Multifocal Cerebral Venous Malformations and Associated Developmental Venous Anomalies in a Case of Blue Rubber Bleb Nevus Syndrome

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Summary

We report a sporadic case of probable BRBN (blue rubber bleb nevus syndrome) with multiple CNS (central nervous system) involvement. These features consisted of multiple VMs (venous malformations) and DVAs (developmental venous anomalies) in supratentorial brain, cerebellum, and diencephalon. Since its first description by Bean, there have been many cases of BRBN manifesting with gastrointestinal bleeding with or without associated hemorrhage. Cases with CNS involvement were rarely reported and many of the descriptions were confusing with different terminologies used to describe them such as capillary venous malformation, hemangiomas, and vascular malformations. The lesions illustrated are venous malformations similar to our case. The association of DVA was recognized in some cases; they are likely to be underestimated when revisiting the published case illustrations. Although our case is sporadic, the link with HHT1 is unlikely despite the involvement of the same chromosome (Ch 9).

Introduction

Blue rubber bleb nevus syndrome (BRBN) is a rare disease and the exact cause is still unknown. A few cases of autosomal dominant inheritance have been reported, but most cases published are sporadic which may reflect re-

duced penetrance or de novo somatic mutations. BRBN is characterized by multiple cutaneous venous malformations in association with visceral lesions, most commonly affecting the gastrointestinal tract. Some case reports have demonstrated that the central nervous system (CNS), thyroid, parotid, eyes, oral cavity, musculoskeletal, lungs, kidney, liver, spleen, and bladder may also be affected³. Histopathologic examinations of these lesions reveal vascular tissue with tortuous, blood-filled ectatic vessels, lined by a single layer of endothelium surrounded by thin connective tissues⁷. Even though, the CNS involvement in BRBN is rarer than GI tract involvement, these lesions must correspond to venous malformations sharing the same histopathologic and etiologic (genetic) event. The previous descriptions of CNS involvement in the literature are often mislabelled presented as uncertain vascular malformations, hemangiomas, or angiomatosis. The reasons for these misconceptions are partly related to unavailable capabilities of recent diagnostic neuroradiology techniques and misunderstanding of the various lesions described.

Case report

A 21 years old man was referred to the hospital with a diagnosis of large and extensive arteriovenous malformations and multiple cu-

Figure 1 Cutaneous blue nevi on the ankle among many others.

taneous blue nevi, (figure 1) which had been noted for the past four years. The presenting symptoms were chronic headache and intermittent vertigo although the vestibular function test showed no gross abnormality. During that period, he also had ataxia, and horizontal nystagmus. At that time, because of intracranial hypertension due to the stenosis of mesencephalic aqueduct, ventriculostomy followed by ventriculoperitoneal shunt was performed.

Three months before referral, he had experienced worsening neurologic symptoms of vertigo, ataxic gait, and headaches.

MRI showed extensive involvement of venous lesions and anomalies in the posterior fossa including cerebellar hemispheres, diencephalon, and supratentorial brain (figure 2) and a large, centrally located venous collector. The large previously diagnosed AVM was not confirmed, a giant DVA was noted and definitely demonstrated on angiography (figure 3) with capillary stain and rapid transit. Despite the worsening of posterior fossa neurologic sym-

ptoms, endovascular embolization of the posteroinferior cerebellar artery was disregarded due to the risk of possible ischemic complications owing to the normal cerebellar tissue within the capillary bed of the venous anomaly. On the left hemisphere, abnormal venous capillary telangiectasia was noted in the subcortical white matter of the frontal lobe without either shunt or DVA (figure 3).

Association with other organs including GI tract was not found. The diagnosis of BRBN was raised on the clinical appearance of the skin lesions, the clinical history, the giant DVA and the non cavernomatous cortical venous malformation.

Discussion

Genetic aspects of BRBN.

The etiologic classifications of cerebral venous malformations can be categorized within four groups (table 1) based on the supposed timing of the causative defect;

- inherited germinal mutations (familial multiple cavernomas, ...)
- somatic mutations (sporadic BRBN, ...)
- metameric diseases (CVMS; cerebrofacial venous metamerism syndrome)¹⁵ similar to CAMS (cerebrofacial arteriovenous metamerism syndromes)¹⁶
- late altered venous modelling and remodelling processes (port-wine stains, single cavernoma, ...)

