Presentation, course and outcome of post-neonatal presentations of vein of Galen malformation- a large, single-institution case series

Vignesh Gopalan BSc[1], Adam Rennie MBBS[2], Fergus Robertson MBBS[2], Lakshmi Kanagarajah MBBS[2], Claire Toolis DipHE[3], Sanjay Bhate MD[3], Vijeya Ganesan MD[1,3]

[1] Developmental Neurosciences, UCL Great Ormond Street Institute of Child Health.

[2] Radiology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London.

[3] Neurology Department, Great Ormond Street Hospital for Children NHS Foundation Trust, London.

Word count:

Abstract- 199

Main body - 2587 (exc. references)

Correspondence to:

Vignesh Gopalan

UCL Great Ormond Street Institute of Child Health

Phone: 07503163594

Email:vignesh.gopalan.13@ucl.ac.uk

Shortened title: Post-neonatal presentation of vein of Galen malformation

Abstract

Objective: To describe presentation, clinical course and outcome in post-neonatally presenting vein of Galen malformation (VGM).

Methods: Children presenting >28days with VGM (2006-2016) were included. Notes/scans were reviewed. Outcome was dichotomised into 'good' or 'poor' using the Recovery and Recurrence Questionnaire (RRQ). Logistic regression was performed to explore relationships between clinico-radiological features and outcome.

Results: 31 children were included, presenting at a median age of 9.6 months (range 1.2 months - 11 years 7 months), most commonly with macrocrania (n=24) and prominent facial veins (n=9). Seven had evidence of cardiac failure. VGM morphology was choroidal in 19. Hydrocephalus (n=24) and loss of white matter volume (n=15) were the most common imaging abnormalities. 29 patients underwent glue embolisation (median 2/child). Angiographic shunt closure was achieved in 21/28 survivors. Three children died of intracranial haemorrhage (one, six and 30 days post-embolisation). 10 patients underwent neurosurgical procedures; to treat haemorrhage in four, and hydrocephalus in the rest. Outcome was categorised as good in 20/28 survivors, but this was not predictable based on the variables listed above.

Interpretation: Post-neonatally presenting VGM has distinctive clinico-radiological features, attributable to venous hypertension. Endovascular treatment is associated with good outcomes, but more specific prognostic prediction was not possible within this cohort.

What is already known

- VGM is a rare intracranial vascular malformation that most commonly presents in newborns
- A quarter of cases are encountered in older children but their characteristics are not well described

What this paper adds

- Clinical and radiological features in older children with VGM relate to venous hypertension rather than circulatory overload or arterial ischaemia
- Outcome is good in most cases with endovascular therapy
- Mortality is low but is related to intracranial haemorrhage

Vein of Galen Aneurysmal Malformation (VGM) is a rare cerebral intracranial vascular malformation developing between primitive choroidal arteries and the median prosencephalic vein (the precursor of to the vein of Galen) at between six and 11 weeks of gestation[1]. VGM contrasts with vein of Galen Aneurysmal Dilatation, where the vein of Galen itself is dilated by draining a high flow arteriovenous shunt elsewhere within the brain. Classification of VGM was initially predominantly based on angiographic features[2], but a more recent classification reflects increasing recognition of the relevance of the mode and age of presentation (specifically whether the child is older than five months, when there is potential for alternative cortical venous drainage through the cavernous sinus)[3].

Most patients present in the newborn period with circulatory overload and multi-organ failure secondary to the effects of the large intracranial shunt. Historically, studies reported high mortality rates and significant morbidity in survivors[2,4]. However, with the advent of endovascular treatments, VGM has become a treatable, and potentially curable condition in many cases. Intervention is high risk and selection of patients in whom the risk:benefit equation favours treatment remains a challenge. Most literature has focussed on neonates but in the context of a nationally commissioned service managing VGM patients in the UK since 2006, our clinical experience was that the clinical manifestations and underlying pathophysiology were distinct in older children. Here we aim to describe such patients presenting to us between 2006-2016.

