Intrahepatic portosystemic shunts, from prenatal diagnosis to postnatal outcome: a retrospective study

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ABSTRACT

Objective Congenital intrahepatic portosystemic shunts (IHPSS) are rare vascular malformations resulting in blood bypassing the liver to the systemic circulation. Previous studies included symptomatic patients diagnosed postnatally, but the outcome of IHPSS diagnosed prenatally is rarely reported. We present a cohort of children prenatally diagnosed with IHPSS and report their natural course and outcome.

Methods and design This was a retrospective study of all fetal cases diagnosed by ultrasound with IHPSS between 2006 and 2019 at a single tertiary centre which were prospectively followed up at the paediatric gastroenterology unit. The postnatal outcome was compared between patients with a single versus multiple intrahepatic shunts.

Results Twenty-six patients (70.3% boys) were included in the study, of them, eight (30.8%) patients had multiple intrahepatic shunts. The median gestational age at diagnosis was 29.5 weeks. Growth restriction affected 77% of the cohort. Postnatally, spontaneous shunt closure occurred in 96% of patients at a median age of 7.5 months (IQR 2.2–20 months). Failure to thrive (FTT) and mild developmental delay were observed in eight (30.8%) and seven (26.9%) patients, respectively. FTT was significantly more prevalent in patients with multiple shunts compared with patients with a single shunt (62.5% vs 16.7%, p=0.02); however, the rate of shunt closure and age at time of closure were similar between these groups. All patients survived with limited to no sequelae.

Conclusions IHPSS usually close spontaneously by 2 years of age. Children with prenatally detected IHPSS may develop FTT and mild developmental delay. Close surveillance at a paediatric gastroenterology unit may be beneficial.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Congenital intrahepatic portosystemic shunts (IHPSS) are rare vascular malformations.
⇒ Previous large cohorts reported on postnatally diagnosed shunts, showing a high prevalence of severe complications and a low rate of spontaneous shunt closure.
⇒ The literature on the outcome of prenatally diagnosed shunts is scarce.

WHAT THIS STUDY ADDS

⇒ Prenatally diagnosed IHPSS usually close spontaneously by 2 years of age.
⇒ Up to one-third of patients may develop failure to thrive and mild developmental delay.
⇒ No severe complications are expected.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We recommend a wait-and-see approach for patients with IHPSS, which usually close spontaneously by 2 years of age.
⇒ Close observation of growth and development is warranted.

INTRODUCTION

Congenital portosystemic shunts (CPSS) are rare vascular malformations with an estimated prevalence of 1:30 000 children.[1] The abdominal systemic and hepatic veins develop between the fourth and sixth weeks of gestation.[2] The initially communicating primordial vessels undergo involution, resulting in non-communicating, separate portal and systemic venous systems,[3–5] with the exception of the ductus venosus, which closes after birth.[6–8] Lack of complete involution of one or more primordial vessels gives rise to abnormal portocaval venous shunts, resulting in intestinal blood bypassing the liver.[9] Potential long-term consequences of CPSS are widely documented in the literature.[10–16] Direct hyperbilirubinaemia, liver atrophy and abnormal coagulation are a result of liver ischaemia due to vascular deprivation.[14 15] Incomplete hepatic blood filtration might result in hypoglycaemia, indirect hyperbilirubinaemia, hyperammonemia, encephalopathy, increased serum galactose-1-phosphate, pulmonary hypertension and pulmonary arteriovenous shunts.[1 2]

Previous case series included mainly postnatally diagnosed symptomatic shunts, highly associated with complications.[1 7 15] With the advancement of prenatal ultrasound (US) and growing knowledge of the fetal portal system, the prenatal detection of CPSS is increasing.[17–19] However, current literature on the long-term outcome in prenatally diagnosed CPSS is scarce.[20–22] CPSS are divided into intrahepatic and extrahepatic portosystemic shunts (IHPSS and EHPSS),[23] differing in clinical manifestation, management and outcome. While EHPSS have a more complicated course and require surgical closure, IHPSS vary in the severity of presentation and may close spontaneously. The aim of the study was to report the postnatal outcome of prenatally

diagnosed IHPSS and to compare the outcome of single and multiple shunts.

