Diagnosis and management of Abernethy syndrome

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INTRODUCTION

Abernethy syndrome (AS or extrahepatic portosystemic shunt) is an uncommon congenital malformation consisting of agenesis or hypoplasia of the portal vein (PV) in such a way that splanchnic venous blood drains directly into the systemic circulation through aberrant communications, resulting in a portosystemic shunt that bypasses the liver (1).

AS is an underdiagnosed condition with unknown incidence and complication rate given that symptoms are usually absent. AS identification is increasingly common because of improved imaging techniques, hence prognostic implications and clinical management need be understood (2). This editorial reviews the natural history of AS and its diagnostic-therapeutic implications, illustrating the process with a series of cases from our institution.

SERIES OF CASES

Table 1 lists the clinical and radiographic characteristics of four adult patients with AS. The three younger males, aged from 18 to 23 years, had elevated liver enzymes, hence we

ordered an abdominal ultrasound and then an angio-CT scan (Figs. 1-4). Only one of them had a congenital heart defect diagnosed at 6 years of age, which was approached conservatively by Cardiology.

The fourth case is an adult female that presented with abdominal pain and an abdominal palpable mass, and was diagnosed with a large liver lesion using CT. She underwent liver resection in 2014, with histology being consistent with hepatocellular carcinoma. Her AS was subsequently diagnosed in a follow-up angio-CT scan. In 2016 she was started on sorafenib for extrahepatic tumor relapse (histologically confirmed left supraclavicular lymphadenopathy). In 2018 treatment was discontinued because of intolerance.

All these patients are presently symptom-free with preserved liver function. None of them required surgery for their portosystemic shunt. However, three of the patients have uncharacterized focal liver lesions under close follow-up using alpha-fetoprotein measurement and magnetic resonance imaging (MRI) every 3-6 months. In one of the subjects with multiple liver adenomas transplantation was ruled out on technical grounds because of the AS.

TYPES

According to the anatomical classification by Morgan-Superina, two types of AS exist. Type 1 is characterized by the absence of intrahepatic portal venous branches, and the presence of complete end-to-side portocaval shunt. Two subtypes may in turn be recognized—1a, where the splenic and superior mesenteric veins separately drain into the inferior vena cava (IVC), and 1b, where both merge into a common trunk before reaching the IVC. Furthermore, in type-2 AS intrahepatic portal branches do exist but are hypoplastic, leading to side-to-side shunts that partially drain portal blood into the general circulation (2-6). Drainage into other systemic veins (renal, inferior mesenteric, iliac) or even the right atrium has also been decribed. AS should be differentiated from acquired extrahepatic shunts as in cirrhosis, and from congenital intrahepatic portosystemic shunts, which originate from a portal branch, usually close spontaneously during childhood, and neither induce symptoms nor increase the risk of liver malignancies (2,7).

PRESENTATION

Patients with AS display a wide range of manifestations. Most cases are asymptomatic; however, 29 % will develop symptoms of hepatic encephalopathy (HE), whether episodic or chronic, and 15 % may develop shortness of breath secondary to portopulmonary hypertension. Hepatopulmonary syndrome is rare but may develop in 3 % of patients. Bleeding from rectal varices has been anecdotally reported. Delayed maturation may be present in childhood (1-3,8-10). Up to 44 % of AS cases are associated with other congenital abnormalities, particularly cardiac defects but also including musculoskeletal, genitourinary, gastrointestinal, hepatobiliary, vascular, and bronchopulmonary conditions (1,2,11,12).

DIAGNOSIS

AS cannot be suspected based on specific laboratory changes. Some patients may show mildly elevated bilirubin, cholestasis enzymes and/or transaminases. Liver function is usually preserved. Hyperammonemia and high serum galactose may occur in childhood from the passage of these molecules into the systemic circulation (13-15).

