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CASE REPORT

Suggested Protocol for Antenatal and Postnatal Action in Response to Absence of the Ductus Venosus, Referring to Nine Cases of Prenatal Detection

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ABSTRACT

Absence of the ductus venosus is a rare condition, the systematic study of which is only now beginning. It can provoke severe cardiovascular problems in the foetus, especially when associated with other malformations. Postnatally, it could generate hepatic problems, due to hyperammonaemia arising from the shunt. When this condition occurs in isolation, the prognosis is good.

We believe this condition merits further study. We propose an integrated antenatal and postnatal protocol for action, based on the observation of nine clinical cases detected at our hospital between May 2011 and December 2013.

Introduction

The absence of the ductus venosus (ADV) is a rare congenital vascular malformation, with an estimated incidence of 1/2532 foetuses diagnosed by ultrasound in week 11-14 of gestation. Its prevalence in the general population is unknown, because no systematic screening for this condition is performed [1].

The ductus venosus (DV) is a foetal shunt that connects the intra-abdominal section of the umbilical vein (UV) and the portal sinus with the inferior vena cava (IVC). It is funnel-shaped, with the narrow end located in the UV, which enables a greatly increased blood flow velocity. Most of the oxygen-saturated blood originating from the UV, with great kinetic energy, reaches the right atrium, through the Eustachian valve, and the rest enters the left atrium via the foramen ovale; thus, the left-cardiac cavities receive blood with a higher percentage of oxygen to supply the brain and the myocardium, through the aorta and the coronary vessels [2].

Under normal conditions, the DV allows 20-30% of oxygen-rich blood from the UV to reach the IVC, bypassing the portal circulation. This blood flow represents the transition from a high-pressure system (UV) to a low-pressure one (the systemic venous circulation). After birth, the DV undergoes a fibrotic transformation, which results in the venous ligament being formed. No specific factor triggering this closure has been identified [3,4].

ADV represents a failure of the anastomosis between the portal-umbilical and the hepatic-systemic venous systems. This malformation gives rise to the

formation of umbilical portosystemic shunts (UPSS), which can impact strongly on antenatal and postnatal life. UPSS produce a situation in which umbilical portomesenteric blood drains the hepatic veins or the systemic veins, often bypassing the liver. The foetus may suffer haemodynamic changes, provoking heart failure and/or hydrops fetalis, and after birth, hyperammonaemia and hepatic encephalopathy. On the other hand, it may be asymptomatic [5,6].

In such circumstances, the umbilical blood flow must seek alternative routes, which take the form of connections, or shunts, to the systemic venous circulation. There are two types of shunts, according to their location: intrahepatic and extrahepatic. In most case reports of such shunts, their anatomy is poorly described because they are often very difficult to distinguish and classify.

Intrahepatic shunts create connections between the branches of the portal vein (PV), after its division, and the hepatic veins or the IVC [5]. Park et al. [7] classified these shunts into four morphological types:

Type 1: A large vessel that connects the right branch of the PV to the IVC.

Type 2: A liver segment that has one or more communications between the peripheral branches of the PV and the hepatic veins.

Type 3: An aneurysmal communication between the peripheral PV and the hepatic veins.

Type 4: In both hepatic lobes, there are multiple connections between the PV and the hepatic veins.

In an unknown percentage of cases, spontaneous closure of the shunt, in the first or second year of life, has been reported. Of the above types of shunt, type 1 is the most common, and may be with associated with hepatic or cutaneous hemangiomas [8].

In *extrahepatic shunts*, anastomoses take place between the portomesenteric vasculature and a systemic vein, before the division of the PV, bypassing the liver [5]. Morgan and Superina [8] classified these shunts as follow, according to the pattern of anastomosis between the PV and the systemic veins.

Type 1: No intrahepatic PV contribution. This situation is almost always associated with congenital heart disease and polysplenia and occurs mainly in females. Some authors call this "congenital absence of the portal vein". Two subtypes exist: *1a:* the splenic and the mesenteric veins separately drain to a systemic vein, *1b:* the splenic and the mesenteric veins form a common trunk and jointly drain to a systemic vein.

