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SHORT REPORT

Cerebral dural arteriovenous fistulas in patients with *PTEN*-related hamartoma tumor syndrome

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Abstract

Central nervous system (CNS) dural arteriovenous fistulas (DAVF) have been reported in *PTEN*-related hamartoma tumor syndrome (PHTS). However, PHTS-associated DAVF remain an underexplored field of the PHTS clinical landscape. Here, we studied cases with a *PTEN* pathogenic variant identified between 2007 and 2020 in our laboratory ($n = 58$), and for whom brain imaging was available. Two patients had DAVF (2/58, 3.4%), both presenting at advanced stages: a 34-year-old man with a left lateral sinus DAVF at immediate risk of hemorrhage, and a 21-year-old woman with acute intracranial hypertension due to a torcular DAVF. Interestingly, not all patients had 3D TOF/MRA, the optimal sequences to detect DAVF. Early diagnosis of DAVF can be lifesaving, and is easier to treat compared to developed, proliferative, or complex lesions. As a result, one should consider brain MRI with 3D TOF/MRA in PHTS patients at genetic diagnosis, with subsequent surveillance on a case-by-case basis.

KEYWORDS

cancer genetics, cerebrovascular disorders, Cowden syndrome, DAVF, dural fistula, genetic predisposition to disease, MRI, PHTS, PTEN

For affiliations refer to page 4

1 | INTRODUCTION

PTEN-related hamartoma tumor syndrome (PHTS) is an overgrowth and cancer susceptibility syndrome associated with heterozygous germline pathogenic variants (PV) in the *PTEN* gene. The umbrella term of PHTS includes overlapping syndromes referred to as Cowden (OMIM #158350) macrocephaly/autism (OMIM #605309), and Bannayan-Riley-Ruvalcaba syndromes. PHTS is characterized by macrocephaly, and manifestations of variable penetrance such as neurodevelopmental delay, breast, endometrial, thyroid and renal cancer, colorectal polyps, skin and mucosal papillomas, dysplastic ganglioma of the cerebellum (Lhermitte-Duclos disease), as well as extracerebral and cerebral vascular anomalies.[1,2]

Benign developmental venous anomalies are the most frequent cerebral vascular anomalies.[3,4] Dural arteriovenous fistulas (DAVF), which are the focus of this manuscript, are also reported, sometimes with dramatic outcomes (Table S1). DAVF consist of arteriovenous communications between the meningeal arteries and dural venous sinuses and/or subarachnoid veins. In the general population, they are rare, with an estimated annual incidence of 0.16 per 100.000, and occur at a median age of 64 years (range 24–83),[5] in most cases, with no known etiology. Annual rate of neurological events, such as hemorrhagic stroke, or acute edema, is 15%.[6] In PHTS, DAVFs are likely caused by the loss of inhibition of PTEN on the mTOR-pathway,[1] triggering angiogenesis through secretion of angioproliferative factors.

DAVFs have been described in several PHTS patients. Prats-Sanchez et al. reported a 46 year-old man with PHTS and an acute left anterior temporal hemorrhage associated with a left parasagittal subarachnoid hemorrhage.[7] Imaging revealed an advanced lesion with multiple dural and epidural high-flow arteriovenous fistulas. Despite multiple procedures of embolization, the patient died of status epilepticus. As for case series, Tan et al. observed one right posterior DAVF with bilateral transverse sinus occlusion in a 9-year-old boy, out of nine PHTS patients who had brain MRI with contrast.[8,9] Dhamija et al. studied 22 patients with suspected PHTS, of which seven were proven *PTEN* PV carriers.[3] Two had evidence of DAVF on brain MRI.

To get more insight into DAVF prevalence and manifestations in PHTS, we retrospectively studied brain imaging in 58 patients with a variety of neurodevelopment and tumor phenotypes.