Methods

Since 2006 we have been one of two nationally commissioned centres in the UK treating all cases of VGM. Patients are managed in a standardised manner by a multi-disciplinary team, with clinical evaluation and both cross-sectional brain imaging comprising magnetic resonance imaging (MRI) and diagnostic catheter angiography performed at presentation. This allows a planned, and usually staged, approach to endovascular treatments, which include transarterial glue injection, insertion of coils, or transvenous treatments – although the first of these is by far the most common treatment administered. Patients presenting with hydrocephalus are evaluated for, and undergo endovascular treatment of the shunt in the first instance. Cerebrospinal fluid (CSF) diversion is only undertaken as a secondary measure, when control of intracranial pressure is not achieved by embolisation.

Patients presenting to us between 1/1/2006 and 31/12/2016 after 28 days of age, with a diagnosis of VGM were eligible for inclusion. Clinical data (demographics, presenting features, information regarding the treatment course and any associated complications) was extracted from case records. Brain imaging and cerebral angiograms were reviewed by AR/FR/LK and categorised as summarised in table 1. Initial and most recent imaging studies were evaluated and compared.

Outcome was evaluated from case notes using the Recovery and Recurrence Questionnaire (RRQ), a measure validated for scoring outcomes from case notes in paediatric vascular disorders[5]. Five domains are assessed on the RRQ: (1) right and (2) left sensorimotor function, (3) verbal expression, (4) language comprehension, and (5) cognition and behaviour. A score of zero indicates no impairment, and a maximal score of two indicates severe impairment with limitation of function. Outcome is then dichotomised into 'good' and 'poor' groups; a 'good' outcome is a score of ≤0.5 in every category, indicating no significant neuro-developmental impairment in any of the five domains. A score of 1 or more in any category meant that the child was assigned to have 'poor' outcome.

Ethical Approval

The hospital audit department confirmed that ethical approval was not required for retrospective evaluation of this clinical data and the project was registered with them as a clinical service evaluation.

Statistical analysis

Based on descriptive statistical analysis of the data collected, we used a univariable logistic regression model to explore the relationship between specific clinico-radiological features (presence of brain injury, presence of abnormal venous outflow and presence of hydrocephalus) and outcome. With consideration of the parameters detailed by Peduzzi et al.[6], we had the intention of entering any significant predictors into a multivariable model.

Review of the literature

We performed a literature search using PubMed, EMBASE and the Cochrane Library using the search terms 'vein of Galen malformation', 'VGM', 'infant', and 'post-neonatal' in various combinations. References found within the articles were also assessed. A total of 29 articles describing 556 cases of post-neonatally presenting VGM since 1964 were found. We extracted information regarding clinical features at presentation, treatment course and outcomes for comparison with our own findings. Most articles described small cohorts or isolated cases of post-neonatally presenting VGM, with the majority of cases in our review coming from one centre- the Bicêtre Hospital in Paris, who published a series of 193 patients[7].

Description of presenting features was sparse in most articles, and the age of the child at presentation was not reported with regard to their presenting features. Treatment methods included transarterial or transvenous glue embolisation, or insertion of coils, with the former being the most common. Data on adjunctive procedures and complications was not consistently reported and so this was not examined in this review. Outcome measures also varied, with some studies using radiological elimination of the shunt[8,9] and others basing outcome on post-intervention survival rates[10,11]. Post-operative neurodevelopmental sequalae were reported by some centres, most comprehensively detailed by Fullerton et al.[12] who described six cases of post-neonatal VGM, five of whom (83%) were intact at follow-up, with the remaining child reported to have severe abnormalities on neurological examination and significant developmental delay. Reports from other centres[7,13,14] lacked long-term follow up and did not differentiate between the degree of neurological deficit, instead broadly classifying children as "impaired".

Results

Demographics

31 children (18 male) were included, of whom 28 were still alive. Median age at presentation was 9.6 months (range 1.2 months - 11 years 7 months), with most children presenting in the first year of life. The median age of surviving children was 7 years 5 months (range 1 year 1month - 15 years 10 months).

Macrocrania was the most common clinical presentation (n=24) with nine children having a head circumference larger than the 99.6th centile for their age. Other clinical features (not mutually exclusive) included prominence of facial veins noted by parents (n=9), developmental delay (n=8), focal neurological deficits (n=8), heart failure (n=7), seizures (n=5) and headache (n=5). Of note, headache and prominence of facial veins were only observed in children presenting after the age of 2 years.