Type 2: A PV contribution exists. The intrahepatic PV is intact, but part of the portal flow is diverted to a systemic vein through a shunt.

In this type of shunt, only one case of spontaneous closure has been reported [6].

The pathologies most frequently associated with this type of shunt are liver tumours and hepatic focal nodular hyperplasia.

In 24-65% of cases, ADV is associated with heart disease, chromosomal abnormality, malformation, hydrops fetalis and/or heart failure, and in 35-59% of cases it occurs in isolation. In the latter situation, the prognosis is normally good [9].

Prenatal Monitoring **(Figure 1)**

In first-trimester screening for chromosomal abnormalities, the ductus venosus waveform should be examined systematically, as this inspection has been shown to enhance the detection of aneuploidies [10]. It also highlights the presence of ADV and is the only way to determine the real incidence of this pathology.

Cases where DV cannot be detected or where its absence is suspected should be referred to the corresponding prenatal diagnosis unit for evaluation. Given the potential consequences of this condition, we always recommend antenatal screening for DV in week 20 of gestation, and henceforth close monitoring and control.

Due to the high incidence of foetal abnormalities and adverse outcomes associated with ADV, we suggest that a detailed morphological examination be performed to detect anomalies, together with echocardiographic monitoring [1,11].

From week 25 of gestation, the effects on foetal haemodynamics can increase, and therefore closer monitoring is necessary. Increased foetal abdominal circumference would be indicative of the condition. This development would precede the haemodynamic impact,

reflecting the congestive liver that is the forerunner of foetal heart failure and hydrops fetalis [12].

We recommend that a foetal ultrasound be conducted every 15 days from week 25, with a foetal doppler examination, echocardiographic assessment and biometrics.

When ADV is diagnosed, the clinician should determine whether the drainage from the umbilical vein is intrahepatic or extrahepatic [11,13]. In the latter case, it would be very useful to measure the diameter of the shunt, as a foetal prognostic factor, since a narrow shunt, i.e., one with a smaller diameter than that of the UV, is expected to provide a good prognosis, because the portal system will be reasonably well developed [14].

It is also important to consider the portal system; if the portal vein is normal and there are no associated anomalies, the case will probably be less severe [15].

Foetal karyotyping should be conducted according to the associated anomalies observed, but not in every case in which ADV is diagnosed, because if it is an isolated condition, not associated with other malformations, the prognosis is good [9].

Communication and information to patients and their partners should be cautious because if there are no other associated abnormalities or chromosomal disorders, in principle the prognosis is good.

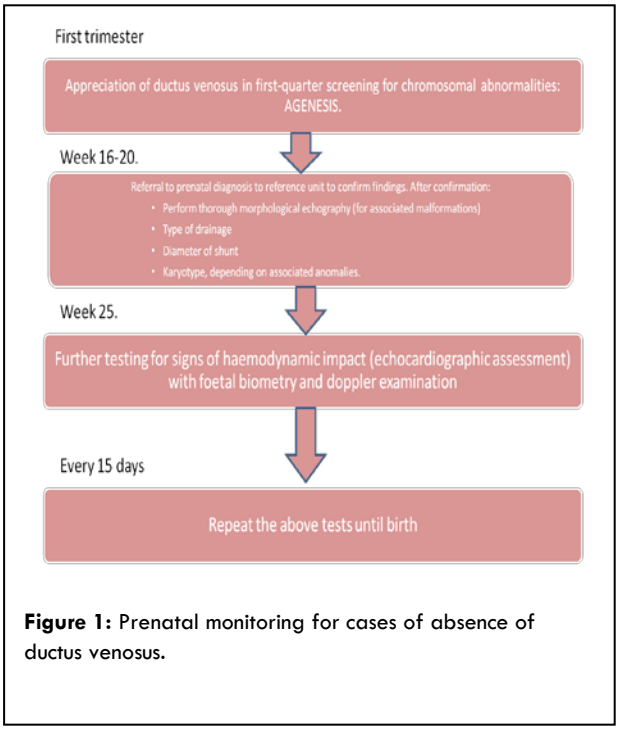

Figure 1: Prenatal monitoring for cases of absence of ductus venosus.

