Symptomatic Developmental Venous Anomalies

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MHMBEN002

THE UNIVERSITY OF CAPE TOWN in the fulfilment of the requirements

for the degree

MMed Neurosurgery

Faculty of Health Sciences

UNIVERSITY OF CAPE TOWN

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ACKNOWLEDGEMENTS

To my wife Haifa, who tells me I deserve to have it all.

To my children Ibrahim, Rylam and Nareez, who are the reason for it all.

I would also like to thank my supervisors, Professor Allan Taylor and Professor David Le Feuvre.

Finally, to my father Ibrahim and my mother Julie. Thank you for always being so proud of me.

Mohammed Ben Husien

DECLARETION

I, MOHAMMED BEN HUSIEN hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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PART A: RESEARCH PROTOCOL

Introduction

Developmental Venous Anomalies(DVA) are a normal variant that may be associated with other cerebral vascular malformation they have bean previously referred to Venous angiomas. DVAs are the most frequently encountered cerebral vascular malformation and their incidence is reported to be high as 2.6%[(3)].The term cerebral developmental venous anomaly was coined by Lasjaunias. DVA's represent an extreme version of venous drainage of the brain using dilated trans-cerebral veins to reach either deep or superficial pathways.

The normal cerebral Venous Angioarchitecture: -

The veins of cerebral hemisphere can be divided in two systems.

1-A superficial system draining the cerebral cortex and the subcortical white matter. The superficial system collects into the pial veins.

2-A deep system, which consist of the deep medullary veins draining the deep white matter and striate body. These veins are tributaries of the internal cerebral vein and the basal veins, mainly through the sub ependymal veins located along the external and superior aspect of the lateral ventricle.

The connection between the cortical and the deep venous system through veins that cross the entire thickness of brain parenchyma have been described as trans cerebral veins.

Developmental Consideration

It is postulated that DVA's form during embryonic development due to an alteration in trans-cerebral venous flow. There may be associated cavernomas in some patients and cortical migratory abnormalities have also been described [(3)]

Natural History

Detection is almost always incidental during CT or MRI scanning as parenchymal venous drainage is adequate. Where cerebral haemorrhage is part of the patient's presentation, bleeding from an associated cavernoma should be considered [(2).] There have also been descriptions of cerebral arteriovenous malformation(AVM's) which drain into a DVA and

these can potentially present with symptoms related to the AVM [1]. DVA's are rarely symptomatic in isolation but patients can present with seizures or neurological deficit related presumably to venous congestion and ischemia [3]

STUDY AIM

To describe the patients presenting to a single unit over a 10-year period with symptoms attributable to a DVA.

HYPOTHESIS

DSA angioarchitecture of DVA will have features that correlate with venous congestion, ischemia and the patient's symptoms.

Study method

1-Study design

A retrospective study of patient from Groote Schuur hospital and UCT private hospital, over a period from Jan 2003 to August 2013.

2-Patient selection

Patients will be selected from Neurosurgery database, and includes all patients presenting with symptoms that could be related to a DVA where no other lesion was present.

3-Data collection

Data collection is done in electronic sheet and see the variables of age, sex symptoms, investigation, pathology, clinical outcome and treatment.
Digital subtraction angiography (DSA), Computed Tomography (CT) brain and Magnetic resonance imaging(MRI) will be reviewed with the aim of correlating the patient symptoms with the DVA angioarchitecture.

4-Intervention

This will be an observational study, and no intervention is planned.

5-Ethics

The study protocol was presented to surgical department for an MMed and was approved, following which it was approved by Ethics committee.
Patient privacy and confidentiality will be respected. Care will be taken not to link any personal or identifiable characteristics of the subjects to the data collected or published.

The outcome of the study will be published in Neuro-intervention journal and will be submitted for Master of Medicine in Neurosurgery {MMed in Neurosurgery}.

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PART B: LITERATURE REVIEW

Introduction: -

Developmental Venous Anomalies (DVA) were first described in 1986 by Lasjaunias [18]. Previously they had been described as venous angiomas. These lesions were described as being composed of dilated venous medullary channels draining into an intra - or extra-parenchymal collector. These lesions are now called DVAs. These cerebral vascular anomalies are revealed when Computer Tomography (CT) and Magnetic Resonance Imaging (MRI) scans are done and in most cases these venous anomalies are considered to be benign and coincidental. Studies have revealed a 2.6% incidence from autopsies on 4,069 brains [13] and imaging revealed an incidence of around 0.5% [14].

DVAs are extreme anatomical variations of normal cerebral venous drainage. They are a collection of dilated medullary veins (also called trans-cerebral/cerebellar veins) that are composed of multiple venous channels which then unite to form a large collecting vein., This vein is usually dilated and will drain normal brain parenchyma, creating the appearance of a 'caput medusae'. Some studies of DVAs have noted abnormal brain parenchyma (cortical dysplasia). Cortical dysplasia has been suggested to be associated with prominent or abnormal venous drainage [33]. During early fetal and late embryonic periods active neural migration emanating from the periventricular germinal matrix is affected by the dilated or abnormal venous drainage leading to cortical dysplasia [33].

DVAs are classified into two types based on draining veins. Either deep or superficial. Those that drain into sub-ependymal veins are classified as deep and those that drain into cortical pial veins are classified as superficial. The trans-cerebral veins join either the deep or superficial venous systems by crossing a varying length of the brain parenchyma, but usually one drainage pathway predominates [12].

The volume of the brain parenchyma affected by DVAs can vary from the whole hemisphere, an entire cerebral lobe, an entire or part of the cerebellum, brainstem and circumscribed wedge of the periventricular white matter or a few sulci. DVAs are mostly revealed at subcortical, juxtacortical or periventricular sites, and are most often observed supratentorially predominantly in the frontal lobes [8]. One study has observed more than two DVAs in the brain that coexist in separate regions in 1.2% to 16% of cases [12]. The likelihood of observing a DVA is slightly higher in males between the ages of twenty and fifty years. [12]

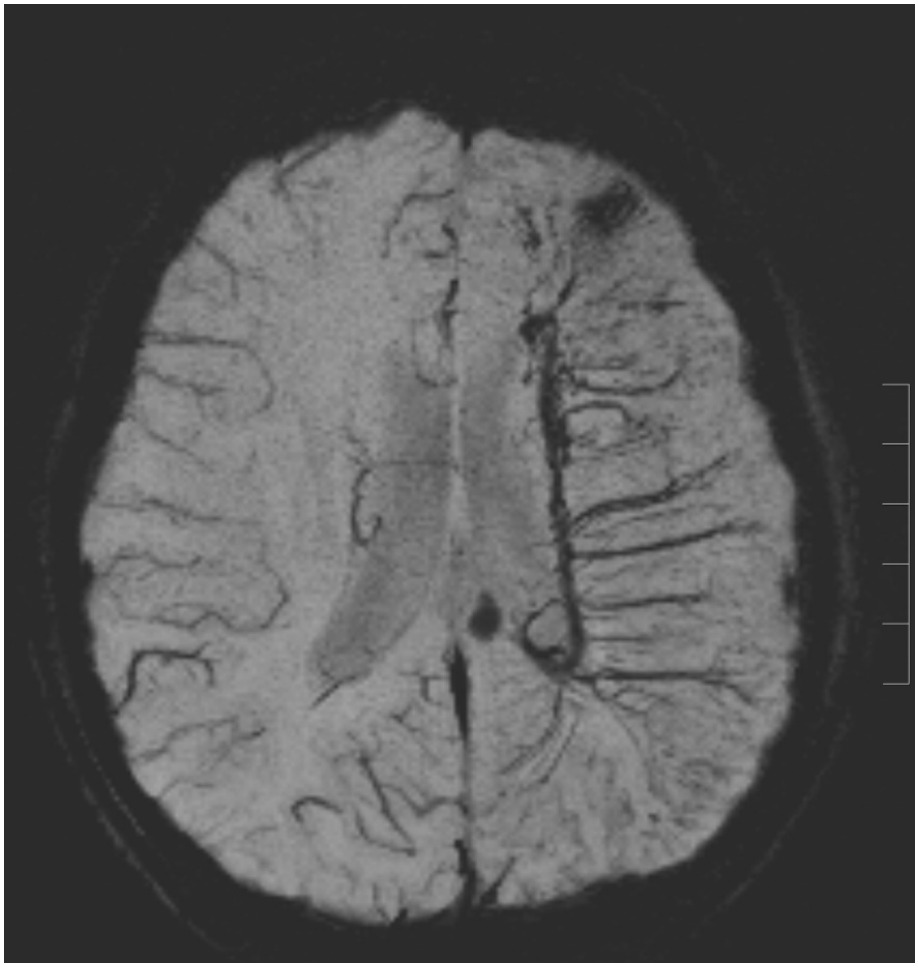

Fig 1.MRI brain showing a large DVA, draining the entire left cerebral hemisphere
(patient from Groote Schuur Hospital).

