain or unsatisfactory because the syndrome is associated with a combination of complex heart disorders.

The aim of this study was to report the clinical characteristics and outcome of right isomerism in our hospital population.

METHODS

This was a retrospective cohort design study including 72 consecutive patients with right isomerism who attended the Hospital Nacional de Pediatría "Prof. Dr. Juan P. Garrahan", between 1997 and 2011, with median follow-up of 5.1 years (1 to 26 years).

The geographic distribution of patients is shown in Figure 1; 62.5% corresponded to the Central and Littoral zone, 12.5% to the Northwestern zone and 8.3% to the zone of Cuyo.

All patients were evaluated at our institution by physical examination, electrocardiogram, pulse oximetry, teleradiography of the thorax, transthoracic color Doppler echocardiography, abdominal ultrasound, cardiac catheterization and lately with multislice computed tomography.

The diagnosis of right atrial isomerism was based on radiographic findings of the bronchial pattern andposition of the liver; juxtaposition of the abdominal aorta and inferior vena cava and spleen anomalies were revealed with abdominal ultrasound, and the sequential segmental analysis and description of complex heart diseases (Figure 2) was performed with transthoracic color Doppler echocardiography; and subsequently confirmed by catheterization or multislice

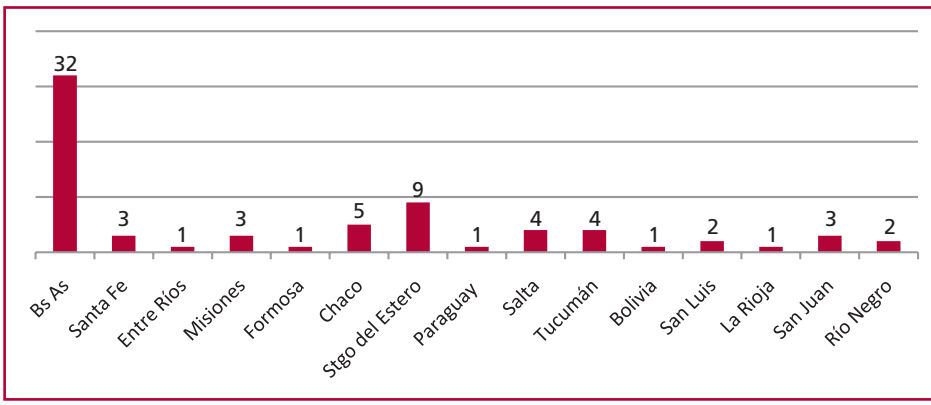

Fig. 1. Patient origin

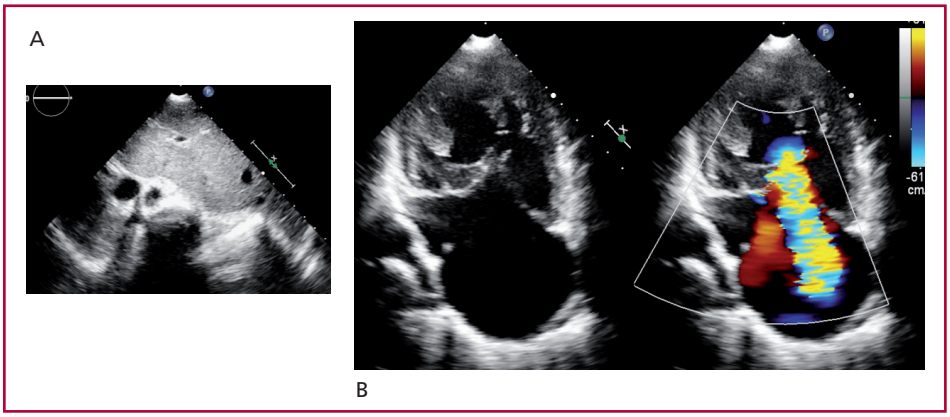

Fig. 2. Color Doppler echocardiography. **A.** Situs ambiguous, liver in bar to the left. **B.** Single atrium, common atrioventricular valve, unbalanced atrioventricular canal, severe atrioventricular valve regurgitation.

computed tomography scan and with the direct visualization in surgery or anatomic pathology.