2 | MATERIALS AND METHODS

All cases in whom a *PTEN* (likely) pathogenic variant ((L)PV), according to ACMG criteria,[10] had been identified at the Cancer and Vascular Genetics laboratory, Sorbonne Université, and for whom brain imaging was available, were selected. Whenever possible, we also included first-degree relatives of index cases who had been tested elsewhere and obligate carriers. Patients' images were reviewed by an expert neuroradiologist (A.B.). A second expert reviewed images of the two patients with DAVF (O.N.).

All patients (or their legal representatives) had signed a genetic testing informed consent form, mentioning a potential use of their DNA/data for research purposes related to their phenotype. An information note for this study with a possibility to opt out was sent to patients. Given the retrospective nature of the study, French law did not require ethics committee approval.

3 | RESULTS

3.1 | Genetics

We identified 58 PTEN (L)PV carriers from 50 families. There were 39 males and 19 females. Brain MRI was available in 57 cases, CT angiography (CTA) in one. Mean age at PHTS diagnosis was 16 years (range 6 months–58 years). Primary reported cause for genetic exploration was neurodevelopmental delay ($n = 24$), cascade testing ($n = 13$), malignant or benign tumor ($n = 7$, e.g., breast cancer or colorectal polyps), macrocephaly ($n = 4$), LDD ($n = 4$), and soft-tissue hamartoma ($n = 1$). It was unknown in four cases. One individual was an obligate carrier. Among the *PTEN* PV, 14 were frameshift ($n = 18$ patients), 10 nonsense ($n = 13$), 19 missense ($n = 22$), 3 splicing ($n = 3$), and 2 were intragenic deletions ($n = 2$) (Table S2).

These 58 cases were part of a series of 137 carriers identified in our laboratory. Reason for brain imaging was documented in 56/58 cases: macrocephaly and/or neurodevelopmental delay ($n = 40$), peripheral vascular malformations ($n = 1$), routine imaging following PHTS diagnosis ($n = 9$), and CNS symptoms (e.g., ataxia, hypoacousia, headaches, seizures, $n = 6$). It was unknown in two cases.

3.2 | Brain imaging and DAVF

The brain MRI protocol included at least one fluid attenuated inversion recovery (FLAIR) or Fast Spin Echo sequence ($n = 56/57$), and in most patients either gradient echo T2 (T2*) or susceptibility-weighted imaging ($n = 45/57$). However, 3D time-of-flight (TOF)/MRA images were only performed in 6 of 57 patients. 3D TOF/MRA are the optimal sequences to detect high-flow DAVF, which are characterized by a hyperintense signal within intracranial venous structures. As for contrast-enhanced images, they had been performed in 20 of 57 patients. They provide indirect evidence of DAVF since they show venous congestion, illustrated by enlarged tortuous pial veins over the cerebral or cerebellar convexities. One patient underwent CTA.

Two patients had DAVF (2/58, 3.4%). In both cases, DAVF was diagnosed at advanced stages, strongly suggesting that earlier diagnosis would have prevented severe clinical manifestations.

The first patient was a 34-year-old man with macrocephaly and learning difficulties who presented to the emergency department after a first episode of seizures (Patient 58, Table S2). Brain MRI, including T2 FLAIR and angiography, showed multiple DAVFs, in particular a right lateral sinus DAVF with significant reflux into the cortical veins, posing a substantial risk of subsequent brain hemorrhage (Figure 1A–D). The patient underwent several endovascular embolizations. He died aged 42 after accidental leakage of the embolization