A definitive diagnosis with AS requires imaging tests to reveal an extrahepatic shunt. This malformation is usually incidentally identified during childhood through youth. Ultrasound is the modality that most commonly leads to suspect this diagnosis by failing to adequately identify the portal vein or its branches. In order to establish a confirmation diagnosis and AS type dynamic vascular imaging is required, whether CT angiography or magnetic resonance angiography. Likewise, a diagnosis may be established after CT or MRI scans reveal liver lesions that were initially detected by ultrasound. On occasion shunt occlusion angiography is required to demonstrate hypoplastic intrahepatic veins in type-2 AS (1,15-19). No experience is available on the role of transient elastography in these patients.

While liver biopsy is unnecessary for diagnosis, it may show absent or hypoplastic portal branches or other nonspecific histological changes such as sinusoidal congestion, periportal fibrosis or steatosis (20).

FOCAL LIVER LESIONS

The presence of liver lesions is common at diagnosis (40-65 % of individuals); these may be single or multiple, usually benign lesions in 70 % of cases, including focal nodular hyperplasia and nodular regenerative hyperplasia. However, adenoma and hepatocellular

carcinoma have been demonstrated with a prevalence of 15 % and 12 %, respectively, among other neoplasias. Adenomas are more common in women whereas hepatocellular carcinoma seems associated with male sex and type-1 AS, likely because of the larger involvement of portal liver perfusion in this subtype, with excessive arterial vascularization. Its development does not require that cirrhosis be present. Characterization of these liver lesions may be challenging given their atypical dynamic behavior in dynamic imaging. It is advisable to round up the study with liver biopsy whenever malignancy is suspected (1,21-24).

TREATMENT

Patients may initially require routine medical treatment for pulmonary complications and HE, although effectiveness will be lower. Shunt closure using surgical ligation or through the percutaneous endovascular route allows redirection of portal vasculature to the liver, and to restore blood flow within intrahepatic portal branches, even in type-1 AS. Such intervention may be considered both for patients with significant clinical manifestations and symptom-free patients to prevent complications long-term. Choosing the surgical or endovascular technique will depend on shunt size and may be involve a two-step process, particularly when occlusive arteriography shows portal hypertension. A significant decrease in ammonium levels, increased liver volume, and remission or improvement of symptoms (especially HE) and liver nodules have been seen in patients with successful portosystemic shunt occlusion (1,15). Complications are uncommon but cases exist of splenic and/or mesenteric venous thrombosis that require anticoagulation.

Surgical hepatectomy may be considered for adenomas or hepatocellular carcinomas. Furthermore, while liver transplantation may be challenging because of a modified vascular anatomy, it may represent a therapeutic option in case of complications refractory to medical treatment (with symptom resolution, this being the classical therapy of choice for type-1 AS), associated biliary atresia, high portal pressure and/or presence of adenomas or hepatocellular carcinoma (25).

COMPLICATIONS SCREENING AND FOLLOW-UP

The cumulative incidence of complications and/or tumors in individuals with AS gradually increases with age, which makes regular clinical reviews necessary. A baseline MRI scan of the brain should be performed to rule out organic neurological disease in patients with HE, with T1 hyperintensity of the globus pallidus being the most common finding in such cases. Furthermore, it is recommended that a baseline echocardiogram with bubbles or echo-enhancers be made to rule our structural heart disease and/or arteriovenous communications in the pulmonary circulation. Some cases may require a blood gas test or Swan-Ganz catheterization when pulmonary complications are suspected. Regular measurement of oxygen saturation is also advisable.

Along the condition's course the number and size of the liver nodules usually remain stable, but cases of dysplastic adenomas progressing to hepatocellular carcinoma exist, particularly starting at the fourth decade of life. Therefore, nodule monitoring and hepatocellular carcinoma screening with abdominal ultrasound are required every six months, even after surgical shunt closure, as is MRI scanning when adenoma or hepatocellular carcinoma are suspected. Alpha-fetoprotein level measurements may be useful during follow-up (1).