Statistical analysis

Microsoft Office Excel 2003 was used to record data. The statistical analysis was performed with Statistix 8.0 software package.

Frequency and/or percentage distribution in relation to the total number of cases was established for all variables, and accordingly, values were expressed as ratios, mean and standard deviation or median. Fisher's exact test or the chi-square test was used for ratios. A p value of <0.05 was considered statistically significant.

Ethical considerations

The protocol was reviewed and approved by the Institutional Ethical Board

RESULTS

Clinical characteristics

In 91.7% of patients clinical manifestation occurred in the neonatal period, cyanosis being the main form in 66 patients, while only 6 patients presented symptoms of heart failure.

Anatomical characteristics

In the sequential segmental analysis the most frequent findings were: situs ambiguous abdominal manifestation in 54 patients, situs inversus in 12, situs solitus in 6, levocardia in 50 and dextrocardia in 20, common AV valve atrioventricular connection in 56 and with single AV valve in 5; pulmonary flow obstruction in 67 (pulmonary stenosis in 42 and pulmonary atresia in 25); aortic coarctation in 2; double outlet ventriculoarterial connection in 27 and transposition in 44; single atrium in 25, single superior vena cava in 25 and bilateral vena cava without innominate vein in 30 patients.

Pulmonary venous return was anomalous in 45 patients, total in 43 patients (supracardiac in 22, cardiac in 11, infradiaphragmatic in 7, and mixed in 3) and partial in 2; in the remaining 27 patients pulmonary venous return was normal and two of them had pulmonary vein stenosis. Obstructive anomalous pulmonary venous return (APVR) was described in 14 cases (31%).

Hepatic veins were normal in 65patients.

Asplenia was present in 53 patients, and hypoplastic spleen in one case. Liver in bar was described in 52 patients.

Extracardiac anomalies

Extracardiac anomalieswere detected in 11 patients (15%), tracheoesophageal fistula in 2, intestinal atresia in1, skeletal malformations in 2, alveolopalatal fissure in 1, macrocephaly in 2, genetic syndrome (chromosome 22q 11 deletion) in 1, maturation delay in 1 and hypothyroidism in 1 patient.

Cardiovascular surgery indications

Surgical treatment was indicated in 76.38% of cases (55/72) and 23.6% was considered without surgical possibilities. Single ventricle pathway was indicated in 54 patients and only 1 patient reached one and a half ventricular correction.

Without surgical treatment

Fifteen patients were not considered surgical candidates (22.2%), 14 of whom had total APVR (infradiaphragmatic 5, supracardiac 3, cardiac 4, and mixed 2), which was obstructive in 9 cases. The other causes that conditioned the indication were diverse; among those registered in medical histories are: pulmonary hypertension crisis, aortic arch interruption, pulmonary branch hypoplasia, very low weight, multiple aortopulmonary collaterals, neurological damage and delayed referral.

Of these untreated patients, 12 died at a mean age of 7 days and 3 patients returned to their place of origin with unverified outcome.

Two patients were not submitted to surgical procedures: one patient referred at 12 years with natural cardiac disease progression, with single ventricle physiology and poor lung anatomy, with moderate to severe AV regurgitation and another who at 18 months was candidate for a Glenn anastomosis, did

not attend the surgical appointment and was lost to follow-up.

Palliative procedures

Patients identified with palliative surgery were 14, 7 of whom had APVR (supracardiac 3, infracardiac 1, cardiac 2 and mixed 1).

Systemic pulmonary anastomosis was performed in 10 patients, repair of an anomalous systemic-pulmonary anastomosis in 3 patients and pulmonary artery banding in 1 patient.