Controversy surrounds their exact clinical significance, as DVAs are rarely symptomatic. The symptoms displayed by a patient can be related to a lesion that is associated with DVAs, such as a cavernoma, which can cause symptoms, for example if they bleed [(2)]. Other symptoms that can be linked directly to DVAs include hydrocephalus (caused by compression of the aqueduct from mechanical compression) [(9)], trigeminal neuralgia caused by compression of the fifth cranial nerve [(10)], or indirectly linked to DVAs like seizures or headaches. [(4)]

Pathogenesis

There are four stages in the development of the normal cranial vasculature [27] [28]:

Stage one {between weeks 2-4}: The neural plate is open and the developing nervous tissue is fed by the diffusion of amniotic fluid.

Stage Two {during week 4}: The meninx primitive that is a dense network of developing connective tissue causes the neural tube to close, so that the neural tube is now supplied with nutrients by vascular plexus from the developing primitive dorsal aorta and drained by the cardinal veins.

Stage Three {between weeks 6-7}: At the beginning of this stage the venous drainage is transitory as important brain vesicles differentiate, and a part of the meninx primitive becomes folded back to form a cavity by invagination into the neural tube. This now contains the median prosencephalic vein a large midline vein. The posterior part will begin to form the vein of Galen, and the anterior part will regress to form internal cerebral veins.

Stage Four {during week 12} The meninx primitive develops intrinsic capillaries to supplement the supply of nutrients because nutrients can no longer be provided by diffusion alone as the neural tube has become too thick.

DVAs are typically described as having a “caput medusa” appearance. This is the result of the venous channels converging into a collecting vein [12]. “Caput Medusa” is a Latin word describing the head of Medusa a mythological Greek monster having snakes for hair. [13]

There is insufficient understanding of the embryological origin of DVAs. There are 2 current theories

The one is that during early fetal and late embryonic development anomalies of neural migration could result from vascular infections or expressions of genetic disorders during this time. Venous development may be restricted resulting in insufficient subcortical and cortical development leading to a greater risk of venous development failure. These activities produce primitive venous channels that are enlarged along the course of the parenchymal anomaly that will then lead to the development of DVAs [30].

Lasjaunias (1986) on the other hand disagreed with this.

He argued that DVAs were anatomical variations created by hemodynamic needs, which contribute to transhemispheric anastomotic pathways being recruited [18] Due to arrested development or thrombosis of local veins there may be recruitment of regional veins to compensate for a portion of the normal cerebral venous system being absent (Stage Three) [29].

The microscopic structure of normal cerebral veins reveals adventitia, tunica media and tunica intima. The adventitia is mainly made up of collagen fibers and is thicker than the tunica media. The tunica media contains collagen fibers mostly arranged in a circulatory manner within the smooth muscle. The tunica intima has a thin sub-endothelium layer of internal elastic membrane and connective tissue elements.

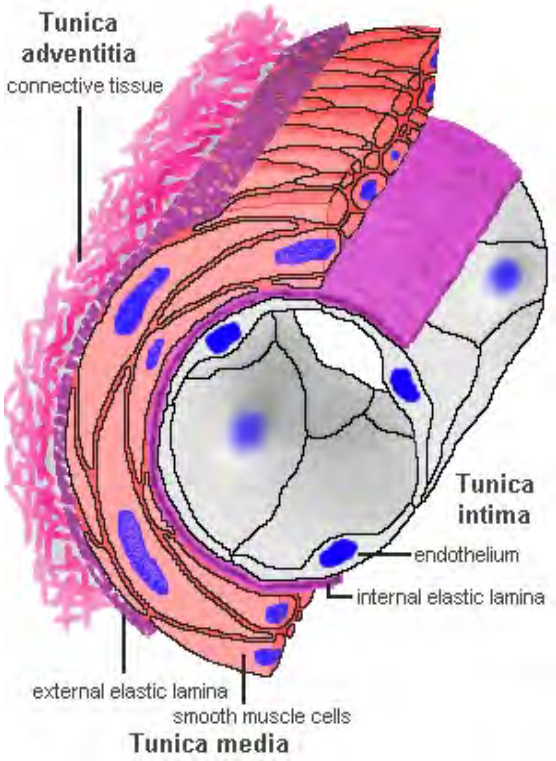

Fig 2. Normal vein histology reveals Tunica intima (inner mast layer), Tunica media and Tunica adventitia (outer layer) (Author UCT 2013).

There are few histo-pathological descriptions of DVAs. Generally, DVAs have thinner walls. The smooth muscle layers are more loosely arranged than is seen in normal veins. There is also an absence of elastic lamina and parietal fibrous thickening [12] [26].

Normal Cerebral Angioarchitecture

The intracranial venous system can be divided in to two systems, the deep and superficial venous drainage systems.

Deep Venous System

The deep venous system has two components to it.

1. The internal cerebral vein, the great cerebral vein (of Galen) and the basal vein (of Rosenthal).
2. The trans cerebral venous system.

Internal cerebral veins

These veins drain the most of the deep subependymal and the choroid venous system of the cerebral hemisphere; this vein is located inside the velum interpositum and have the following tributaries [45]

Septal vein
Posterior septal vein
Thalamostriate vein
Anterior caudate vein
Direct lateral vein
Superior choroidal vein
Anterior thalamic vein
Medial choroidal vein
Medial atrial vein
Direct lateral atrial vein
Common atrial vein
Superior thalamic vein
Habenular veins
Third ventricular choroidal veins
Corpus callosum vein

The Internal cerebral veins are formed by the confluence of the anterior septal, choroidal, and thalamostriate veins at the interventricular foramen. They then pass within the tela choroidea posteriorly along the midline, to reach the suprapineal recess where confluence occurs with the contralateral internal cerebral vein to form the great cerebral vein of Galen. Along the length of the internal cerebral veins there are connections with the superficial cortical venous system by transcerebral veins [45].

Ventricular veins and Deep Cisternal Collectors

These are classified into two main groups, the lateral and the medial veins that are located at the same level as the lateral ventricles. The lateral group drains the deep nuclei, while the medial group drains the septum pellucidum and fornix. Thus, two concentric rings can be described: an interventricular (outer ring) and an extraventricular (inner ring) at the choroid fissure. They unite at the interventricular foramen and the uncus. The

intraventricular ring drains the lateral and the medial groups, whereas the extraventricular ring is the venous outlet for the deep ventricular venous system [45].
The quadrigeminal veins are small group of veins, usually three veins, the inferior, middle, superior quadrigeminal veins, that then join each other to drain into the precentral cerebellar vein and then drain into vein of Galen. The great cerebral vein is a large collecting vein which starts at the site of fusion of the internal cerebral veins in the space between inferior aspect of the splenium of the corpus callosum and the pineal body to the anterior end of the straight sinus, that is found at the junction between the falx cerebri and the tentorium. Other tributaries to the vein of Galen [45] [6]

- Basal vein, that communicates with the cortical veins of the anterior part of the lateral cerebral fissure and the cavernous sinus as well as anterior perforator substance.
- Splenial and the occipital veins.
- Anterior vermian vein.

The System of the Basal Vein of Rosenthal

Multiple cortical tributaries contribute to the basal vein laterally. Basal vein anterior draining into the deep middle cerebral vein and posterior drainage into the great cerebral vein

The tributaries of the basal vein [45] [6]

Anterior cerebral vein	Posterior perforated substance vein
Olfactory vein	Peduncular vein
Inferior striate vein	Lateral mesencephalic vein
Inferior frontal vein	Hippocampal vein
Deep middle cerebral vein	Inferior temporo-Occipital vein
Anterior hypothalamic veins	Internal occipital vein
Posterior hypothalamic veins	

Common venous outlets for the venous system [45]

Venous tributary	Venous Outlet
Straight sinus	Torcular-transverse sinus
Medial parietal and occipital vein	Superior sagittal sinus
Lateral and ponto-mesencephalic vein	Petrosal vein
Basal vein	Deep sylvian vein
Hippocampal vein	Infratemporal vein
Transcerebral vein	Cortical vein, superior sagittal sinus
Ant and Post communicating veins	Contralateral basal vein
Falcine sinus	Superior longitudinal sinus
Tentorial sinus	Transverse sinus

Superior Vermian vein inferior vermian vein

The Transcerebral veins

The transcerebral veins drain the white matter of the cerebral hemisphere. They are also called medullary veins and cross the white matter connecting the deep veins with the cortical cerebral veins (Duret 1874). They are classified as superficial and deep medullary veins [45].