Radiological findings

Cross-sectional brain imaging (CT and or MRI) and cerebral angiography was reviewed in all patients and the results are summarised in table 1. The most common brain abnormalities were hydrocephalus and loss of white matter bulk – these were difficult to distinguish and a clinical judgement was made by the three neuroradiologists as to the appropriate diagnostic label in individual cases. Even taking into account head circumference it was often difficult to distinguish between these, but the relevant observation is that the white matter bears the brunt of the injury in these patients. Accrual of brain injury after initial presentation was rare in the survivors, occurring in only 2 cases.

Angiographic features were dominated by the impairment of venous drainage, often associated with stenosis of the venous outflow channels at the skull base. In those patients with symptomatic venous congestion, the aim of the embolisation procedures was to reduce the shunt and improve cerebral venous drainage. A complication of embolisation was venous escape of the embolic material, and this is reflected in the rise in the number of children with venous outflow obstruction.

Cavernous sinus capture (drainage of cortical veins via the cavernous sinus) was also assessed from the first available cerebral angiogram. The results are displayed in table 2 with regards to whether or not the child was older than five months, as this is when the alternative pathways through the cavernous sinus are through to have formed. There was no significant difference in the rate of cavernous sinus capture between patients who had good outcomes compared with those with poor outcomes (chi^2 test, p= 0.6).

Ten patients (32%) had a residual arteriovenous shunt on their most recent angiogram.

Treatment course and complications

One patient had spontaneous collapse of the VGM sac and thus did not require any endovascular treatment. Another has not had embolisation carried out to this date- they have both therefore been excluded from the analysis in this section.

The remaining 29 children underwent a total of 68 embolisation procedures. Two procedures were coil embolisations and the rest were glue embolisations. A median of 2 embolisations were carried out per child (range 0 - 6 embolisations), with the median time to embolisation being four days from presentation (range 0 - 322 days).

19 embolisations in 14 patients were associated with intra-procedural complications. Escape of glue into the venous sinuses was the most common of these (n=12), associated with venous sinus thrombosis in four cases. All four underwent endovascular interventions (stenting/thrombolysis) to resolve this, leaving no permanent neurological sequelae. Other complications included iliac artery occlusion (n=1) and intraventricular haemorrhage (n=1).

Neurosurgical intervention (third ventriculostomy/external ventricular drainage/ventriculo-peritoneal shunt insertion) was required in 10 children. Four procedures were carried out to resolve acute peri-procedural intracranial haemorrhage. Eight CSF drainage procedures were undertaken, two of which were undertaken as emergencies.

Outcome

Median length of follow up was 1 year 11 months (range 2 years 5 months - 6 years 2 months). Three patients died during their treatment course, and have been excluded from the analysis below. Death occurred one, six and 30 days after their most recent embolisations, that had been otherwise uncomplicated, as a result of catastrophic spontaneous intracranial haemorrhage. One of these patient's had an emergency extraventricular drain placed to relieve the intracranial pressure, but died shortly after due to brain herniation.

Of the remaining 28 patients, a 'good' outcome was seen in 20 patients; it is notable that although 2/3rds of the children had abnormal scans, outcome was categorised as good in a similar proportion. The most common domains of concern in the RRQ related to language, cognition or behaviour. In contrast only one child exhibited motor impairment.

Statistical analysis

Significance level was set at an arbitrary threshold of 5%, and was two-tailed. The results of the univariable regressions [Table 3] showed that the clinico-radiological parameters assessed had no significant effect on outcome. We did not carry out a further multi-variable regression analysis.

Review of the literature

Out of the 556 cases extracted, only 86 (15%) offered description of presenting features [Table 4], reflecting the paucity in the literature describing presentations of post-neonatal VGM. Hydrocephalus, macrocrania and cardiac failure were the most common presentations. 456 children had undergone treatment of their VGM, with 296 (65%) categorised as having a 'normal' outcome by the measures specified by the authors. The death rate in the review population was lower than 15%. This may be a result of reporting bias between centres, or due to the less severe presentation of infants compared with neonates. Thus, broadly, our results were comparable in terms of clinical presentation but perhaps more positive in terms of outcome.