METHODS

We performed a retrospective study of all fetuses diagnosed with IHPSS between January 2006 and December 2019 at a single tertiary centre. Data were retrieved from computerised maternal and neonatal medical records. Missing data were completed by a telephone interview after receiving parental consent. Prenatal shunt characteristics and data on fetal outcome were collected from early anomaly scan reports (14–17 weeks of gestation), mid-trimester anomaly scan reports (19–25 weeks of gestation) and targeted scan reports (any week referred). Fetuses with IHPSS were followed up for growth, development, cardiac function and well-being at regular intervals of 4 weeks, at our centre. The gestational age at shunt diagnosis, number of shunts, presence of the portal system and ductus venosus, signs of cardiac overload, intrauterine growth restriction (IUGR), associated anomalies and genetic abnormalities were recorded.

The presence of an IHPSS was determined postnatally by US in all cases. Data retrieved from the neonatal records included birth weight, gestational age at birth, length of neonatal intensive care unit (NICU) admission, time to shunt closure, weight gain and laboratory tests, including serum glucose, bilirubin, ammonia and liver enzymes. Post-discharge, follow-up was carried out at the paediatric gastroenterology unit at regular intervals, every 6 months, with routine abdominal US and laboratory tests. Abdominal US was performed for shunt follow-up and for surveillance for any hepatic lesions. Our primary outcome was spontaneous shunt closure. Secondary outcomes included metabolic and growth abnormalities during follow-up. Compared were the outcomes of patients with a single versus multiple IHPSS.

Prenatal/postnatal shunt concordance

The concordance between prenatal and postnatal shunt characteristics on US was categorised as 'no concordance', 'partial concordance' or 'complete concordance', including number of shunts and shunt anatomy. When all shunt characteristics differed prenatally and postnatally, this was defined as 'no concordance'; when at least one parameter differed, the definition was 'partial concordance'; and when all characteristics were similar, this was defined as 'complete concordance'.

IHPSS were classified according to the Park classification.[24] Type 1 is a single large vessel connecting the right portal vein to the inferior vena cava. Type 2 is a localised peripheral shunt/shunts with one or more communications in a single hepatic segment. Type 3 is a connection through an aneurysm, and type 4 is multiple communications in several segments.

Definitions

Hyperbilirubinaemia was defined at or above the high-intermediate risk zone according to Bhutani curve,[25] used for neonatal hyperbilirubinaemia management. Cholestasis was defined as direct bilirubin >1 mg/dL after 2 weeks of age.[26]

Hypoglycaemia was defined as blood glucose below 40 mg/dL on the first day of life or below 50 mg/dL, thereafter. Hyperammonemia was defined as above 170 µg/dL.

Failure to thrive (FTT) was defined as weight for age below the third percentile, on more than one occasion, or a decrease of two or more major percentile lines.[27] Developmental delay was defined as patients carrying the diagnosis of 'speech delay', 'gross motor delay', 'fine motor delay' and/or 'autistic spectrum disorder'.

Table 1 Demographic data and prenatal shunt characteristics

	IHPSS (n=26)
Gestational age at diagnosis (weeks)	29.5 (23.2–33)
Mode of delivery	
Vaginal	8 (30.8%)
Caesarean section	18 (69.2%)
Type of scan	
Early (14–17 weeks)	2 (7.7%)
Mid-trimester (19–26 weeks)	10 (38.5%)
Targeted (>26 weeks)	14 (53.8%)
Male gender	18 (70.3%)
IUGR	20 (76.9%)
Prenatal cardiac overload	4 (15.4%)
Gestational age at birth	37 (35.6–37.6)
Birth weight	2062 (1720–2608)
Normal karyotype	18/18 (100%)
Normal chromosomal microarray	14/15 (93.3%)
Cardiac anomalies	10/26 (35.7%)
Associated anomalies	9/26 (34.6%)

Data presented as median (IQR) or n/N (%).
IHPSS, intrahepatic portosystemic shunt; IUGR, intrauterine growth restriction.