CONCLUSIONS

AS is an underdiagnosed condition whose incidence is increasing because of improvements in liver imaging. Clinical manifestations are variable, with cases progressing to HE, portopulmonary hypertension, another complications. Benign focal lesions are common, and some of them, such as adenomas, may potentially undergo malignant transformation to hepatocellular carcinoma. Shunt correction may be useful for treating complications and to prevent tumors from developing.

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Table 1. Series of cases of Abernethy syndrome collected at Hospital Universitario Reina Sofía (Córdoba, Spain)

Patient	Sex	Age	Personal history	Presentation	Laboratory	Imaging	
						Anatomic vascular changes	Liver lesions
1	♂	22	– Congenital heart disease: dilated right heart cavities (preserved RV fuction). Mild tricuspid regurgutation – Celiac disease. Intestinal malrotation – Atrophic left testicle: orchiectomy (2015) – ADHD, OCD: sertraline	Asymptomatic	Mild mixed hyperbilirubinemia, cholestasis, and hypertransaminasemia	Absence of truncal PV and intrahepatic branches. SV, SMV, LRV drain through a retroaortic common trunk into IVC, the latter having a large caliber (AS Ib). Splenomegaly	Several liver lesions (those of 5 cm in segment IV, those of 4 cm in segment VII), mildly hypervascular, with intracellular fat, suggestive of adenomas (histological confirmation after biopsy)
2	♂	23	Not relevant	Asymptomatic Bilateral gynecomastia	Mild cholestasis and hypertransaminasemia	A truncal PV, 20 mm in length, originates from the confluence of SV and SMV, with shunt to retrohepatic IVC. No repermeabilization of intrahepatic portal branches (AS Ib). Signs of portal hypertension	Multiple liver lesions, hypervascular, with sustained uptake, mildly hyperintense on T1, suggestive of regenerative nodular hyperplasia
3	♂	18	– Fetal distress at birth	Asymptomatic	Hyperbilirubinemia,	Enlarged (15 mm) main PV with	Multiple liver lesions, the largest two (6 cm in

			– ADHD in childhood	cholestasis and hypertransaminasemia	portosystemic shunt directly communicated with the right atrium (orifice apart from IVC); no left or right PV branches, no intrahepatic portal circulation identifiable (AS Ib). Splenomegaly	segment VII and 3.5 cm in LHL) with central scarring, no enhancement in the arterial phase, and mild liver-specific contrast hyperintensity in the hepato-biliary phase, suggestive of focal nodular hyperplasia. In the two smaller lesions no differentiation is feasible between focal nodular hyperplasia and some type of adenoma (such as the inflammatory type)
4	♀	46	Not relevant	Asymptomatic normal	Intrahepatic PV cannot be seen. Portosystemic shunt through a common SV-SMV trunk into IVC (AS Ib)	– Large liver lesion in LHL (27 x 16 cm): hepatocellular carcinoma. Surgery: segmentectomy II-III and splenectomy (2014) + sorafenib (2016) – Liver lesion, 22 mm in size, in medial segment VI/VII, with central contrast enhancement in the arterial phase without clear washout; hepatocellular carcinoma cannot be ruled out given the patient's history (2022)