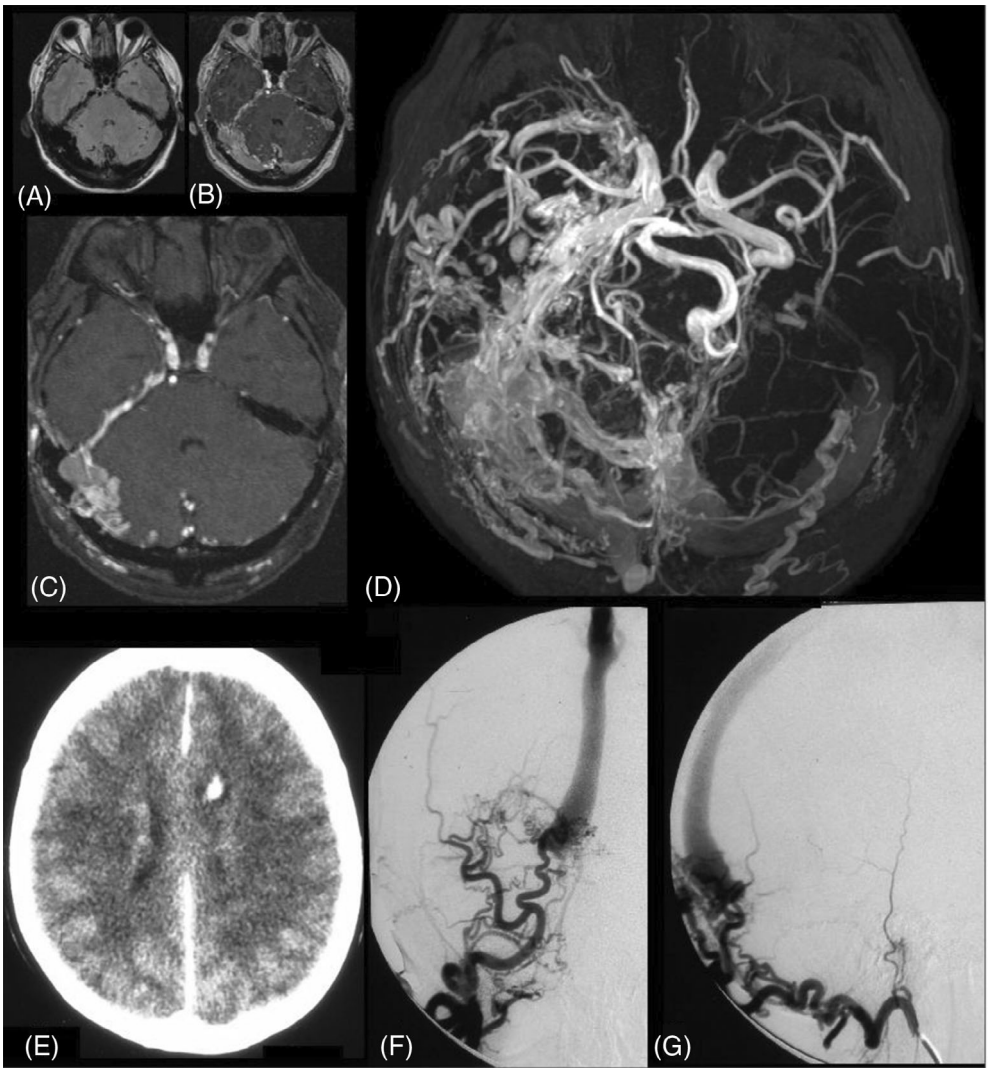

FIGURE 1 Dural arteriovenous fistula and *PTEN*-related hamartoma tumor syndrome. (A–D) 34-year-old male. Serpiginous dilated cortical veins are seen as flow voids on T2 FLAIR (A) and after contrast (B) in the posterior fossa and temporal lobe, associated with an enlarged right lateral sinus. 3D-TOF images (C, D) show a high-flow arteriovenous shunt with abnormal early venous filling of cerebellar cortical veins and lateral sinus. (E–G) 21-year-old female. Computed tomography and angiography show left lateral ventricle intraventricular hemorrhage and longitudinal cerebral fissure subdural hematoma (E), associated with diffuse bilateral white matter hypodensity. Angiography (F-G): abnormal torcular opacification with superior sagittal sinus retrograde opacification, confirming the presence of a torcular DAVF.

product during a procedure. He was an obligate *PTEN* PV carrier since (i) his sister, the index case referred to clinical cancer genetics with a history of bilateral breast cancer, thyroidectomy, and macrocephaly, carried the p.His118Profs*8 *PTEN* PV, and (ii) the PV was identified in the patient's three children.