Statistical analysis

Normality of the data was tested using the Shapiro-Wilk or Kolmogorov-Smirnov tests. Continuous variables are presented as median and IQR and categorical variables are presented as number (%). Comparison between unrelated variables was conducted with Student's t-test or Mann-Whitney U test, as appropriate. The X^2 and Fisher's exact tests were used for comparison between categorical variables and Kruskal-Wallis test for continuous variables. P value of <0.05 was considered statistically significant. Data analyses were performed using SAS V.9.4 software.

RESULTS

Between 1 January 2006 and 31 December 2019, 27 patients were prenatally diagnosed with IHPSS. The prenatal demonstration of IHPSS is presented in online supplemental figure 1. One patient refused to participate in the study and was excluded. The distribution into Park types is presented in online supplemental figure 2. Most of the patients (88.4%%, 23 of 26) had Park type 2. The background and prenatal shunt characteristics of the study group are presented in table 1. There was a male predominance (70.3%, 18 of 26). Most of the shunts were detected on a third trimester targeted scan (53.8%, 14 of 26), 38.5% (10 of 26) were detected on the mid-trimester scan (19–25 weeks) and 7.7% (2 of 26) were detected on the early anomaly scan (14–16 weeks). IUGR was present in 76.9% (20 of 26) of cases. Intrauterine cardiac overload was documented in 15.4% (4 of 26) of cases.

Associated anomalies and genetic aberrations

Associated anomalies are presented in table 2. Congenital anomalies, detected in 57.6% (15 of 26) of cases, were mostly cardiac (35.7%, 10 of 26). Genetic investigation, either karyotype or chromosomal microarray analysis (CMA), depending on what was offered at the time, was performed in 69.2% (18 of 26) of patients. An additional patient performed non-invasive prenatal

Table 2 Associated congenital anomalies in newborns with IHPSS

	IHPSS (n=26)
Cardiac anomalies	10 (35.7%)
Patent foramen ovale	7
Ventricular septal defect	1
Bilateral peripheral pulmonary stenosis	1
Patent ductus arteriosus	1
Right aortic arch	1
Aberrant left subclavian artery	1
Non-cardiac anomalies	9 (34.6%)
Tethered spinal cord	1
Unilateral clubfoot	1
Hypoplastic thumbs	2
Laryngomalacia	1
Bilateral inguinal hernia	1
Eventration of the diaphragms	1
Cutaneous haemangiomas	4
Congenital hypothyroidism	1

IHPSS, intrahepatic portosystemic shunt.

testing, which was normal. Karyotype was normal in all cases. CMA was normal in 14 patients and in an additional case, a 15q11.2 microdeletion, associated with neurological dysfunction and developmental delay, was found. Two patients had whole-exome sequencing analysis. One was unremarkable and the second was found to have a mutation in the EPHB4 gene, which plays an essential role in vascular development.[28] This patient had a right aortic arch, right renal vein thrombosis, bilateral renal cortical cysts and arteriovenous malformations of the skin.

Prenatal and postnatal anatomical concordance and shunt closure

Eighteen (69.2%) patients had a single shunt and eight (30.8%) had multiple shunts. Complete concordance was found in 11 (42.3%) newborns, partial concordance in 7 (26.9%) and no concordance in 7 (26.9%) newborns. There was a non-significant trend of increased concordance in single versus multiple shunts (58.8% vs 25%, p=0.19) (table 3).

Spontaneous shunt closure occurred in 96% (24 of 25) of patients during the study period. One patient was lost to follow-up after the initial postnatal US. The median time for shunt closure was 7.5 months (IQR 2.2–20). In one patient with two shunts, one closed spontaneously and the second was patent at the age of 38 months.