Postnatal Monitoring (Figure 2)

After birth, complementary tests are performed to detect possible liver disease. The most important of these are imaging tests, mainly ultrasound (confirmation by magnetic resonance angiography is rarely necessary). If the portal vein is detected and the portalcaval shunt is excluded, this is sufficient evidence for the monitoring protocol to be concluded.

If shunting with extrahepatic drainage persists, serial testing is essential due to the association between this phenomenon, the absence of the portal system [15] and the presence of liver tumours and/or lymph node hyperplasia [16].

When the drainage is intrahepatic, ADV is less frequent but this possibility and the existence of shunting should also be ruled out [15]. For this purpose, the method of choice is doppler ultrasound examination of the liver. In inconclusive or positive cases, magnetic angioresonance is the most reliable technique for assessing the anatomy of the liver and its vessels. The main drawback is that very young children must be sedated for this technique to be used.

When the presence of a portosystemic shunt is established, with intrahepatic or extrahepatic drainage, and if there is no hyperammonaemic encephalopathy, the condition should be monitored for up to two years, due to the possibility of reappearance. After that time, if the shunt persists, consideration should be given to its closure, by sclerosis, intravascular devices or surgery.

We propose a monitoring schedule for such cases (Figure 2). As part of this process, imaging tests are essential, as they define anatomy, reveal possible short circuits and/or the existence of hepatic masses, which are especially frequent in these patients. In this respect, a useful measure is the shunt index, which is obtained by doppler examination, dividing the volume obtained at the short circuit by the total portal flow volume. If the resulting ratio exceeds 60%, there is a high possibility of encephalopathy and/or hepatic dysfunction, in which case treatment to occlude the shunt will be required [17]. Other tests included in this protocol are primarily designed to test liver function.

At age six years, if the situation has not resolved, oxygen saturation is added to the monitoring schedule to screen for hepatopulmonary syndrome [16,18].

At age ten years, a further cardiological examination should be performed, primarily to study pulmonary pressures, as late pulmonary hypertension is associated with the presence of congenital portosystemic shunts [19].

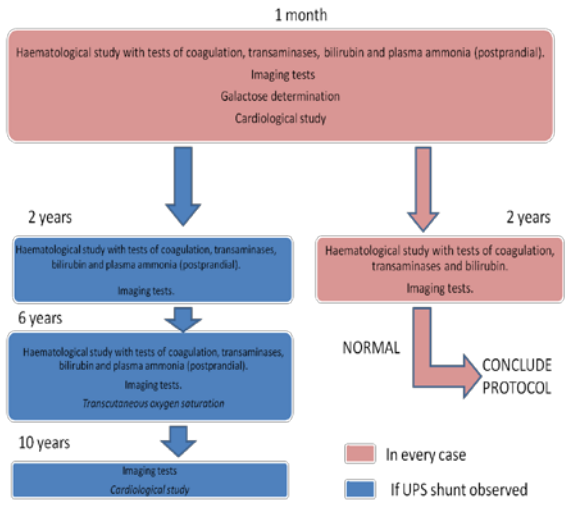

Figure 2: Postnatal monitoring of cases of absence of ductus venosus.

The monitoring schedule should include the following aspects:

1. At one month of life

- Blood count, with analysis of coagulation, transaminases, total and fractional bilirubin and postprandial ammonium.
- Liver ultrasound and doppler examination.
- Echocardiography.
- Analysis of galactose in blood/urine.

2. At age two years

- All the above tests, except cardiological study and analysis of galactose.
- Assessment of nutritional status and somatometry.