The second patient was a 21-year-old woman with intracranial hypertension symptoms (Patient 46, Table S2). A DAVF of the torcular was observed on CTA, alongside diffuse vasogenic edema and intracranial hemorrhage (Figure 1E–G). Treatment consisted of DAVF endovascular occlusion. She subsequently developed epilepsy, which was considered a sequela of the DAVF. Other PHTS features were a multinodular goiter, labial papillomatosis, and macrocephaly.

4 | DISCUSSION

DAVFs have been reported in at least 10 patients with PHTS to date (Table S1) with a median age at diagnosis of 27 years among the five patients with in whom age is documented (range 9–46). In this study, we report on brain imaging in a series of 58 PHTS cases ascertained mainly through cancer and neurodevelopment phenotypes: two had DAVF at ages 21 and 34 years (3.4%).

In both our cases, DAVF presented at advanced stages and were associated with severe clinical manifestations; seizures and intracranial hypertension respectively. DAVF also had long-term consequences in both. The first patient underwent successive embolization procedures, while the second had secondary epilepsy. It is likely that earlier DAVF diagnosis and treatment would have led to improved outcomes.

Actual DAVF prevalence in PHTS is hard to estimate. Selection bias in our study might have led to prevalence overestimation, since imaging was, in a minority of cases, performed for reasons potentially associated with DAVF. Admittedly, the two reported DAVF cases did present with acute of subacute symptoms, that is, seizures, headaches. On the other hand, only a minority of brain MRI included optimal sequences for DAVF detection. Six out of 57 and 20 of 57 included 3D TOF/MRA and contrast-enhanced sequences, respectively. 3D TOF/MRA are the best sequences to identify DAVF, with an estimated sensitivity of 80%–90%.[11,12] DAVF—albeit asymptomatic or paucisymptomatic at the time of study—might thus have been

TABLE 1 Propositions for brain neuroimaging in *PTEN*-related hamartoma tumor syndrome (PHTS).

Imaging modality	Sequences	Starting age	Long-term surveillance
Brain MRI	T2 FLAIR T2*/susceptibility-weighted imaging Large 3D TOF/MRA	At PHTS diagnosis	Case-by-case basis Attention to symptoms of intracranial hypertension

missed in our series. In addition, none of our cases had *PTEN* germline testing specifically because of CNS DAVF. What we mean here is that neuroradiologists and neurologists rarely refer their patients with DAVF for genetic testing, as there are no data on PHTS prevalence in this context. One could imagine that a subset of PHTS cases do have DAVF as the main phenotype (alongside macrocephaly), and that these cases are rarely identified, leading to prevalence underestimation.

Given the potentially devastating consequences of DAVF in PHTS,[13] one should consider brain MRI at PHTS diagnosis in all patients. Early diagnosis of DAVF is paramount, given the potential for cure using mainly endovascular approaches.[14] Our study highlights the necessity for a specific protocol sensitive to DAVF detection. MRI should include at least 3D TOF/MRA sequences in addition to T2 FLAIR and susceptibility-weighted imaging (Table 1). Another advantage of routine brain MRI would be the identification of other PHTS-related CNS abnormalities (Lhermitte-Duclos disease or LDD, Arnold-Chiari malformations).[4] We do acknowledge the risk of overdiagnosis should our proposition be adopted, for example of asymptomatic LDD. We also recognize that systematic MRI might induce anxiety in some patients.

Subsequent surveillance should be discussed on a case-by-case basis, as there is the possibility of new lesions appearing with time. Naturally, one must be attentive to symptoms suggestive of intracranial hypertension, such as headache, pulsatile tinnitus, or double vision. Prospective, multinational studies are warranted to better define DAVF prevalence and screening indications and modalities. The physiopathology of DAVF should also be investigated, as it could lead to targeted therapy perspectives for affected cases.

AUTHOR CONTRIBUTIONS

Study conception and design: PB, CM, Data collection: all authors; Analysis and interpretation of results: AG, Manuscript preparation: AG, CM, PB, Supervision: PB, CM, Reanalysis of brain imaging: AB, ON. The manuscript has been read and approved by all authors. All persons who satisfied authorship criteria are listed.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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