♂: male; ♀: female; RA: right atrium; LHL: left hepatic lobe; AS: Abernethy syndrome; ADHD: attention deficit/hyperactivity disorder; OCD: obsessive-compulsive disorder; IVC: inferior vena cava; RV: right ventricle; SV: splenic vein; SMV: superior mesenteric vein. PV: portal vein; LRV: left renal vein.
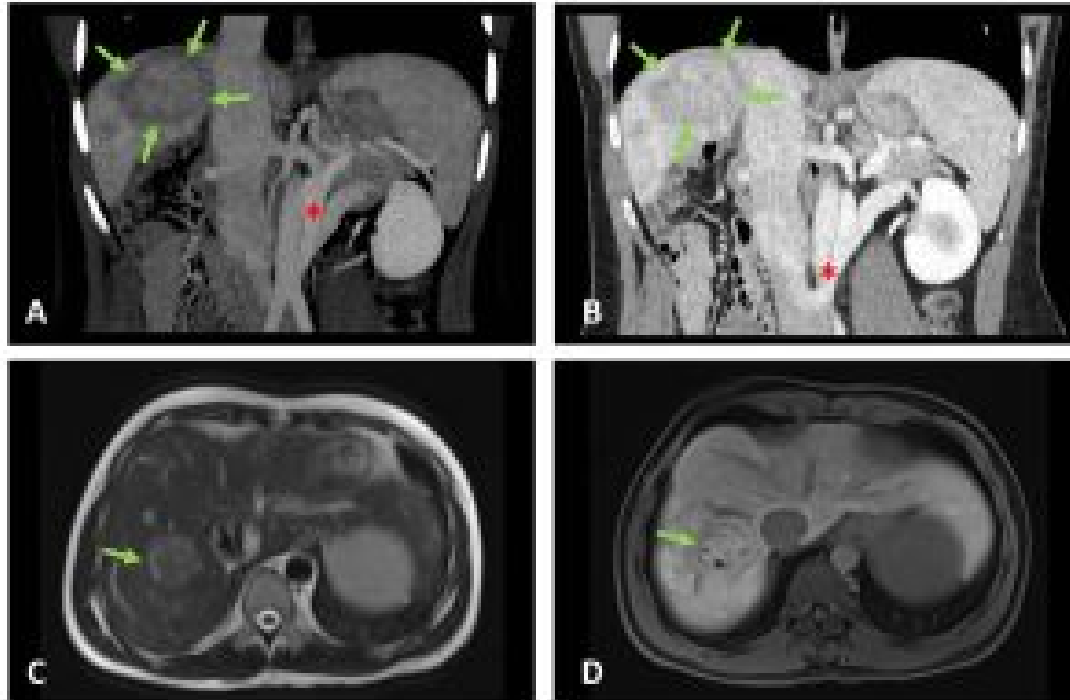
Fig. 1. Patient 1. Abdominal CT scan, coronal (A, B) sections: the splenic, mesenteric, and left renal venous systems drain through a retroaortic common trunk into the IVC (*). Liver lesion in segment VII (green arrows). Abdominal MRI scan, axial (C T2, D T1) sections: liver lesion suggestive of adenoma (green arrows).
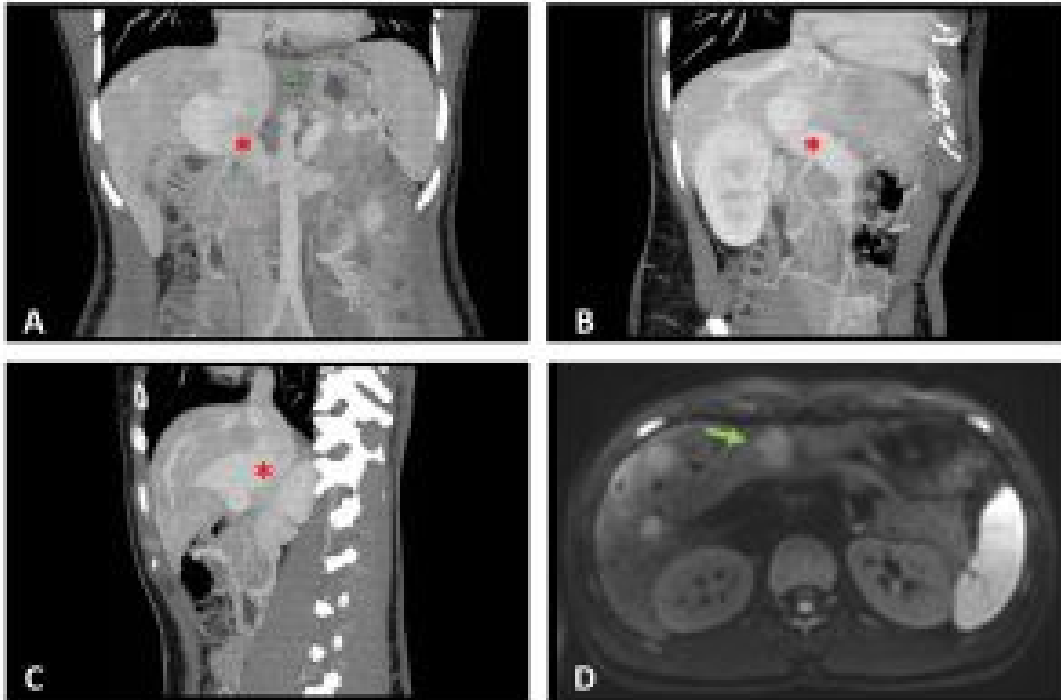