1-Superficial medullary vein drain the white matter into the superficial venous system of the cerebral cortex.

2-The deep medullary veins that also drain the white matter deep into the subependymal veins of the ventricular wall.

The two draining medullary veins (the superficial and the deep medullary veins), have direct anastomotic veins, they may vary in number from 2,000 to 4,000 [45]. The medullary veins will have a fan-shaped appearance that is the result of their meeting at the superolateral angle of the lateral ventricles; they will have a different direction in each cerebral lobe.

1-The frontal system has more anteroposterior and more medial course, forming an anastomotic connection between the vein of the internal frontal system with the septal and anterior caudate veins [45].

2-The medullary veins of the frontorolandic and parietal region, unite with the body of the ventricle by the longitudinal and caudate veins before they reach the thalamostiate veins [45].

3-The veins of the posterior parietal region and occipital region travel forward to unite with the lateral atrial vein [45].

4-The medullary veins of the temporal lobe have an ascending direction to unite with the inferior ventricular veins, and the lateral atrial veins run more posteriorly [45].

Superficial Veins and Sinuses

These have bean classified into two groups, a mediodorsal group that opens in the superior and inferior sagittal sinus and a posteroinferior and middle cerebral group, which open into the cavernous sinus [45] [6].

- The mediodorsal system composed of the cortical tributaries that open into the superior sagittal sinus or the inferior sagittal sinus, as well as the straight sinus.
- The latero-ventral system composed of the veins that open into the lateral sinus, the parieto-temporal veins
- The anterior system is composed of fronto-parietal and temporal veins that drain into the cavernous sinus.

Dural Sinuses

The superior sagittal sinus: - This forms part of the convex or attached margin of the falx cerebri that has its origin at the foramen caecum where it is joined by a vein from the nasal cavity. Then, running backwards, close to the occipital protuberance the direction deviates to either side, but more often the right side. It then continues as the corresponding transverse or lateral sinus. Superior cerebral veins open on each side of the sinus [46].

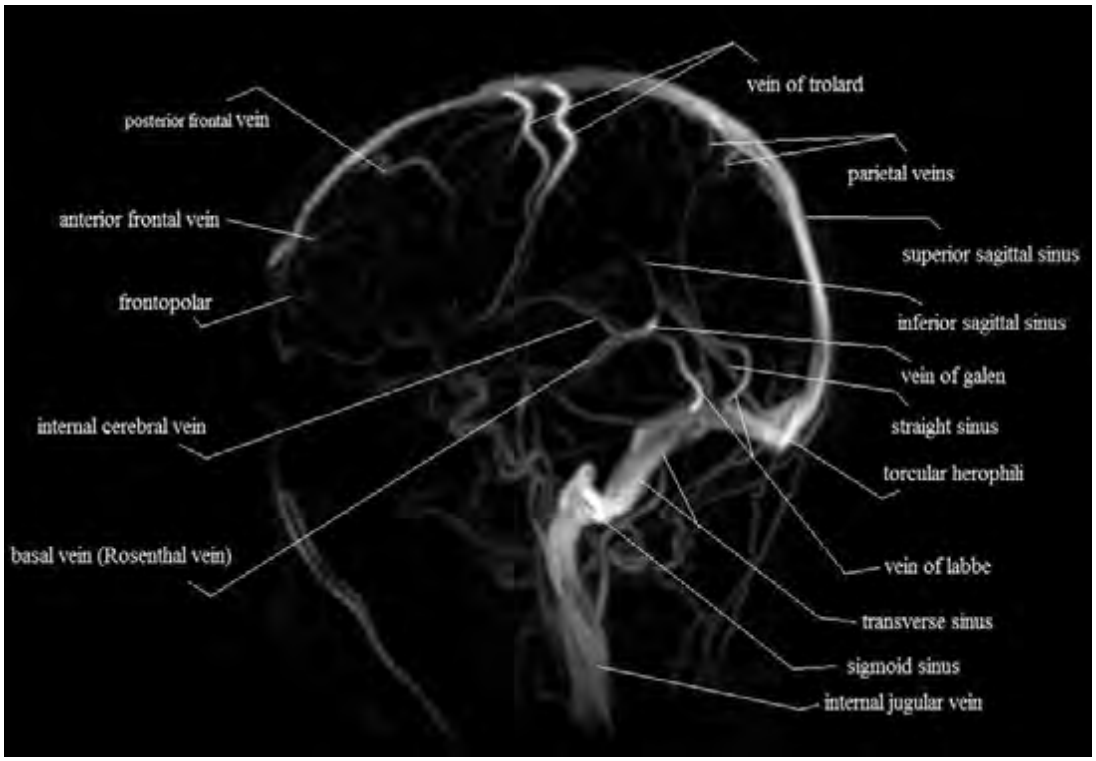

Fig 3. Magnetic Resonance Venography (MRV) image that demonstrates the deep venous system and normal superficial systems of the brain.

Inferior sagittal sinus: - This is located within the falx cerebri at the posterior half of its free margin and comes to an end in the straight sinus.

The straight sinus: - This is located between the tentorium cerebelli and the falx cerebri at their line of junction. It is prolongation of the vein of Galen. It empties in the confluence. It preferentially drains into the left transverse sinus [46].

The transverse and sigmoid sinuses: -These normally begin at the internal occipital protuberance and drain the superior sinus, straight sinus and occipital sinus. It runs laterally to the mastoid where it becomes the sigmoid sinus. The sigmoid curves downwards when leaving the tentorium and then medially until it reaches the jugular foramen. At this location it ends as the internal jugular vein that is located in the temporal bone where it grooves the mastoid part being known as the sigmoid sinus [46].

The occipital sinus: - This single sinus is located at the attached margin of the falx cerebelli and represents the smallest cranial sinus. Sometimes there are two sinuses. It originates from the margin of the foramen magnum and travels through many small venous channels where it joins the transverse sinus at its terminal part [46].

The confluence of the sinuses: - This is located at one side of the occipital protuberance and has a form that is irregular, and relates to the dilated extremity of the superior sagittal sinus. This is derived from the same side as the transverse sinus, so that blood is received from the occipital sinus, as there is a connection with the transverse sinus of the opposite side across the midline [46].

There are two inferior petrosals, two intercavernous, two superior petrosals and two cavernous sinuses that make up the anterior-inferior group of sinuses.

The cavernous sinus: -These are located on each side of the body of the sphenoid bone and have a form that is irregular. It is larger and narrows anteriorly and extends from the superior orbital fissure to the apex of the petrous part of the temporal bone. These drain into the petrosal sinuses posteriorly. The internal carotid artery is located on the medial wall of each sinus with the abducens nerve running lateral in the sinus next to the artery. The lateral wall is the location of the maxillary and ophthalmic divisions of the trigeminal nerve, as well as the oculomotor and trochlear nerves. The superior ophthalmic vein opens into the cavernous sinus after passing through the superior orbital fissure, and the cavernous sinus also receives small spheno-parietal sinuses, the deep sylvian veins and can drain the medial temporal lobes. `Posteriorly the cavernous sinus uses the superior petrosal sinus to communicate with the transverse sinus and uses the inferior petrosal sinus to communicate with the internal jugular vein. Inferiorly using the foramen lacerum, foramen ovale and foramen vesalii there is communication with the pterygoid venous plexus. Medially, the posterior and anterior intercavernous sinuses are used for the two sinuses to communicate with each other [46].

There are two ophthalmic veins the superior and inferior.

The superior ophthalmic vein: - This is located at its origin in the nasofrontal vein at the inner angle of the orbit, and follows a similar course to the ophthalmic artery and has draining veins corresponding to the branches of this artery. The superior ophthalmic vein travels between the two heads of the rectus lateralis in the form of a short single trunk, and through the superior orbital fissure at the medial part and ends in the cavernous sinus.

The inferior ophthalmic vein: - This is located at its origin at the forepart of the floor and the medial wall of the orbit as a venous network, and has two branches that run backwards at the lower portion of the orbit. One branch enters the cranium through the superior orbital fissure and the other branch passes through the inferior orbital fissure and joins the pterygoid venous plexus.