If portosystemic shunt is apparent: At age two years, consider closing shunt if it persists. Otherwise:

3. At age six years

- Haematological study, with tests of coagulation, transaminases, bilirubin and postprandial plasma ammonia.
- Imaging tests.
- Transcutaneous oxygen saturation.

At age ten years

- Imaging tests.
- Cardiological study, with special attention to pulmonary pressures.

Case Studies

From May 2011 to December 2013, a total of 4110 first-trimester screenings for chromosomal abnormalities were performed at the San Cecilio University Hospital (Granada, Spain), during which the DV was systematically evaluated. Ultrasound studies were performed in the obstetrics clinic of our hospital by an expert obstetrician who was advised when required by a paediatric cardiologist. Of these 4110 cases, DV was classified as normal in 3971 (89.7%), as abnormal in 59 (1.4%) and as absent in 3 (0.07%). 77 cases (1.9%) were unexamined. The recorded incidence, therefore, was 1/1370, which is higher than has been reported elsewhere [1]. The higher incidence found in our study may be due to the active nature of the search for this prenatal anomaly and indicates that, even today, many cases may remain undiagnosed.

The study was approved by the Hospital's Ethics Committee and the confidentiality of the data collected regarding the patients' clinical history was always respected.

From the introduction of the integrated monitoring protocol until December 2013, the antenatal examination revealed nine cases of ADV, to which the monitoring protocol was applied. All of these cases presented intrahepatic drainage and a normal karyotype. The patients were closely monitored, and the foetal welfare developed in a satisfactory way during the pregnancy. Four of the mothers gave birth at a hospital other than that of the antenatal monitoring, and so were lost to follow-up. Thus, the programme was applied postnatally to five children, after a prenatal and neonatal period without incident. Shunt image tests

were normal in all cases. Similarly, the liver function tests performed, galactose levels, ammonia and the coagulation study presented no abnormalities. A striking feature was the presence of associated cardiac abnormalities in four of the five cases. Case 1 presented the most evident changes, with a normally functioning bicuspid aortic valve and significant coarctation of the aorta requiring surgery in early infancy. The diparesis observed was possibly of perioperative origin. In Case 2, the only notable outcome during the monitoring was a slight increase in transaminases at one month of life, which normalised by month three. In Case 3, too, cardiological anomalies were observed during monitoring; namely a bicuspid aortic valve (without impaired function) and the presence of patent ductus arteriosus, without haemodynamic significance, during the evaluation period. Case 4 presented minor cardiovascular manifestations, with ductus arteriosus and the presence of an apical muscular interventricular communication, in both cases with no haemodynamic impact. In addition, there was a slight increase in transaminases, but no other abnormalities were revealed in the liver function tests during lactation, and this parameter subsequently normalised. Case 5 presented aortic narrowing in the coarctation area, with no associated bicuspid valve, and a mild degree of coarctation which did not require further action. During gestation, a cystic adenomatoid malformation appeared, but subsequently reverted. In general, all these patients evolved favourably during the monitoring period.

Discussion

In recent decades, advances in prenatal diagnosis have made it possible to detect foetal abnormalities that previously went unnoticed, and whose real clinical significance is still not fully known; such is the case of ADV. To determine the real significance of this pathology, it is important to acknowledge its possible existence, in order to make a good early diagnosis. Accordingly, we believe testing for ductus venosus should be generalised in first-trimester prenatal screening, as this is the only way to determine the actual incidence of ADV.

Some authors do not recommend the routine assessment of DV in morphological ultrasound examination, given the low incidence of ADV and the good prognosis if it is found in isolation. However, this evaluation is recommended if cardiac disorder, hydrops fetalis or an anomalous course of the umbilical vein in the plane of the abdominal circumference is observed [10].

This malformation causes an abnormal blood flow commonly called an umbilical portosystemic shunt, the drainage of which is either extrahepatic or intrahepatic. Extrahepatic shunts were first described and classified by Abernethy (1973), and subsequently reclassified by Morgan and Superina. Intrahepatic shunts were classified by Park in 1990. A few years earlier, it was shown that ADV could provoke neonatal portal hypertension (Meyer, 1966). In the introduction to this paper, we describe the different forms of ADV.