Table 3 Prenatal and postnatal shunt diagnosis and follow-up

	IHPSS (n=26)
AST (IU/L, Nl 3–100)	72 (52–93)
ALT (IU/L, Nl 7–41)	21 (12–36)
GGT (IU/L, Nl 7–39)	127 (50–302)
Hyperbilirubinaemia	18 (69.2%)
Cholestasis	2 (7.7%)
Hyperammonemia	12/21 (57.1%)
Hypoglycaemia	13 (50%)
Developmental delay	7 (26.9%)
Failure to thrive	8 (30.8%)

*Data presented as median (IQR) or n/N (%). One case did not perform postnatal ultrasound follow-up.
ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IHPSS, intrahepatic portosystemic shunt; Nl, normal index.

Table 4 Early and late postnatal outcome of infants with IHPSS

	IHPSS (n=26)
Prenatal and postnatal shunt anatomy agreement	
None	7 (26.9%)
Partial	7 (26.9%)
Complete	11 (42.3%)
Unknown	1 (3.7%)
No of shunts	
1 shunt	18/26 (69.2%)
≥2 shunts	8/26 (30.8%)
Shunt closure*	24/25 (96%)
Age at shunt closure (months)	7.5 (2.2–20)

Data presented as median (IQR) or n/N (%).
IHPSS, intrahepatic portosystemic shunt.

Postnatal outcome

The early and late postnatal outcomes of infants prenatally detected with IHPSS are presented in table 4. During follow-up, 30.7% (8 of 26) developed FTT, 7 were born IUGR. Seven patients (26.9%) were diagnosed with some degree of developmental delay, one was diagnosed with autistic spectrum disorder. There were no differences detected in the rate of IUGR (73.7% vs 85.7%, p=1), hyperbilirubinaemia (68.4% vs 71.4%, p=1), hypoglycaemia (52.6% vs 42.9%, p=1) or hyperammonemia (64.3% vs 42.9%, p=0.4) between normally developed patients and those with developmental delay.

Hyperbilirubinaemia appeared in 69.2% (18 of 26) of newborns, of which, 3 were direct. Cholestasis appeared in 7.7% (2 of 26) of cases. In one case, liver biopsy showed paucity of bile ducts. The patient was treated with ursodiol, with jaundice resolving by 3 months of age. In a second case, biopsy was not performed. Jaundice resolved spontaneously by 11 weeks of age. Hyperammonemia appeared in 57.1% (12 of 21) of patients and resolved spontaneously after 1–2 days.

Hypoglycaemia was detected in 50% (13 of 26) of cases. Eleven required up to 3 days of intravenous dextrose support and two patients required up to 4 weeks of intravenous dextrose support, with gradual weaning. In one case, continuous glucose monitoring was required until 3 months of age.

Single and multiple shunt comparison

A comparison of clinical characteristics and outcomes between single and multiple shunts is shown in table 5. FTT was more common in multiple compared with single shunts (62.5% vs 16.7%, p=0.02). There was no difference in the rate of shunt closure (100% vs 87.5%, p=0.3) and in time to shunt closure, between single and multiple shunts (8 vs 7 months, p=0.1). No differences were observed in other outcomes, including IUGR, genetic abnormality, associated anomalies, cardiac overload or postnatal metabolic changes.

DISCUSSION

To the best of our knowledge, this is the largest published series of prenatally diagnosed IHPSS with prospective postnatal follow-up. IHPSS closed at a median age of 7.5 months of age and was associated with IUGR and FTT, mandating close follow-up, prenatally and postnatally.