Discussion

There are encouraging outcomes in the majority of children presenting with VGM beyond the neonatal period, with 2/3rd of our population showing no, or mild neurological impairment at follow up. The lack of prospectively collected outcome data and the relatively small sample size limit our ability to comment on predictors of outcome. Due to the breadth of the categories on the RRQ, subtle deficits in functional status may have not been picked up, and the ability of children classed as having a 'good' outcome may have been overestimated in some cases. Lack of a power calculation (made difficult due to the rarity of post-natal presentation of VGM) meant that a non-significant finding may in fact have been true.

The most frequent presentation of VGM is in neonates with brain ischaemia and multiorgan dysfunction secondary to hypoperfusion – a truly life-threatening situation with a high rate of death and impairment even with treatment. In contrast, the 'hydrovenous' features that are prevalent in older children are far more insidious, and relate to both abnormally high volumes of blood being shunted into the venous system and, often, an acquired outflow obstruction at the level of the jugular bulb. The latter is thought to, at least in part, be secondary to the chronic effects of venous hypertension and is challenging to treat or reverse, as stenting is rarely successful in any sustained way. Although alternative routes of cortical venous drainage may afford a degree of protection against venous hypertension, we were not able to demonstrate a difference in outcome according to whether or not there was cavernous sinus capture. Hydrocephalus in this context is thought to relate both to impairment to CSF resorption in the high pressure venous system, but also to direct compression of the cerebral aqueduct by the VGM sac[15]. Of note, parents tell us that the significance of presenting features (macrocrania, prominent facial veins) often goes unrecognised for a long time, even by medical professionals. We had a minority of cases presenting with developmental arrest; however, none of these were associated with the catastrophic so-called “melting brain syndrome” that indicates critically decompensated acute venous hypertension. The urgency of this presentation cannot be overemphasised and thus developmental standstill or seizures in VGM should be treated as medical emergencies.

White matter volume loss was the most common brain injury in this cohort, however, surprisingly, did not cause impairment of motor function as assessed on the RRQ. However study of a similar cohort of 28 children at the Royal Hospital for Sick Children in Glasgow, using more detailed and face to face assessment paradigms reported motor delay as the most significant finding (McArthur I, Yeo T H, Bhattacharya J, 2015, personal communication), although of note, these often coexisted with delays in other aspects development. Potential explanations for this are that the RRQ is relatively crude, or that the children in the Glasgow study had a more global pattern of impairment. Historically, outcome in the treatment of VGM has been measured by mortality rates and shunt elimination but in an era where endovascular embolisation has significantly lowered death rates, and with angiographic exclusion not necessarily being a good predictor of outcome[2,16], there is an argument for utilising neurodevelopmental morbidity and functional status at follow-up as potential outcome measures, and for prospective and serial neurodevelopmental assessment to form an integral part of our care pathway.

Our results add to a growing body of evidence of improved outcomes in the era of endovascular treatment for VGM - a good outcome in non-neonates is generally seen despite a high rate of abnormal scan at presentation. Analysis of clinical and radiological features contrasts the importance of venous hypertension and outflow obstruction in this group with those of arteriovenous shunting and circulatory failure in neonates. Currently the treatment paradigms and approaches in both groups are similar but these data and the literature review suggest that these should be more targeted to the physiological dysfunction in specific cases. Whilst timing of intervention and the specific approach to blocking the arteriovenous shunt can be tailored, technical limitations to strategies to relieve venous outflow obstruction continue to be a challenge in this group.