In the group of genetic diseases, some are hereditary (familial) while others are not, indicating a non-transmittable single somatic mutation. Few genetically based diseases have been related to a chromosome disorder, some have already been localized to a single gene. The usual occurrence of BRBN is sporadic and is believed to result from somatic cellular mutations. However, some familial forms of BRBN with autosomal dominant trait have been reported in the literature with involvement of chromosome 9. In the family of Boon¹⁷ and Gallione¹⁸, the disorder they reported was indeed identical to the BRBN. As in their observations, they pointed out that the family originally described by Bean had gastrointestinal bleeding from vascular lesions. They also depicted that the chromosomal loci of BRBN in family members having autosomal dominant trait manifested as multiple cutaneous and mu-

Figure 2 MRI findings of multiple lesions: venous malformations and developmental venous anomalies: A) Axial contrast enhanced T1 weighted image of the posterior fossa shows bilateral diffuse contrast enhanced lesions with centripetally converging venous drainage (DVA) patterns (black arrows). B) Axial section in another image of posterior fossa typically illustrates the huge centrally draining deep venous collector as DVA (black arrow). C) Axial section of diencephalon shows deep-seated, circumscribed pattern of venous malformation in the sub cortical region of the right frontal lobe. D) Axial section in another image of the diencephalon shows deep draining vein adjacent to the venous malformation.

Table 1. The hypothetical disorders representing cerebral vascular malformations, “Giant Telangiectasias”.

Primary disorders	Illustrative type	Gross characteristics
Genetic, Familial	Familial cavernomas	Multifocal, (chr. 7)
	BRBN	Multifocal, (chr. 9p)
	HHT1	Multifocal, (chr. 9q)
“Genetic”	BRBN	Multifocal
Sporadic non familial	VHHT1	Multifocal
Metameric	CVMS	Cerebrofacial segmental distribution.
	CAMS	Cerebrofacial segmental distribution
Post migration defect	Cavernoma	Single or multiple
	VGAM, DSM, AVM	

BRBN blue rubber bleb nevus syndrome; **AVM** arteriovenous malformation; **CVMS** cerebrofacial venous metamerism syndrome; **CAMS** cerebrofacial arteriovenous metamerism syndrome; **VGAM**; vein of Galen aneurysmal malformation; **DSM** dural sinus malformation, **HHT1** hereditary hemorrhagic telangiectasia.

Figure 3 Angiographic findings of venous malformation and developmental venous anomalies with deep venous collector: A, B, C) Frontal and lateral projection of both vertebral artery injection show bilateral cerebellar capillary stain with rapid transit and drainage into the precentral vein in venous phase. D, E) Venous phases of both frontal and lateral vertebral artery injection show venous filling of the vein of Galen (arrow) with venous stenosis at galeno-dural junction. The secondary venous reflux to deep veins, internal parietal and occipital veins, and transcerebral veins are also noted. F, G, H) Lateral projection of the left carotid artery injection show two venous malformations described as telangiectatic lesions at the late arterial phase.

C

D

E

F

G

H

Table 2 The revised descriptions of previous intracranial manifestations in BRBN: cerebral venous malformations and associated DVAs.

Reference (Age/Sex)	Clinical Manifestations	Imaging Modalities	Multiplicity and Types of Cerebral lesions	Topography	Associated DVAs
6 (11 m./F)	Partial seizures	MRI, MRA	+ ; supratentorial, cerebral VM circumscribed, diffuse	Cortical Cortico-ventricular	+(?) anomalous venous sinus
3 (5 m./F)	Complex partial seizures	MRI	+ ; cerebral VM	Cortical, cortico-ventricular	No
8 (16 y./F)	No neurologic symptoms	MRI, CT	No; single lesion N/E	Cortical,	No; dilated vein of galen
9 (6 m./M)	Growing forehead mass	CT angiography	No; single lesion Varix	Cortical,	+ ; Sinus pericranii
5 (82 y./F)	Ataxia, dementia	MRI	+ ; supratentorial, cerebellum, <i>Cavernomas</i> (? , N/E)	Cortico-ventricular	No; N/E
4 (19 y./M)	Ataxia, ophthalmoplegia,	CT angiography	+ ; supratentorial, cerebellum, (<i>phleboliths</i>) cerebral VM circumscribed, diffuse	Cortical, Cortico-ventricular	No; N/E
7 (19 y./M)	Headache, focal seizure, hemianopsia, monoparesis, ataxia	CT, angiography (N/E), autopsy	+ ; supratentorial, cerebellum, <i>telangiectasias</i> (? , N/E)	Cortico-ventricular	+ ; Multiple(?) thrombosed aneurysm of Galen
10 (N/E)	N/E	MRI	N/E	Cortico-ventricular	+ ; Multiple, Sinus pericranii
Present case (21 y./M)	Ataxic gait, nystagmus, intermittent vertigo, chronic headache	MRI angiography	+ ; supratentorial, cerebellum, cerebral VM , circumscribed, diffuse	Cortico-ventricular	+ ; Multiple

VM venous malformation; **DVAs** developmental venous anomalies; **MRI** magnetic resonance imaging; **MRA** magnetic resonance angiography; **CT** computed tomography; **N/E** not explored.

cosal venous malformations. The dominantly inherited gene lies within a 24-cM interval on chromosome 9p, defined by the markers D9S157 and D9S163. The alpha and beta inter-

feron gene cluster and the putative tumor suppressor genes MTS1 and MTS2 are also incorporated into this locus, chromosome 9p. Further characterization of the gene responsible

for this inherited form of BRBN should be done to shed more light on the mechanisms involved in these various venous lesions.