Table 5 Comparison of one versus multiple congenital intrahepatic shunts

	1 shunt (n=18) Median (IQR)	≥2 shunts (n=8) Median (IQR)	P value
Age of diagnosis (weeks)	26.2 (22.6–31.6)	31.1 (26.1–33)	0.92
Birth weight (g)	2248 (1932–2835)	1663 (1585–2441)	0.1
Gestational age at birth (weeks)	37.1 (36–38.1)	36.2 (35.1–37.1)	0.3
IUGR	13 (72.2%)	7 (87.5%)	0.63
Cardiac overload	2 (11.1%)	2 (25%)	0.56
Normal karyotype	13 (100%)	5 (100%)	
Normal chromosomal microarray	10 (100%)	4 (80%)	0.33
Pre/postnatal shunt anatomy concordance			
None	4 (23.5%)	2 (25%)	
Partial	3 (17.6%)	4 (50%)	
Complete	10 (58.8%)	2 (25%)	0.19
Hyperbilirubinaemia	12 (66.7%)	6 (75%)	0.67
Cholestasis	1 (5.6%)	1 (12.5%)	0.53
Elevated ALT	22.2% (4/18)	0%	0.28
Elevated AST	27.8% (5/18)	12.5% (1/8)	0.63
Elevated GGT	38.9% (7/18)	37.5% (3/8)	1
Hyperammonemia (33–170)	9 (64.3%)	3 (42.9%)	0.4
Ammonia (33–170 IU/L)	167 (142–246)	160 (115–279)	0.9
Hypoglycaemia	7 (38.9%)	6 (75%)	0.2
NICU days	7 (0–16)	18 (2.5–20)	0.62
Cardiac anomalies	7 (38.9%)	3 (37.5%)	1
Non-cardiac anomalies	6 (33.3%)	3 (37.5%)	0.84
Developmental delay	5 (27.8%)	2 (25%)	1
Failure to thrive	3 (16.7%)	5 (62.5%)	**0.02**
Shunt closure*	17/17 (100%)	7/8 (87.5%)	0.3
Time to shunt closure (months)	8 (3–24)	7 (1–12)	0.1

Data presented as median (IQR) or n/N (%).
*One lost to follow-up.
ALT, alanine transaminase; AST, aspartate aminotransferase; GGT, gamma-glutamyltransferase; IUGR, intrauterine growth restriction; NICU, neonatal intensive care unit.

Previous studies included patients with IHPSS and EHPSS presenting mainly postnatally with a high rate of reported shunt complications. Sokollik *et al*[15] reviewed 328 patients, mostly having EHPSS, diagnosed between the prenatal period and 84 years of age. More than half of the patients presented severe symptoms, such as pulmonary complications, liver mass and hepatic encephalopathy. Spontaneous shunt closure was reported in only 11 patients (3.3%), of which 10 were IHPSS. Bernard *et al*[14] reviewed 245 published cases, mostly (218, 89%) detected postnatally. Spontaneous closure was observed in 14 patients (5.7%), most of which were IHPSS (12, 85.7%). Complications such as liver tumours, hepatopulmonary syndrome, pulmonary hypertension and hepatic encephalopathy occurred in 26%, 13%, 12% and 26%, respectively.

More recently, the outcome of prenatally diagnosed IHPSS was reported in several small case series of up to 15 patients.[29–32] Spontaneous shunt closure was reported to occur in 83.3% (10 of 12), 80% (8 of 10) and 100% (15 of 15) of children by 2 years of age. These high spontaneous closure rates are comparable with our study, implying that most congenital IHPSS are expected to close spontaneously. The median age of shunt closure in our series was 7.5 months, similar to previous studies reporting a median of 4.5 months[30] and 11 months.[29]

The high spontaneous closure rates of prenatally diagnosed IHPSS are different from postnatally diagnosed CPSS. A possible explanation is that postnatal diagnosis is usually made when severe complications develop in cases of large, persistent shunts. In our cohort, patients were regularly evaluated until 6 months after shunt closure, and none developed severe symptoms. Furthermore, postnatal studies did not distinguish between IHPSS and EHPSS, which, unlike IHPSS, are usually persistent and symptomatic. Therefore, in prenatally diagnosed IHPSS, conservative management seems reasonable.