Fig. 2. Patient 2. Abdominal CT scan, coronal (A), sagittal (B) and oblique (C) sections: confluence of the superior mesenteric and splenic veins into a truncal shunt towards the retrohepatic IVC (*). Abdominal MRI scan, axial (D T1) section: multiple images with high b-values suggestive of regenerative nodular hyperplasia (green arrow).
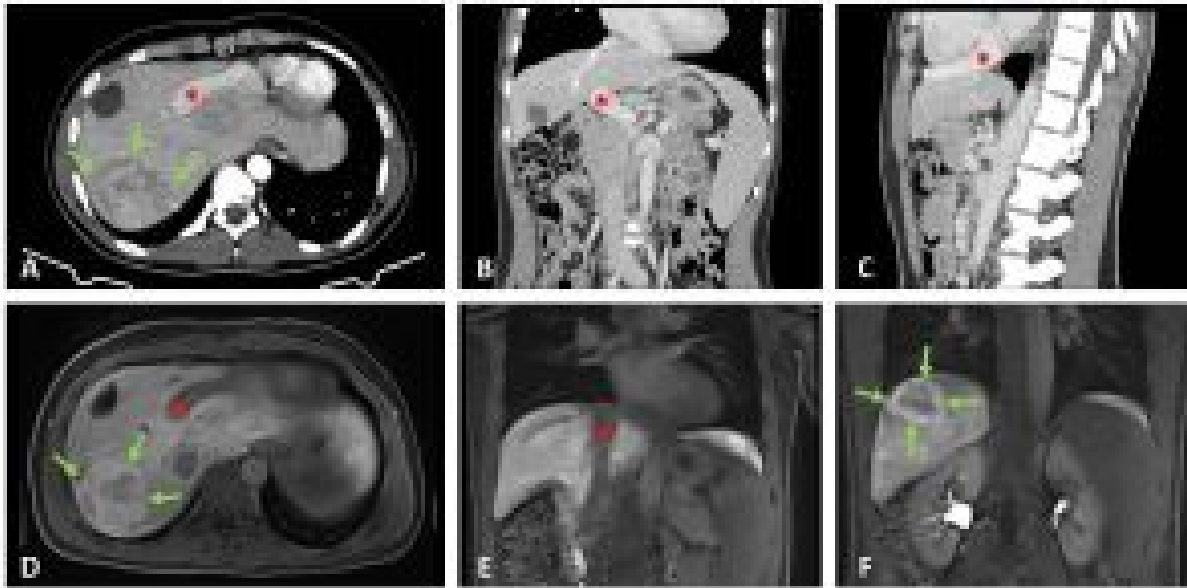
Fig. 3. Patient 3. Abdominal CT scan, axial (A), coronal (B) and sagittal (C) sections: portal trunk with portosystemic shunt direct to the right atrium (*). Lesion in segment VII with non-contrast enhancing centrfal scarring (green arrows). Abdominal T1 MRI, axial (D) and coronal (E, F) sections: portosystemic shunt (*) and lesion in segment VII with liver-specific contrast uptake, suggestive of focal nodular hyperplasia (green arrows).