The intercavernous sinuses: - There is an anterior and posterior sinus that connects the two cavernous sinuses across the midline. The posterior passes behind the hypophysis and the anterior passes in front. In conjunction with the cavernous sinuses they create a venous circle surrounding the hypophysis. However, one of these sinuses is sometimes absent, and normally the anterior sinus is the larger of the two.

The superior petrosal sinus: - This is located at the attached margin of the tentorium cerebelli and in the superior petrosal sulcus of the temporal bone, it connects the cavernous and transverse sinus, and in terms of size is narrow and small. It travels from the posterior end of the cavernous sinus and across the trigeminal nerve, until joining the transverse sinus where this curves downwards to the inner surface of the mastoid portion of the temporal bone, and receives inferior cerebral veins and the petrosal cerebellar veins, as well as veins from the tympanic cavity.

The inferior petrosal sinus: -This is located at the inferior petrosal sulcus of the temporal bone originating at the post-inferior portion of the cavernous sinus, and then passes through the anterior portion of the jugular foramen finally travelling to the superior bulb of the internal jugular vein. Veins from the medulla oblongata, pons, internal auditory veins, as well as from the under surface of the cerebellum open into the inferior petrosal sinus.

Emissary Veins and Transcranial Drainage

The emissary veins connect the extra cranial venous system with the intracranial venous sinuses. In general, when these superficial veins and sinuses are being considered, the feature of the balance between the drainage of the internal jugular vein and the external jugular vein should be kept in mind [45] [6]

The collecting systems drain into either the internal jugular vein (IJV) or the external jugular vein (EJV) system, in general, the torcular-lateral and the sigmoid sinus drain into the IJV, controversially; the emissary veins open into the EJV system

The emissary veins

Condyloid emissary	Hypoglossal emissary
Marginal Sinus	Mastoid sinus
Inferior petrosal sinus	Parasagittal emissaries
Petro squamosal emissary	Cavernous sinus emissary

The emissary veins of the dorsomedial confluent are located at the midline, from the frontal region to the torcular area. The frontal emissary veins connect the superior sagittal sinus to the nasal cavity. The emissary veins of the ventrolateral system include the petrosquamous sinus which communicates with the EJV through the petrosquamous foramina [45].
The emissary veins of the anterior collector will join either the EJV through the cavernous sinus (Pterygoid venous plexus connection) or the IJV by inferior petrosal sinus

Imaging findings

DVAs may be seen on CT and MRI. In order to be seen on CT contrast needs to be given but on MRI DVAs have characteristic features, but their demonstration can be improved significantly on MRI if contrast is administered.

Computer Tomography (CT)

When CT scans are uncontrasted it is seldom possible to identify DVAs. When contrast is administered the venous convergence into the enhancing collecting vein or the typical “caput medusa” may be seen. It is possible to detect the venous collector of the DVA as having curvilinear or linear enhancement. In superficial DVAs this curvilinear or linear enhancement travels from the deep white matter to the superficial cortex. In deep DVAs the curvilinear or linear enhancement travels from superficial to deep [43].

Magnetic Resonance Imaging (MRI)

MRI is far superior to CT for evaluation and detection of DVAs and of parenchymal abnormalities and cavernomas [13]. As with CT scans DVAs are best seen post contrast.
When gadolinium-based contrast MRI scans are done the medullary veins and venous collectors enhance significantly giving the spoke-wheel appearance of DVAs. Although these veins are small at the periphery, they become larger as they collect to form the draining vein. This spoke-wheel appearance gives the “caput medusa” appearance [31].

On T2 weighted images DVAs are seen secondarily to the flow void created by the collecting vein of the DVA.

Digital Subtraction Angiography (DSA)

When a DSA is done it is, during the early to middle venous phase that it is possible to visualise the DVA angiographically. Again the typical appearance of the "caput medusa" with transmedullary veins that drain into a large venous collector is seen. This can extend to or from the superficial or deep venous system [16].

The Rodesch classification is a clinical and radiological grouping of DVAs into those that are [4]:

1. Asymptomatic for deep and superficial DVAs.
2. Asymptomatic DVAs with capillary stain.
3. Symptomatic DVAs with capillary stain.
4. DVA draining a true arteriovenous (AV) shunt on DSA.

Arterialised DVA

Arterialised DVAs are an atypical form of DVA. Huang [19] first described DVAs with an arterio-venous shunt. The characteristics of non-arterialised DVAs and arterialised DVAs are similar on CT and MRI scanning, and it may be impossible to differentiate arterialised from classic forms using these imaging modalities. For this a DSA is required to differentiate an arterialised DVA from a classic DVA. DSA reveals arterio-venous shunting during angiography and the lesion is clearly represented in the arterial phase of injection. The review of literature reveals 53 case reports of arterialised DVAs [20].

Classification of arterialised DVA

DSA studies have reported that during the mid or late arterial phase, early angiographic opacification of the DVA may be observed, and three types of arterialised DVAs have recently been classified [12]:

Type 1. These are typical DVAs without evidence of arterial feeders but where caput medusae blush occurs during the mid or late arterial phase.

Type 2. These are arterialised DVAs with blush occurring in the arterial phase. There are arterial feeders to the caput medusae that are enlarged, but without an angiographically demonstrable arteriovenous malformation (AVM) in its central portion or nidus.

Type 3. These would include DVAs draining an angiographically demonstrable AVM.

DVAs associated with Cavernomas

When a patient has a DVA and intracranial haemorrhage is detected, it is important to exclude an associated cavernoma as the cause. Review of literature reveals that the association of cavernomas with cerebral DVAs has a frequency that ranges from 8% to 33% [14] [24].

In the general population the incidence of cavernomas ranges from 0.4% to 0.9 %[22]. The most common mixed vascular malformation is DVAs with a cavernoma [14]. In general patients with cavernous malformations (CMs) associated with DVAs have a more aggressive clinical course than those who only present CMs [23].
The association between DVAs and cavernomas is well described but the pathogenesis is not well understood.
A proposed hypothesis is that DVAs will lead to the development of cavernomas. This is based on the fact that DVAs develop at an early embryological time between week five and seven (Stage Three). While cavernomas usually develop later in life. The proposed hypothesis suggests that when the intraluminal pressure is chronically increased in the DVAs, this will lead local hypoxia that will stimulate angiogenic factor to increase locally, this could induce the formation of a vascular malformation [25].

Fig 4. Groote Schuur Hospital admitted this male seventeen-year-old patient, who for a period of three years and at irregular intervals had a history of generalised tonic-clonic seizures. This CT scan with enhanced contrast reveals abnormal tortuous deep veins in (the left hemisphere (a), DSA (b, c) lateral and (d) AP shows classic DVA with the features of caput medusae with the large superficial to deep system DVA from digital subtraction angiograms (patient from Groote Schuur Hospital 2010).