Five patients died during the immediate postoperative procedure while 8 patients were lost to follow-up.

Single ventricle pathway

Forty patients were considered candidates for single ventricle pathway.

Glenn

Glenn stage was reached at a mean age of 15 monthsin 17 patients and 5 patients (29%) died in the immediate postoperative period.

The 5 patients who died in the immediate postoperative period underwent bilateral Glenn procedure (p=0.04). The causes of immediate postoperative mortality were low cardiac output, multiple organ failure, development of pulmonary vein stenosis in mixed APVR and ischemic involvement due to multiple left dominant coronary stenosis in 1 patient (Table 1).

Of the 12 patients who survived, 4 had contraindication for complete total subpulmonary ventricular bypass (PVBP) due to development of pulmonary vein stenosis in 2 patients, poor lung anatomy and severe AV valve in 1 patient and pulmonary hypertension and high end diastolic pressure in another. There were 4 patients lost to follow-up and the remaining 4 patients are awaiting PVBP.

Subpulmonary ventricular bypass

The stage of subpulmonary ventricular bypass was reached by 23 patients, at a mean age of 58 months, with an immediate postoperative mortality of 21.76% (n=6).

The causes of immediate postoperative mortality were multifactorial: upper limit pressures, anatomical difficulty (heart tip at the same side as the inferior vena cava), development of pulmonary vein stenosis and aortopulmonary collaterals, among others (Table 2).

Remote events were frequent and occurred in 13 patients (72%), arrhythmias in 5 patients (4 patients with paroxysmal supraventricular tachycardia, and 1

Table 1. Characteristics of deceased patients in the immediate postoperative Glenn period

Patient	Hemodynamic data	Surgery	Mortality Cause
1	LPA(14) -RPA (18) SV- 10 O_2 saturation: 75%	Bilateral Glenn+supracardiac APVR	Poor ventricular function Catheterization: left dominant coronary artery with multiple stenoses
2	PA (19) SV - 8 O_2 saturation: 70%	Bilateral Glenn	Low cardiac output – Effusion Diaphragmatic paralysis
3	PA (18) SV - 10 O_2 saturation: 78%	Bilateral Glenn+mixed APVR	Low cardiac output Catheterization: inferior pulmonary vein stenosis
4	PA (12) SV - 10 O_2 saturation:80%	Bilateral Glenn	Unknown: dies at one month after discharge
5	Glenn (13) SV - 11 O_2 saturation: 81%	Bilateral Glenn+supracardiac APVR	Multiple organ failure

LPA: Left pulmonary artery. RPA: Right pulmonary artery. PA: Pulmonary artery. SV Single ventricle

Table 2. Characteristics of patients deceased in the immediate postoperative subpulmonary ventricular bypass period

Patient	Glenn	SVEDP	Anatomical difficulty	Postsurgical findings
1	16	9		Pulmonary vein stenosis Thrombus
2	8	10		Brain lesion
3	7	10	Yes	
4	19	8		Glenn stenosis-right superior vena cava aneurysm Innominate thrombosis
5	15	10		Respiratory tract bleeding Aortopulmonary collaterals
6	13	11	Yes	

SVEDP: single ventricle end-diastolic pressure

with sinus node syndrome requiring pacemaker), and thrombi in 3 patients. Two patients were reoperated (1 with diaphragmatic paralysis and the other with sinus node dysfunction who developed duct thrombi and AV valve regurgitation).

During follow-up 10 interventional catheterization procedures were performed in 7 patients. In most cases catheterization was due to cyanosis and in one case for hemoptysis. Indications and different procedures are detailed in Table 3.

During follow-up 1 patient died from unknown causes at one year after surgery.

Type one and a half ventricular correction

One case was evaluated for type one and a half ventricular correction. This was a patient with previous Glenn procedure who underwent ventricular septation with aortico-left ventricular tunnel, supracardiac venous return anomaly correction,right ventricle-pulmonary artery connection with pulmonary homograft and tricuspid valve plastic surgery, who evolved with ventricular dysfunction and is in functional class II-III, with cardiac medication.