Postnatally, the most common metabolic abnormalities were hypoglycaemia and hyperammonemia. Hypoglycaemia occurred in 50% (14 of 28) of neonates, 13 of which had IUGR and 1 born prematurely, both of which are significant risk factors for early hypoglycaemia,[33 34] implying that IHPSS was not the direct cause of hypoglycaemia. Two patients had persistent hypoglycaemia with low insulin levels, attributed to IUGR and not to IHPSS, since hypoglycaemia due to IHPSS is associated with hyperinsulinism.[35 36]

Mild, transient hyperammonemia was observed in over half of cases, higher than previously reported in a single prenatal study (6.7%, 1 of 15).[32] Hyperammonemia in IHPSS results from intestinal blood bypassing the liver; however, its rapid resolution within 1–2 days of life suggests a transient patent ductus venosus is the cause.[37]

Cholestasis was present in 7.7% of our patients (2 of 26) and resolved spontaneously. A higher rate (19%) was reported in a previous study[1]; however, other plausible aetiologies of cholestasis such as biliary atresia or infections were present in part of the patients.

Our cohort presents a higher rate of IUGR compared with previous studies (75% vs 33%–67%).[29 30 37] The pathophysiology of IUGR is not well understood, but it is assumed to result from impaired hepatic perfusion,[38] due to shunting of oxygenated blood, with a subsequent decrease in liver insulin-like growth factor-I and II mRNA expression, leading to decreased tissue proliferation.

The increased FTT rates in patients with multiple shunts have no clear explanation, since IUGR, time to shunt closure and additional malformations were similar to those with one shunt. In 87.5% of the FTT patients, IUGR developed prenatally. Hence, we assume that the underlying cause for FTT is its preceding IUGR. Fortunately, a higher growth velocity with eventual catch-up by 2–3 years has been observed in IUGR infants[39]; therefore, these patients are expected to thrive later in life.

Developmental delay was prevalent in our cohort. This was not associated with indirect hyperbilirubinaemia, hypoglycaemia or hyperammonemia. Furthermore, these imbalances were not profound or prolonged enough to have a neurological effect. Hence, we assume a different aetiology for the developmental delay other than metabolic imbalances.

This study has several limitations. First, despite being the largest prenatal series with postnatal outcome, it is still relatively small for advanced statistical stratification. Second, the growth and development data were partly obtained retrospectively by telephone interviews and not directly assessed, exposing the study to recall bias. Another potential bias lies in the different management of the patients of the cohort, which were scanned every 4 weeks at a tertiary centre, compared with the low-risk population which undergoes two routine scans during pregnancy at a community

health centre. This might have led to a higher detection of anomalies. This type of bias has been previously reported[40 41] and should be kept in mind in comparative studies. As the current study does not compare the study group with a control group, this bias is of less concern. Third, since the patients were only followed up half a year after shunt closure, long-term follow-up of developmental delay and FTT was not available.

The strengths of the study include a high-resolution description of prenatal and postnatal events in prenatally detected IHPSS, providing valuable information which is expected to improve the consultation and management of this poorly studied condition.

In conclusion, prenatally diagnosed IHPSS usually close spontaneously within the first 2 years of life, allowing a 'wait-and-see' approach. Limited and minor postnatal metabolic changes can be expected, especially in coexisting IUGR, warranting close monitoring and appropriate correction. Delivery at a tertiary centre offering multidisciplinary care including paediatric gastroenterologists, radiologists and a skilled NICU team may be beneficial. Close follow-up at a paediatric gastroenterology unit is recommended, including routine laboratory tests and abdominal US. Management should also target FTT and developmental delay, which were common in our cohort.

Contributors OSS was involved in the conception of work, created data collection plan, interpreted the data and wrote the original draft. TW was involved in the conception of work, created data collection plan, interpreted the data, performed formal analysis and wrote the original draft. RA supervised and guided the data collection, and gave his final approval for the manuscript. MPZ and AAH were part of the data collection team. YH reviewed the manuscript and gave her final approval of the manuscript. BW was involved in the conception of the work and creating the data collection plan. She supervised and revised the manuscript. OS is guarantor.

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