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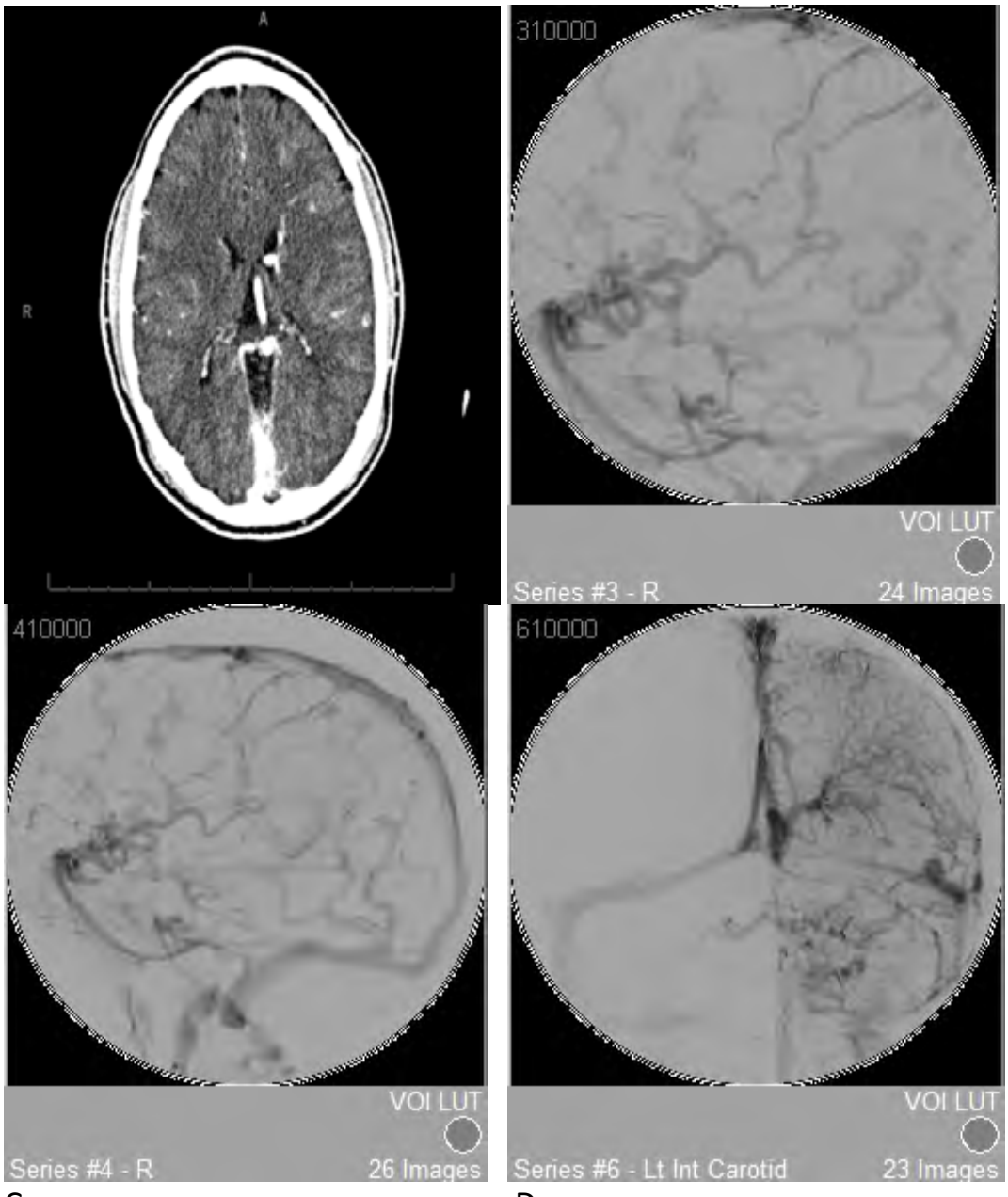
A B



C D

Clinical presentation

Normally a DVA is revealed coincidentally on neuroimaging as, generally, patients presenting with DVA are asymptomatic. According to Pereira [10], DVAs can contribute to symptoms by their pathophysiological mechanisms that are usually divided into two groups:

Group A. Compressive mechanism

Group B. Flow related mechanism

This could be subdivided to either
1.DVA having increased inflow
Or
2. DVA having reduced outflow

Group A

Would include conditions in which the DVA causes mechanical compression of the surrounding structures. This may cause cranial nerve dysfunction or obstructive hydrocephalus. Research carried out by Pereira reported that for a sample population of 69 patients presenting with symptomatic DVAs, 14 patients presented because of mechanical compression and 49 patients presented with flow related causes. This study also revealed that mechanical compression caused the neurological symptoms in 32.7% of cases of symptomatic DVAs. The most commonly compression symptoms were trigeminal neuralgia (TN), facial hemispasm, brain stem deficit, tinnitus and hydrocephalus [10].

1- Trigeminal neuralgia.

DVAs can be a cause of trigeminal neuralgia. 17 cases have been reported in the literature [21], and symptoms are caused by indirect or direct compression of the fifth nerve at the nerve root entry zone. (Vein alone or in combination with the superior cerebellar artery) Three of these 17 cases had insufficient information provided by the researcher and were excluded. Lack of information included distribution of pain, time of the symptoms and location of the DVAs.
Nine patients received microvascular decompression as treatment (MVD) (Vein reposition or Vein ligature) and one glycerol rhizotomy was done. Complete pain relief was achieved for all patients. Five patients received DVA ligature as treatment and

complete pain relief was achieved in 4 patients, but predictably cerebellar infarction resulted in the death of one patient. The preferred treatment for TN is currently MVD because the mortality is less than 1%, and long-term results are good. In contrast, DVA ligature sacrifices cerebral venous drainage, has a high mortality rate of 20%, and is no longer recommended [21].

2-Hydrocephalus.

For DVAs to cause hydrocephalus is extremely rare, it is postulated that by compression mechanism (Obstructive mechanism) of DVAs leading to aqueduct stenosis. The review of literature only reports 10 cases [9]. The DVA can produce compression of the aqueduct and this could lead to hydrocephalus. Cerebrospinal fluid diversion (CSF) was used to treat the hydrocephalus effectively, as there is no evidence that endoscopic third ventriculostomy (ETV) is better than a shunt in treating hydrocephalus when caused by a DVA, However, when there is a clinical decision to alter shunt malfunction or when patients are older children, ETV is recommended for consideration [44]. Interestingly there is no suggestion that impaired hydrodynamics related to altered venous drainage could be an alternative cause of hydrocephalus. In light of more recent evidence regarding the importance of transcerebral veins in cerebral water absorption this possibility should be considered.

Group B

Would include conditions where the pressure or flow within the DVA is increased, such as imbalance in the blood outflow or blood inflow in the DVA system [11]. Reasons for increased inflow would be varying degrees of arterial shunting into the DVA collectors. As with the description by Ruiz this may be subtle without clear arterial inflow seen on angiography, a microshunt at the level of the medullary veins or the DVA being used by a typical cerebral arteriovenous malformation as a drainage pathway. [12]. Arterialisation of the DVA poses two main risks, haemorrhage and venous infarction in the territory drained by the DVA. In the review by Periera 66% of the 19 patients identified with increased inflow presented with haemorrhage.

Anatomical obstruction of outflow was reported in 26 cases in the literature and can be due to stenosis of the main venous collector or thrombosis within this vein. [10] Thrombosis (76%) either idiopathic or because of a prothrombotic state is more likely then stenosis (24%). The predominant effect on the brain is venous congestion and oedema resulting in headaches, seizures, neurological deficit and altered neurological state.

Periera [10]. also described a small number of patients, one from their series and 3 further case reports with functional outflow restriction. This arose where a fistula was present that did not drain directly into the DVA but by increasing pressure through out the venous system resulted in poor outflow from the AVM. This group illustrates the point that under most conditions DVA's drain their territory sufficient to maintain normal physiology however compared to normal veins there is less reserve when the system is stressed.

Treatment strategies very considerable given that cases have been reported over an extended time period and in many centers. Radiosurgery has been used to treat fistulas associated with DVA as well as surgical resection achieving good outcomes [Awad 1993, Truwit 1992 – referenced in Pereira paper]. Endovascular embolization of the fistula has also been used successfully [Pereira]. In all cases care must be taken to preserve the DVA while treating the fistula.
Where thrombosis is the cause of outflow restriction there has been an 82% good outcome reported with a combination of conservative therapy and heparinisation as for the treatment of cortical venous thrombosis. [Pereira]

1-Headaches

The symptoms occurring with DVAs most commonly are headaches [3], which are often resolved over time without or with intervention. They can be associated with focal thrombosis of the DVAs collecting vein. Acute thrombosis of the collecting veins could also cause ischemic infarction, haemorrhagic or ischemic infarction transformation to haemorrhage infarction surrounding the DVA[15]. A study of 19 patients presenting with symptomatic DVAs demonstrated subarachnoid and intraventricular haemorrhage (5%), parenchymal haemorrhage (37%) and venous ischemic infarction (53%) [10] and the other 5%.

2- Haemorrhage

Since the use of MRI scans it has been possible to observe the natural history of DVAs. These studies have suggested a benign natural history for isolated DVAs [14] [34]. Based on prospective follow up findings there appear to be very low risks of haemorrhage, and with an annual risk from 0.15% to 0.68% [35] [36]. Mortality is reported to be 0%, and morbidity risks are exceedingly low [37]. Higher risks were initially linked to infratentorial DVAs [39], but recently research has indicated that infratentorial DVAs behave in a benign manner [38].

Haemorrhage cannot only be attributed to DVAs as its source [40] [7], but when DVAs contribute to haemorrhage, there is a very low risk of recurrent bleeding [3]. It is so rare to find a primary haemorrhage from a DVA that another source of bleeding needs to be looked for. However, when there is no evidence of another source of haemorrhage the aetiology could indicate primary thrombosis of the DVA resulting in haemorrhagic transformation and venous infarction [41], instead of indicating a primary rupture. The general prognosis for spontaneous DVA thrombosis is good, but is rare [42].