The multifocal nature of BRBN lesions is suggestive of a random impairment. Although it represents an early antenatal genetic defect from a single somatic mutation at the time of susceptibility, the genetic target seems to be active during a short period of time: during vasculogenesis as well as the early (antenatal) active angiogenetic phases of vascular remodelling. These speculative observations are based upon the fact that the postnatal genetic susceptibility of endothelial cells, particularly in the brain, makes endothelial cell clonal mutations unlikely in comparison to the instability of tumoral cells.

BRBN and HHT1

There was a single report¹⁴ that suggested that there may exist an overlap between BRBN and HHT disease in comparison with the pathology implying more phenotypic expressions than those previously recognized in the literature. Gilardi¹³ suggested that the existence of a common histological pattern might be the different expression of the same basic pathologic process between the multiple systematic, generalized tumors and the BRBN.

Rendu-Osler-Weber disease (ROW) or Hereditary Hemorrhagic Telangiectasias (HHT) is an autosomal dominant disease with two to three genotypes. HHT1 (endoglin-linked) that has several mutations altering the synthesis of endoglin have been found in affected individuals¹². Endoglin is the most abundant Transforming Growth Factor β 1 (TGF β) binding protein at the endothelial surface. TGF β in vivo is a potent angiogenetic factor and a mediator of vascular remodelling, so the earliest event in the expression of endoglin dysfunction in HHT1 can be presented with production of abnormal vessels, a dilatation of the post capillary venules. So the impact of ROW disease on the venous endothelial cells demonstrates that the primary target in the development of the shunt is the vein¹¹. The chromosomal locus in the hereditary form of BRBN is located on chromosome 9p, while the site of HHT1 mutation involves chromosome 9q¹⁷. Yet HHT1 is not particularly associated with DVAs, and AV Shunts or fistulas are not noted in BRBN.

The association of BRBN with DVA.

DVA is an extreme normal anatomic variation that occurs as a form of embryonic or fetal adaptation; it represents dynamic collateralisation compared to normal static venous equilibrium. So the deep and superficial types of DVAs constitute the extremes in the development of the transcerebral venous systems^{1,2}. The association of DVA in BRBN is a relatively well known phenomenon especially presented with multiplicity in some case reports^{9,10}.

The previous reports of BRBN did not clearly describe the DVAs, but retrospective review of the illustrations show their frequency. Our case harbours huge deep bilateral cerebellar DVAs with intense capillary stain and rapid capillary transit. It drains into the precentral vein and later into the vein of Galen via the lateral mesencephalic veins. Secondary reflux into the deep veins and internal parietal and occipital veins is also noted (figure 3). Waybright⁷ describes a dilated vein of Galen but retrospective analysis shows venous disposition similar to ours. Review of previous literature (table 2) found that "multiple cerebral venous malformations" in cortico-ventricular disposition, correspond in almost all cases to DVAs draining into deep venous collectors. (6,7,10, and present case)

Cerebral venous malformations in BRBN

The venous malformations represented in BRBN show a typical appearance of capillary ectatic changes with stagnant vascular pooling. The radiologic findings of cerebral VM also demonstrate its own histopathologic architecture. The cross sectional imaging studies of cerebral VM in BRBN show well enhanced multiple lesions with circumscribed or diffuse masses. Our case showed both circumscribed and diffuse patterns on enhanced MRI scans (figure 2), representing cerebral VM in BRBN; the same morphologic patterns had been identified in previous literature^{4,6}.

The differentiation of DVAs, cavernomas, telangiectasias, AVMs, and VMs should be done for definite descriptions of cerebral lesions when regarding the angiographic and radiologic aspects in individual BRBN cases with cerebral involvement. The cavernomas are angiographically occult. The AVMs show AV shunts with enlarged feeders and draining veins

rarely associated to DVAs and even less draining into DVAs.

Telangiectasias are the vascular malformations of the venules, depicted as dilated medullary capillary or venous structures and often form a mass-like appearance. Angiographic findings need to be read with precision to separate all these entities.

Conclusion

Sporadic BRBN could be classified with single somatic mutation lesions between here-

ditary familial disorders and metamerism diseases. BRBN typically represented herein with various multifocal venous anomalies and malformations involving cutaneovisceral organs and cerebral structures. The most distinct and prominent vascular phenotypic manifestations in BRBN are multiple cerebral venous malformations (those are consistent with cutaneous blue nevi of typical BRBN) and associated multiple developmental venous anomalies. The neurological manifestations might be variable according to the location and severity of the lesions.

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