Haemodynamically, ADV increases pressure in the foetal systemic venous circuit, thus increasing cardiac preload. This circumstance can result in foetal heart failure with hydrops fetalis and sometimes intrauterine death. Foetal cardiocirculatory alteration becomes apparent from 20 to 25 weeks of gestational age. The clinical form that has the worst prognosis [20] is that in which the UV bypasses the liver and connects directly to the right atrium. In reported cases, the presence of polyhydramnios, increased foetal abdominal circumference or deteriorated foetal haemodynamics are suggestive of a poor outcome. Increased foetal abdominal circumference usually anticipates haemodynamic failure [12]. A recent study described a retrospective series of 22 cases of ADV, collected between 2004-2008; the monitoring of these foetuses, together with consideration of another 67 cases reported in the literature, shows that when ADV is present in isolation, the postnatal outcome is favourable regardless of the type of drainage present [9].

UPSS are anomalous venous communications that allow blood from the stomach, intestine, pancreas and spleen to pass directly into systemic circulation without being detoxified and/or metabolised in the liver. Thus, many

toxic substances are diverted directly into the systemic circulation, generating dysfunction in different organs, but especially in the central nervous system (hepatic encephalopathy). In addition, both extrahepatic and intrahepatic drainage are associated with severe disorders to the portal venous system or even its absence [11,13]. The severity of this impact is directly related to the size of the shunt.

In cases of ADV with absence of the portal system, the only treatment is liver transplantation. If the portal is present and there exists a portosystemic shunt, spontaneous closure might occur during the first two years of life. Otherwise, when the blood flow is significant, the shunt must be occluded by embolisation, the application of intravascular devices or surgery in order to prevent hepatic encephalopathy. Cases of extrahepatic drainage are very unlikely to close spontaneously and will require surgery. Nevertheless, one case of spontaneous closure was reported recently [6,16].

During the postnatal period, the monitoring protocol presented here recommends an expectant attitude be taken in the presence of a shunt until the child is two years of age, if there are no adverse symptoms [12,16]. Oxygen saturation is a good screening measure for hepatopulmonary syndrome, a well-known respiratory complication caused by shunts. A cardiological study should be conducted to evaluate pulmonary pressures and to discount pulmonary hypertension, which may occur in these patients in late infancy [19].

In summary, the outcome of this condition depends primarily on the associated malformations (aneuploidies, heart disease, extracardiac malformations) and on the haemodynamic changes generated secondarily, and therefore close prenatal diagnosis and monitoring is essential [9].

Before ADV in the foetus can be diagnosed, it is necessary to define what kind of drainage exists (intrahepatic or extrahepatic) and to conduct extensive and thorough screening for associated abnormalities [11,13]. In cases of suspected heart failure, terminating the gestation must sometimes be considered, and thus prematurity can be considered a further consequence of ADV.

Although the survival rate exceeds 85% when there are no associated anomalies, the effects of ADV can continue postnatally, and so after birth a primary objective must be to assess which patients may develop hepatic encephalopathy, with psychiatric or mental disorders secondary to chronic hyperammonaemia [21]. Other alterations that may occur include hypoglycaemia, galactosaemia, cholestasis, hyperbilirubinaemia or coagulopathy during early infancy. In later stages of life, reports have described various diseases of the liver (fatty infiltration, tumours, focal nodular hyperplasia) and of other organs, such as skin hemangiomas, congenital heart disease, kidney damage, hepatopulmonary syndrome and pulmonary hypertension [11,16,22,23]. However, in the absence of ultrasound evidence of alteration to the portal system and associated abnormalities, these patients appear to have the same prognosis as the general population [14]. A protocol for postnatal monitoring should be applied to take into account the possibility of pathology, especially of the liver, as this could go unnoticed and cause irreversible alterations at a later age.

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