3-Seizures

Seizures associated with DVAs are considered to be the second most likely symptom patients present with (flow related) [3], and indicate a need for a CT or an MRI scan. In a study with a sample population of 67 patients that had been diagnosed with DVAs, fifteen patients presented with seizures, and nine patients presented no other pathology other than a DVA. Generalised tonic-clonic seizures were presented in 5 patients, and complex partial seizures were present in 4 patients. There was correlation between the focal changes on the electroencephalographic study and the location of the DVAs for 7 patients, but not for 2 patients [14].

In a study of 93 patients in Scotland between 1999 and 2003 that had been diagnosed with DVAs the median age at presentation was 44 years [5]. 60% of DVAs were supratentorial, and although 7% were in the brainstem, most of the infratentorial were in the cerebellum. Ninety-one of these patients presented symptoms that were completely unrelated to DVAs, and 2 patients presented symptoms that could be referred anatomically to DVAs. One patient presented with left-sided facial weakness, reduced sensation around the upper lip and nose, and with a sudden onset of loss of balance. A pontine haemorrhage associated with a DVA was revealed on MRI scan. Subsequent surgical evacuation of the haematoma and pathological examination showed the cause to be a DVA, but had originally been considered to be due to a cavernoma.

The American Stroke Association reviewed 15 previous studies describing the clinical course and clinical presentation of 714 DVAs. Less than 1% presented with infarct related symptoms, 4% were associated with epileptic seizures, 6% had caused symptomatic haemorrhage, 6% presented with non-haemorrhage focal neurological deficit, and 23% had an insufficiently clear mode of presentation. 61% were an incidental discovery. The conclusion of this large study was that it would be rare for solitary DVAs to be associated with symptoms. So when DVAs are identified, they tend to have a benign short-term and long-term prognosis. The haemorrhage rate after first presentation was from 0% to 1.28% per year from a study of the clinical course of 422 patients with DVAs [5].

The University of Aachen Department of Neurology Germany also carried out a large retrospective analysis [14], in which they found 67 patients with DVAs. They then obtained 7266 MRI scans and identified 51 patients referred to as group 1. The private practice part of this hospital also carried out 11192 MRI brain scans and found 16 patients with DVAs referred to as group 2. The DVAs were located in the basal ganglia in 2, occipital lobe in 4, parietal lobe in 6, temporal lobe in 6 and frontal lobe in 23 patients. 41 were located supratentorially. 23 were in the cerebellum and 3 in the brainstem. 26 were located

infratentorially. There was one brain tumour and 12 cavernomas, which represented 13 associated lesions.

The reason for obtaining the MRI scans that had lead to the diagnoses of DVAs in 67 patients was the presenting symptom, such as, tinnitus (2 patients), non-neurological indication (3 patients), vertigo (4 patients), cerebral haemorrhage (5 patients), focal abnormality (10 patients), seizures (15 patients), headaches (15 patients) and other neurological symptoms (12 patients), and one patient had cerebral tumour.

Conclusion

Developmental venous anomalies are the commonest vascular malformation with an incidence of between 0,5% and 2,6% on imaging and post mortem studies. They are benign lesions formed of dilated medullary venous channels which drain normal brain parenchyma. Rarely they may be associated with clinical symptoms produced either by associated pathology like cortical dysplasia or cavernoma. Alternatively, symptoms may be related directly to the DVA if a dilated collecting vein causes compression or if there is increased flow into the DVA or restricted outflow.

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PART C: MANUSCRIPT

Symptomatic Developmental venous anomalies

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ABSTRACT

INTRODUCTION

Developmental Venous Anomalies are a normal variant that may be associated with other cerebral vascular malformation. They have bean previously referred to Venous angiomas. DVAs are the most frequently encountered cerebral vascular malformation and their incidence is reported to be high as 2.6%. DVAs are classified into two types based on draining veins. Either deep or superficial. Those that drain into sub-ependymal veins are classified as deep and those that drain into cortical pial veins are classified as superficial. The trans-cerebral veins join either the deep or superficial venous systems by crossing a varying length of the brain parenchyma. Controversy surrounds their exact clinical significance, as DVAs are rarely symptomatic. The symptoms displayed by a patient can be related to a lesion that is associated with DVAs, such as a cavernoma.

Study Aim

To describe the patients presenting to a single unit over a 10-year period with symptoms attributable to a DVA.

Results

Out of 19 patients in the database with the diagnosis of DVA, 10 were identified where the clinical presentation was directly related to the DVA. Seven of the patients presented with haemorrhage, 6 had parenchymal bleeds and one was intraventricular. Two patients had neurological deficit, 1 was transient and one was progressive. One patient had sudden severe headache with no evidence of haemorrhage on CT scan. The age range was from 14 to 55 with a mean of 32,7 years. Four patients were male and 6 were female. Of the patients that presented with haemorrhage only one had a fistula, three other patients with haemorrhage had evidence on DSA of stenosis of the large collector vein, In the remaining 3 patients no reason for the bleed could be detected. One patient presented with left hemianopia that resolved after several hours, DSA showed minimal caput medusa with delayed filling of the collector vein. The other patient that presented with progressive neurological deficit in the form of progressive leg spasticity and dysarthria, Angiography showed a large collecting vein that drains in the jugular bulb was stenosed. The last patient that presented with sudden severe headaches, with no haemorrhage identified on CT scan, On DSA there was early filling of the DVA veins compared to other cerebral veins and two prominent posterior communicating thalamoperforating vessels were seen.

Conclusion

Developmental venous anomalies are the commonest vascular malformation, and are rarely symptomatic unless associated with a cavernoma. In patients that have symptoms linked to DVAs (Haemorrhage, neurological deficit, sudden sever headaches) overall they have a good outcome, and the deficit related to

a DVA tend to improve over time, except for one patient that we had in our group, the DVA draining the pons and the cerebellar hemisphere had a tight outflow stenosis, that lead to progressive neurological deficit. In general, the majority of DVAs that are symptomatic do well.

Introduction

Developmental venous anomalies (DVA) were described by Lasjaunias in 1986 as dilated medullary collecting veins, draining normal parenchyma that drain either into a deep subependymal collector or superficial extra-parenchymal vein. Prior to this description they were mostly termed venous angiomas. Lasjaunias highlighted the fact that where a DVA exists there is no other venous drainage pathway for the brain and as such they represent an extreme but functional anatomical variation [(1)].

They are common with a 2,6% incidence in autopsy series and are almost always incidentally discovered when patients have cerebral imaging [(2)]. DVA can be associated with cortical dysplasia and cavernomas or can be a drainage pathway for a remote brain arterio-venous malformation. These associated pathologies can be symptomatic with haemorrhage from a cavernoma being the most common [(4) (8)].
DVA alone are very rarely symptomatic but there have been recent publications examining the reasons that may produce symptoms [(11) (14)]. Pereira described a group of patients with either mechanical compression by the dilated draining vein or a flow related abnormality [(6)]. Flow could either be increased inflow or reduced outflow and both could result in symptoms. Rodesch also described a cohort of patients with DVA who were symptomatic and had increased T2 signal change around the DVA associated with a prominent capillary staining at the time of digital subtraction angiography (DSA) [(10)]. Ten further patients are presented here who have symptoms considered to be directly related to a DVA.

Methods

A retrospective analysis of the UCT neurovascular database between January 2003 and December 2014 was undertaken using the search term developmental venous anomaly or DVA. A total of nineteen patients were identified. Patient records were then reviewed for demographic and clinical information including the presenting symptoms, management details and outcome. Patients were excluded if their presenting symptom was non-specific such as chronic headache or seizure. Any imaging including CT, MRI and DSA were examined. Patients were excluded if their clinical symptoms could be related to any pathology associated with a DVA such as cortical dysplasia or a cavernoma. Ten patients were felt to have a clinical presentation that was directly related to their DVA.

Results

Out of 19 patients in the database with the diagnosis of DVA 10 were identified where the clinical presentation was directly related to the DVA. Seven of the patients presented with haemorrhage, 6 had parenchymal bleeds and one was intraventricular. Two patients had neurological deficit, 1 was transient and one was progressive. One patient had sudden severe headache with no evidence of haemorrhage on CT scan. The age range was from 14 to 55 with a mean of 32,7 years. Four patients were male and 6 were female.