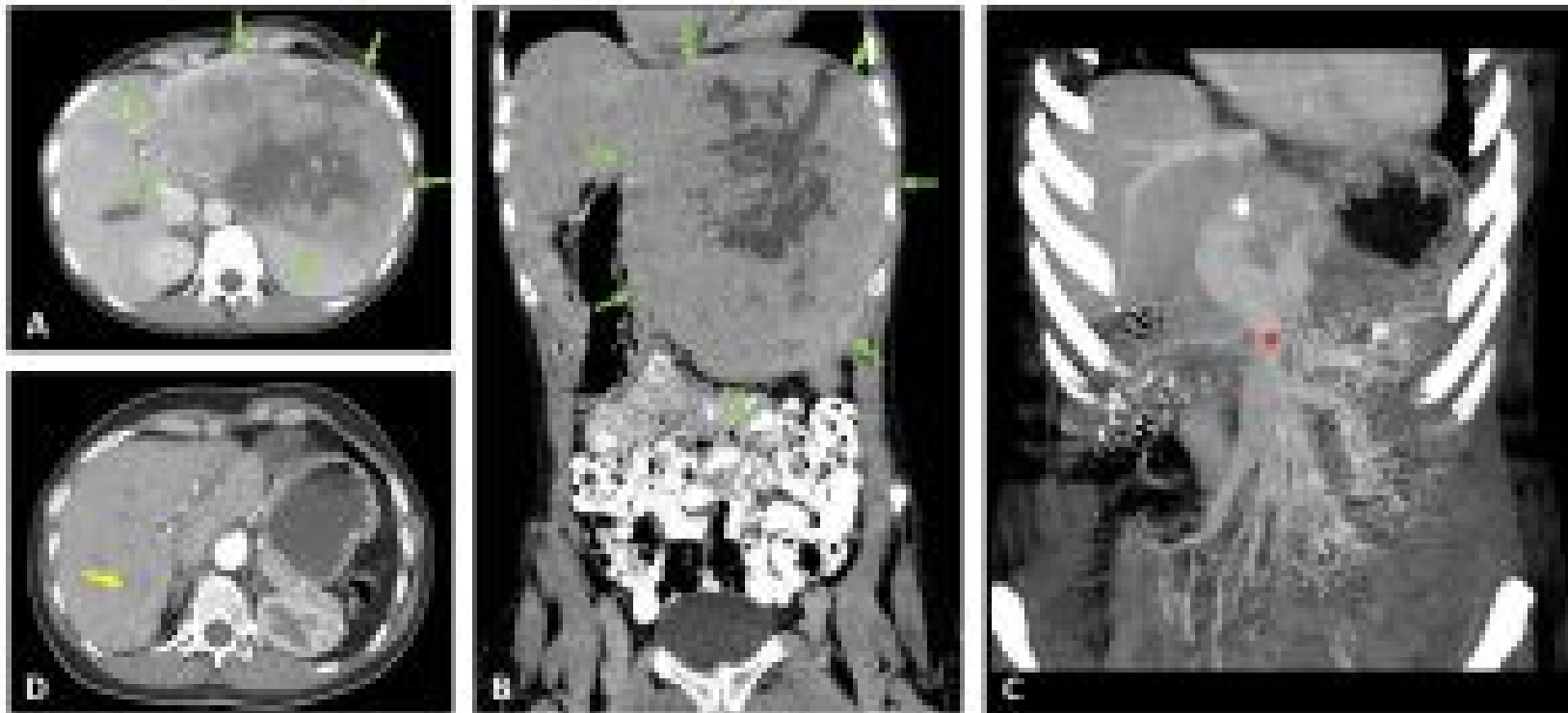
Fig. 4. Patient 4. Abdominal CT scan (2014), axial (A) and coronal (B) sections: a large heterogeneous mass in LHL, with necrotic-cystic areas and abundant vascularization (green arrows), that compresses and displaces other intra-abdominal organs (HCC in surgical specimen). Abdominal angio-CT (2022), coronal reconstruction (C) and axial section (D): post-surgical signs on left hepatic margin and splenectomy. Portosystemic shunt, truncal type, from the splenic and superior mesenteric veins into the IVC (*). Image D shows the focal lesion currently under monitoring.