References

1. Barkovich AJ. Vein of Galen aneurysmal malformation. Diagnostic imaging: paediatric neuroradiology. Salt Lake City, Utah: Amirsys, 2007;1:7–28.
2. Lasjaunias PL, Chng SM, Sachet M, Alvarez H, Rodesch G, Garcia-Monaco R. The Management of Vein of Galen Aneurysmal Malformations. Neurosurgery. 2006;59:S3-184-S3-194.
3. Mortazavi MM, Griessenauer CJ, Foreman P, Bavarsad Shahripour R, Shoja MM, Rozzelle CJ, et al. Vein of Galen aneurysmal malformations: critical analysis of the literature with proposal of a new classification system. J Neurosurg Pediatr. 2013;12(3):293–306.
4. Johnston IH, Whittle IR, Besser M, Morgan MK. Vein of Galen malformation: diagnosis and management. Neurosurgery. 1987;20(5):747–58.
5. Lo WD, Ichord RN, Dowling MM et al. The Pediatric Stroke Recurrence and Recovery Questionnaire: validation in a prospective cohort. Neurology. 2012;79(9):864–70
6. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol. 1996 Dec;49(12):1373–9.
7. Lasjaunias PL. Brain and Spine AVMs, Vein of Galen Malformation. Treatments and Embryological Considerations. Interv Neuroradiol. 2003;9(3):263–72
8. Lylyk P, Viñuela F, Dion JE et al. Therapeutic alternatives for vein of Galen vascular malformations. J Neurosurgery. 1993;78(3):438–45.
9. Karanam LSP, Baddam SR, Joseph S. Endovascular management of vein of galen aneurysm malformation: A series of two case reports. J Pediatr Neurosci. 2011;6(1):32–5.
10. Diebler C, Dulac O, Renier D, Ernest C, Lalande G. Aneurysms of the vein of Galen in infants aged 2 to 15 months. Diagnosis and natural evolution. Neuroradiology. 1981;21(4):185–97.
11. Li A-H, Armstrong D, terBrugge KG. Endovascular treatment of vein of Galen aneurysmal malformation: management strategy and 21-year experience in Toronto. J Neurosurg Pediatr. 2011;7(1):3–10.
12. Fullerton HJ, Aminoff AR, Ferriero DM, Gupta N, Dowd CF. Neurodevelopmental outcome after endovascular treatment of vein of Galen malformations. Neurology. 2003;61(10):1386–90.
13. Hassan T, Nassar M, Elghandour M. Vein of Galen aneurysms: presentation and endovascular management. Pediatr Neurosurg. 2010;46(6):427–34.
14. Moon JH, Cho W-S, Kang H-S, Kim JE, Lee SJ, Han MH. Vein of galen aneurysmal malformation : endovascular management of 6 cases in a single institute. J Korean Neurosurg Soc . 2011;50(3):191–4.
15. Meila D, Grieb D, Melber K, Jacobs C, Maslehaty H, Petridis A, et al. Hydrocephalus in vein of Galen malformation: etiologies and therapeutic management implications. Acta Neurochir (Wien). 2016;158(7):1279–84.
16. Jones B V., Ball WS, Tomsick TA, Millard J, Crone KR. Vein of Galen Aneurysmal Malformation: Diagnosis and Treatment of 13 Children with Extended Clinical Follow-up. Am J Neuroradiol. 2002;23(10):1717–24.

Cross-sectional imaging		
	Frequency on initial imaging	Frequency on final imaging
Brain Injury	21	23
Hydrocephalus	24	21
Angiography		
Venous outflow impairment	16	19
Venous congestion	7	19
Residual shunt		10

Table 1 - Analysis of radiological imaging

Age at earliest angiography	Good outcome (*number of children with cavernous capture*)	Poor outcome (*number of children with cavernous capture*)
<5months	8 (*6*)	2 (*2*)
>5months	10 (*9*)	6 (*4*)
Deceased	3	
No angiogram available	2	

Table 2 - Presence of cavernous sinus capture in relation to outcome

Parameter	Good outcomes (n=20)	Poor outcomes (n=8)	Odds ratio	95% Confidence Intervals		p- value
				Lower	Upper	
Presence of brain injury (first MRI)	12	6	0.6	0.09	3.90	0.60
Presence of brain injury (final MRI)	15	6	1.2	0.18	8.24	0.86
Venous outflow impairment (first angiography)	11	3	1.6	0.29	9.25	0.58
Venous outflow impairment (final angiography)	12	5	0.69	0.10	4.52	0.70
Presence of Hydrocephalus	15	6	1.2	0.18	8.24	0.85

Table 3 - Univariable regression analysis

Presenting feature	Freq.	Outcome		
Hydrocephalus	25	Treated (n=456)	Normal	296
Macrocrania	14		Impaired	93
Cardiac failure	14		Dead	67
Cranial bruit	10			
Seizures	9			
Haemorrhage	4	Untreated (n=44)	Normal	14
Developmental Delay	3		Impaired	15
Prominent facial veins	3		Dead	15
Focal neurological deficits	2			
Headache	2			
		Outcomes in 56 cases were unknown		

Table 4 - Review of the literature