Haemorrhage

Of the patients presenting with haemorrhage only one had a fistula as evidenced by early filling of the DVA collector veins on DSA done at the time of presentation. The DVA was superficial to deep draining a large part of the right cerebellar hemisphere. No treatment was performed and on follow-up angiography 7 years later there was no longer filling of the DVA and the right superior cerebellar artery had remodeled and appeared smaller. It is likely that with resolution of the bleed the fistula regressed and the DVA thrombosed. Three other patients with haemorrhage had evidence on DSA of stenosis of the large collector vein with delayed emptying of the caput medusa. In the remaining 3 patients no reason for the bleed could be detected on angiography although the haemorrhage was in the territory of the drainage of the DVA.

Four of the haemorrhages were in the posterior fossa, 2 in the cerebellum and 2 in the brainstem. One patient had an intraventricular bleed associated with a deep to superficial DVA draining most of the left hemisphere white matter around the lateral ventricle. The remaining 2 patients had lobar bleeds, one parietal and one frontal. Three of the patients had surgery only to drain the haematoma and 4 were managed conservatively. All patients made a functional recovery although the patients with haemorrhage in the posterior fossa had residual neurological deficits.

Neurological deficit

One of the patients presented with left hemianopia that lasted for several hours. MRI scan showed T2 signal change in the right calcerine area and an associated dilated collecting vein of a DVA. Investigation with DSA showed minimal caput medusa with delayed filling of the collector vein. There was no clear stenosis of the draining vein. Partial thrombosis of the caput transmedullary veins was presumed to have caused venous type ischaemia. The other patient with a large DVA draining the pons and right cerebellar hemisphere presented with progressive leg spasticity and dysarthria. There was a stepwise deterioration in function over a period of years which then stabilised. Angiography showed that the large collecting vein which exited the pons at the cerebello-medullary fissure to drain into the jugular bulb was stenosed at the point it entered the

dura. There was a long delay in the emptying of the DVA. No anti-coagulation was given to either patient.

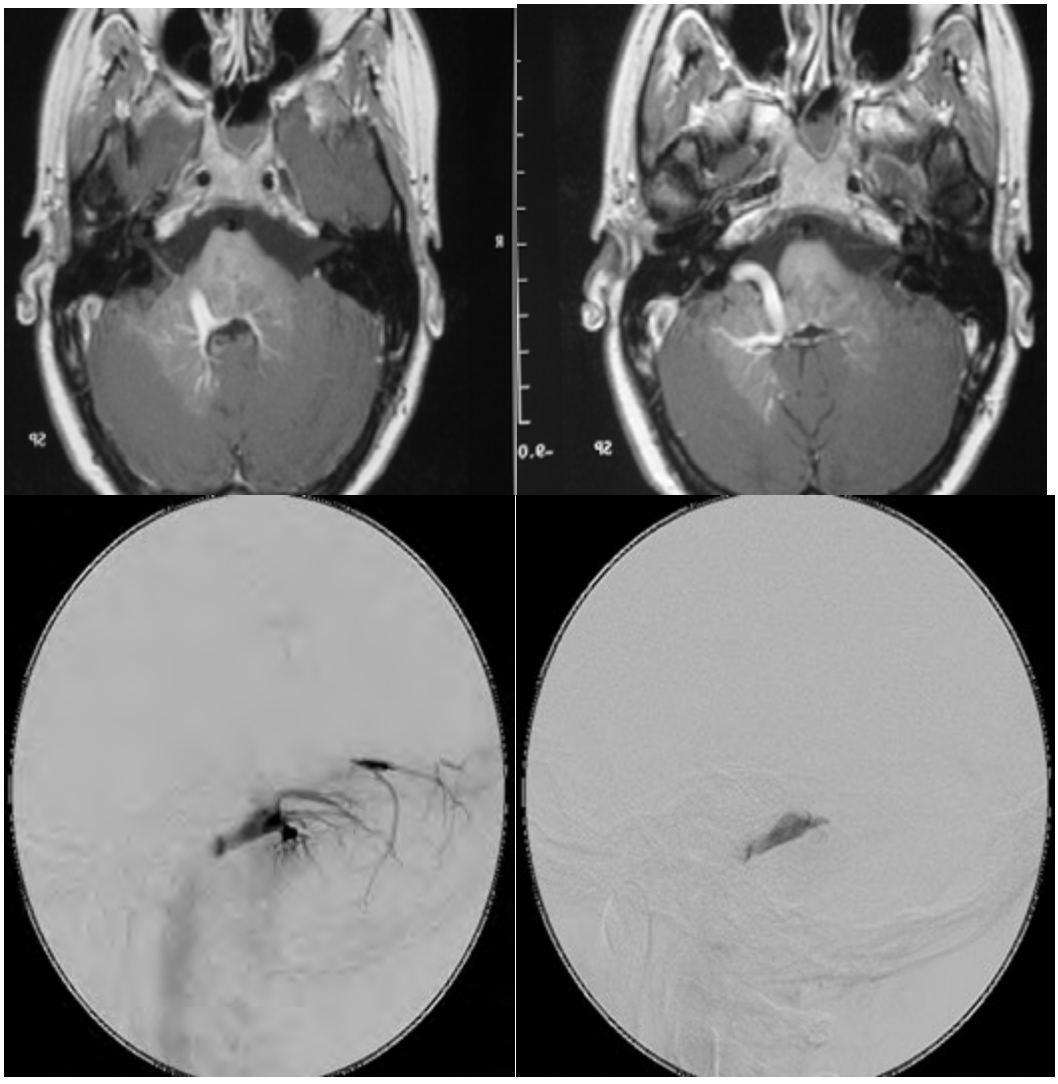
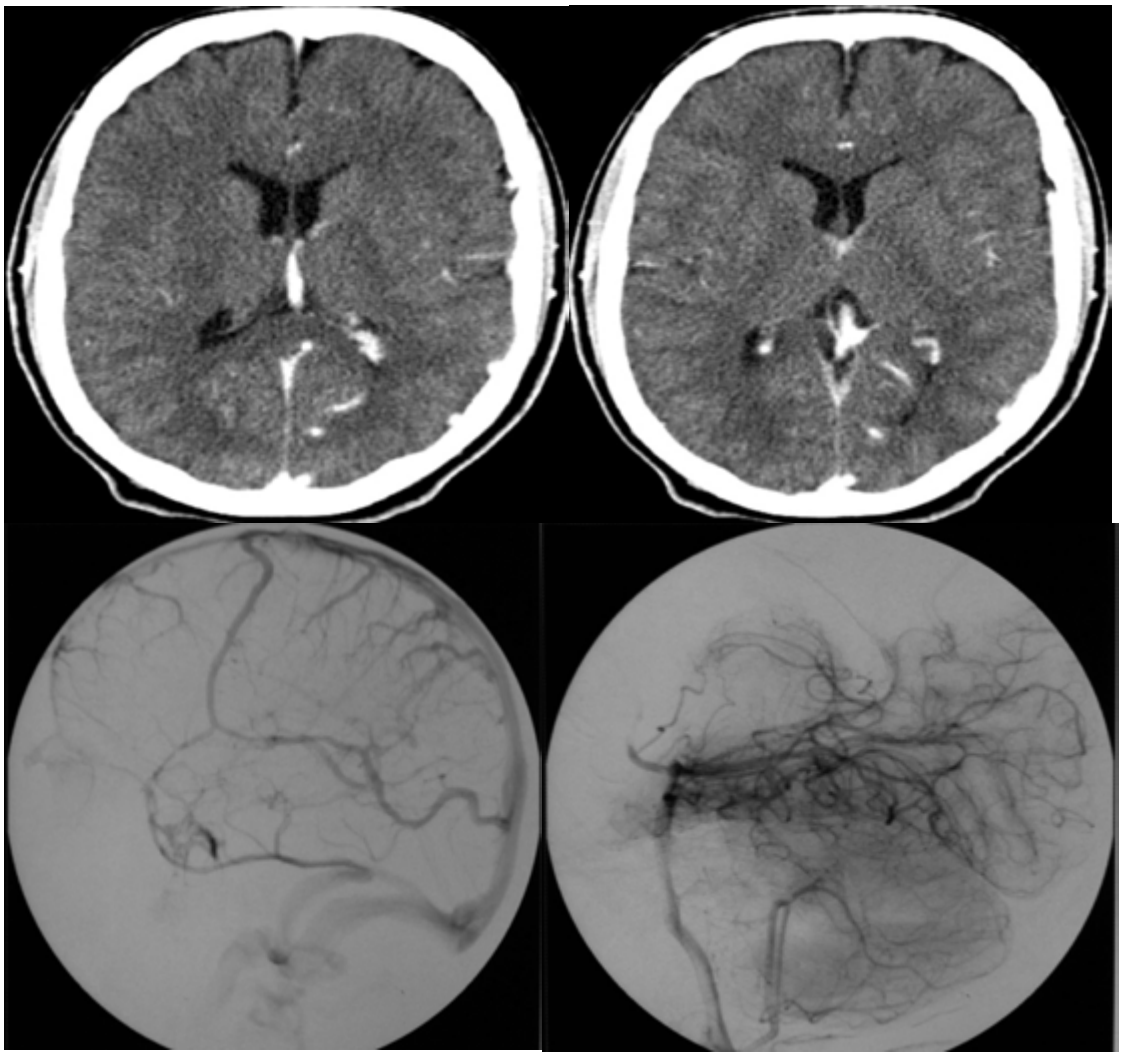