Mortality

In this series, overall mortality was 39.45% (n=28) and surgical mortality was 29% (n=16).

In the univariate analysis, mortality of non-surgical patients and palliative surgery was associated with infradiaphragmatic APVR(p=0.02).

Glenn stage mortality was related to bilateral Glenn procedure (p=0.04), while PVBP mortality was due to different causes.

DISCUSSION

This clinical series assembles a significant number of patients with dextroisomerism and is the first report of our hospital experience.

Clinical presentation, complexity of cardiac anomalies and association with extracardiac malformations were similar to those described by other authors. (2,3)

In a first stage, isomerisms having obstructive APVR were not treate dowing to the disappointing results of postoperative outcome reported by Hashmi et al.; (2) then, the experience of treating these patients was initiated; however, the immediate postoperative mortality of 29% remains high, in accordancewith published reports. (3,4)

Single ventricle correction was the choice for most patients; there was loss to follow-up and high surgical and inter-stage mortality, as reported in other studies. (5) Glenn stage mortality was high, reaching 29% in patients with dextroisomerism, while for other anatomical variants it is less than 3.9% at our center. (6)

Mid- and long-term events of total PVBP in patients with heterotaxy syndrome poses one of the most complex challenges for those monitoring these patients; (7,8) in our series 72% of patients had complications.

Supraventricular arrhythmias are common in patients with dextrosiomerism, reaching 28% of cases in some series. (3, 9) Cases of AV blockage are also described, although the latter event was not found in our group.

The results of biventricular correction in dextroisomerism are disappointing, as reported by several authors, and single ventricle palliation or heart transplantation is sometimes recommended for these patients. (2,10-12)

The mortality associated with APVR has also been described in other publications. (2,4)

Prenatal diagnosis and genetic studies were not considered in this work as was the case in other published studies. (1,3,12)

Study limitations

Our study presents the limitations of a retrospective study.

The patients in our series have resources that are not ideal in addition to geographic, cultural and economic difficulties for diagnosis, treatment and follow-up opportunities.Nevertheless, they were provided with all the available options, and the loss to follow-up is explained by the afore mentioned conditions and

Table 3. Indications and type of interventional catheterization

Cases	Indication	Type of surgical catheterization
1	Cyanosis	Fenestration closure Embolization of 4 aortopulmonary collaterals
2	Cyanosis	Fenestration closure
3	Cyanosis Extracardiac duct stenosis	Suprahepatic vein closure with Amplatzer device Stent in extracardiac duct.
4	Cyanosis Residual shunt	Fenestration closure Stent in duct
5	Cyanosis	Venovenous collateral embolization+pulmonary antegrade flow occlusionwith Amplatzer device+stent angioplasty in left pulmonary branch
6	Cyanosis	Fenestration closure
7	Hemoptysis	Embolization of 3 aortopulmonary collaterals

also to the natural and remote outcome of the disease.

Prenatal diagnosis is a developing area, whereas genetic studies are not implemented in our country, and is an aspect to be considered in the future.

CONCLUSIONS

Dextrosiomerism is one of the most complex forms of congenital heart disease, where a single ventricle physiology is predominant.

The initial mortality was associated to the infradiaphragmatic APVR variant.

Mortality in the Glenn stage was associated with the bilateral type.

Only one third of patients with single ventricle physiology could reach the total PVBP stage,with a multifactorial cause of immediate postoperative mortality.

Adverse events in mid-term follow-up of patients in the Glenn stage and total PVBP are frequent.

The management of patients with heterotaxy syndrome remains a challenge within the group of patients with complex cardiac diseases.

Conflicts of interest

None declared

(See author´s conflicts of interest forms in the web / Supplementary Material)

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