Fig1. 24-year-old female presented with progressive leg spasticity. A and B magnetic resonance imaging (T1-weighted with gadolinium, axial) large right DVA draining the pons and right cerebellar hemisphere with increased signal in the pons and the cerebellar hemisphere. C Angiography showed the DVA with a large collecting vein drain into the jugular bulb with stenosis at the point it entered the dura. D Angiography showing a long delay in the emptying of the DVA.

Severe headache

A 16 year old patient presented with sudden severe headache although no haemorrhage could be identified on CT scan, a dilated vein was noted related to the left lateral ventricle. Angiography showed a deep to superficial type DVA draining the left lateral ventricle region. There was early filling of the DVA compared to other cerebral veins and 2 prominent posterior communicating thalamoperforating vessels were seen. No micro-catheterisation was performed and no intervention was undertaken. The patient had resolution of symptoms over a period of days.

A B



C D

Fig 2. A 16 year old patient presented with sudden severe headache. A and B CT brain (with gadolinium, axial) no haemorrhage could be identified, a dilated vein was noted related to the left lateral ventricle. C and D Angiography showed a deep to superficial type DVA draining the left lateral ventricle region, two prominent posterior communicating thalamoperforating vessels are seen.

Table 1 Clinical presentation and patient's demographics

Patient number	Age	Sex	Clinical presentation	DVA location
1	16	M	Sudden headache	Left Parietal
2	51	F	Headache, meningism	Left Hemisphere
3	36	M	Transient visual field loss	Right Occipital
4	24	F	Leg spasticity	Right Pontine
5	42	F	Weakness of the arm and leg	Midbrain
6	29	F	Ataxia	Right cerebellar hemisphere
7	37	F	Headache, drowsiness	Left Cerebellar hemisphere
8	14	M	Headaches, drowsniess	Right Frontal
9	55	M	Ataxia, Vertigo	Right Cerebellar hemisphere
10	23	F	Headache, R hemiparesis	Left Parietal

Table 2 DVA angioarchitecture

	DVAs drainage	CT / MRI	DSA	Clinical finding	Treatment	Outcome
1	Deep to Falcine vein	Nil	Micro-fistula	Normal examination	Nil	Good
2	Deep to Falcine vein	IVH	Stenosis	Meningismus	Nil	Improved
3	Superficial to deep	Increase T2 signal	? Thrombosis	Minor visual field change	Nil	Improved
4	Deep to superficial	Increase T2 signal	Stenosis	Spastic diplegia	Nil	Step deterioration
5	Deep to superficial	Brainstem bleed	Stenosis	Right hemiparesis	Nil	Improved
6	Deep to superficial	Brainstem bleed	Stenosis	Cerebellar signs	Nil	Good
7	Deep to superficial	Cerebellar bleed	Unknown	Cerebellar signs	Surgery	Good
8	Deep to superficial	Frontal lobe bleed	Nil	Meningismus	Surgery	Good
9	Deep to superficial	Cerebellar bleed	Fistula	Cerebellar signs	Nil	Good
10	Deep to superficial	Parietal lobe bleed	Nil	Right hemiparesis	Surgery	Good

Discussion

Developmental venous anomalies are rarely symptomatic unless associated with a cavernoma[15]. Although anatomically they are an extreme variation of the brain's venous drainage pattern, physiologically the dilated medullary veins and collectors function within normal limits. DVA's associated with cavernomas can present with seizures or symptoms related to haemorrhage [18] [19]. The incidence of DVA with cavernoma varies widely between 8% and 33% [3]
. The Scottish vascular malformation study prospectively identified 93 patients with 94 DVA" s over a period of 4 years [20]. All but 1 of the patients were investigated for symptoms unrelated to the DVA. Over a mean follow up of 5,6 years there were no deaths, haemorrhages or infarctions attributable to the patients DVA. This benign natural history has been confirmed by other studies. Naff followed 63 patients with DVA for a mean of 4,2 years [13]. This was a more selected patient group with sixteen (25%) of the patients having a neurological deficit that was felt to be related to the DVA. Deficits however appeared to be transient and improve without treatment. Two patients in this series presented with haemorrhage attributable to the DVA giving a lesion bleed rate

per year of 0,15%. Almost certainly all of the studies reporting on the incidence of DVA symptoms overestimate the severity because of the large number of unrecognized lesions in the general population.

Despite this benign natural history there have been recent publications (Pereira, Roccatagliata) that highlight the reasons that DVA's may be symptomatic. [6]. Perierra reported on 17 of their own patients and included 52 further published cases. For this selected population of 69 patients presenting with symptomatic DVAs, 14 patients presented because of mechanical compression and 49 patients presented with flow related causes. This study also revealed that mechanical compression caused the neurological symptoms in 32.7% of cases of symptomatic DVAs. The most common compression symptoms were trigeminal neuralgia (TN), facial hemispasm, brainstem deficit, tinnitus and hydrocephalus [6] [7] [9] [16] Flow related pathology was either because of increased arterial inflow (47%) into the DVA or restricted outflow (53%). Increased inflow in most cases was from an arterio-venous malformation draining directly through the DVA which demonstrated dilated and ectatic medullary veins. This configuration was felt to be a high risk for future haemorrhage necessitating treatment of the AVM. Outflow restriction could either be due to a mechanical obstruction like stenosis or partial vein thrombosis or functional if there was a remote fistula causing raised venous pressure within the DVA. Twenty-three of the 49 patients (47%) in the flow group presented with haemorrhage and the rest (53%) a combination of venous congestion or infarction.

Roccatagliata in a later publication [10] described 7 patients with 11 DVA who were symptomatic. Three patients had progressive neurological deficit, 2 had seizures and 2 had haemorrhages. In all cases there was increased hyperintensity on T2 MRI sequence around the DVA and a capillary stain on angiography during the arterial phase. No fistulae were identified and in only 3 of the cases was there felt to be a mild restriction to DVA outflow. They postulated that these lesions had lost haemodynamic balance resulting in venous ischemia and an angiogenetic response resulting both in the capillary dilatation and fragility. None of the patients received any treatment.

Our cases add to the rare group of symptomatic DVA's. Seven of our patients had haemorrhage as the presenting pathology and only one of them had a fistula identified. Of the other 3 patients 2 had neurological deficit, one of which was transient. The other patient had progressive stepwise deterioration in function related to a DVA draining the pons and cerebellar hemisphere. This is an unusual finding as most patients with deficit related to a DVA tend to improve. In this instance there is a particularly tight outflow stenosis with very delayed emptying of the DVA drainage area. One patient had the unusual finding of sudden severe headache without any evidence of haemorrhage on CT. Angiography identified a left thalamic region DVA with early filling from dilated thalomoperforators. No suitable target could be identified for treatment in this eloquent area. The patient's headache resolved without treatment. Three of the 7 patients presenting with haemorrhage

had haematomas that required surgical drainage. This would appear unusual compared to other published cases. In each case the DVA was noted prior to surgery and every effort was made to preserve the DVA at surgery. The good outcomes in our patients supports the evidence that even DVA that are symptomatic do well.

CONCLUSION

Developmental venous anomalies are the commonest vascular malformation, and are rarely symptomatic unless associated with a cavernoma. In patients that have symptoms linked to DVAs (Haemorrhage, neurological deficit, sudden severe headaches) overall they have a good outcome, and the deficit related to a DVA tend to improve overtime, except for one patient that we had in our group, the DVA draining the pons and the cerebellar hemisphere had a tight outflow stenosis, that lead to progressive neurological deficit. In general the majority of DVAs that are symptomatic do well.

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