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Research Article

Maltese Study of Intracranial Vascular Malformations

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Abstract. Intracranial vascular malformations (IVMs) are responsible for 49% of spontaneous intraparenchymal brain haemorrhage in patients under 40 years of age. IVMs may cause recurrent intracranial bleeds, focal neurological deficits, seizures and chronic disability. The aim was to study the incidence of arterio-venous malformations (AVMs) and cerebral cavernous malformations (CCMs) in the Maltese population, assess mode of presentation, patterns of interventions, outcomes and follow-up of the lesions. A word search through the radiology information system was carried out, identifying cases of IVMs between 2008 and 2016 at Mater Dei Hospital. Brain or dural AVM, carotid-cavernous fistulae and CCM were included in the study. A participant was identified as the "incident" case at the time of the first diagnostic image. Interventions, follow-ups and complications were noted. 47 patients had AVM and 35 had CCM. The majority of patients with AVM presented with headaches. MRI was the prevalent imaging modality used at diagnosis. 42.6% of patients received radiosurgery. Haemorrhage was the commonest complication. In the CCM group, seizures and focal signs were common presenting symptoms. 65.7% of patients with a CCM were followed-up with further imaging within one year of diagnosis. The majority of patients received no intervention. IVMs may cause significant morbidity in patients and timely recognition is essential. The risk of haemorrhage in patients with AVMs is 1–4% per annum and this risk directs management. Presently, decisions regarding CCMs are made on a case-by-case basis. There is a need for guidelines, to help direct clinicians on the evidence-based management of IVMs.

Keywords: intracranial vascular malformations, arteriovenous malformation, cavernoma, cavernous malformation

1 Introduction

Intracranial vascular malformations (ICM) are abnormalities in the cerebral arterial and venous systems and can incorporate a vast number of vascular lesions that have differing structure, haemodynamics and prognosis. While some might be life-threatening, such as arteriovenous malformations or a vein of Galean aneurysmal malformation, others might be found incidentally and might remain asymptomatic throughout a patient's lifetime. ICMs are sub-classified into those malformations that occur in the presence of shunting such as arteriovenous malformations (AVMs) and arteriovenous fistula (including dural arteriovenous fistula, dural sinus malformation and vein of Galean aneurysmal malformation) and those which occur in the absence of shunting such as cavernoma and venous malformations.

These ICMs are responsible for over a third of spontaneous intraparenchymal brain haemorrhage in patients under 40 years of age (Ruíz-Sandoval JL & Barinagarrementeria, 1999) hence, making them the leading cause of haemorrhage in this age group. Lesions might be found incidentally or the patient might present with persisting headaches, global or focal seizures, upper motor neurone signs and rarely death due to a significant intraparenchymal bleed. They may be the cause for recurrent intracranial bleed, focal neurological deficits such as hemiplegia, seizures and chronic disability. While therapeutic interventions such as radiosurgery, surgical excision and embolization can be useful in alleviating symptoms in a number of patients, there remains uncertainty on the prognosis such malformations carry in certain individuals and on the clinical course of untreated IVMs.

The aim of the study was to study the incidence of AVMs and cavernomas in the Maltese population, assess their mode of presentation and outcomes. Patterns of interventions and modes of follow-up of lesions were also noted. Outcomes of patients who did not receive inter-

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ventional treatment were also monitored shedding light on the beneficial and adverse effects of the used interventions. Moreover, there haven't been any publications with regards to the incidence of these malformations in the Maltese islands and thus this study is the first published population based study shedding light into the presentation and outcomes of these patients.

2 Materials and Methods

A word search through the radiology information system was carried out, identifying cases of intracranial vascular malformations between January 2008 and October 2016 which were diagnosed at Mater Dei Hospital. Search criteria included cavernoma, cavernous malformation, AV[1] fistula, arteriovenous +/− malformations, AVM/s, AV fistula and arteriovenous fistula. Fistulas or AVMs occurring elsewhere in the body including renal, bladder, trunk or abdomen were excluded from the study. Patients included in the study were aged 14 years or over at the time of diagnosis. Any patient with a brain AVM, dural arteriovenous AVM, including carotid-cavernous fistulae and cavernous malformation with or without a venous malformation diagnosed between 2008 and 2016 were included in the study. Vein of Galean aneurysmal malformations were included in the study yet all other aneurysms were excluded. A participant was identified as the "incident" case at the time of first diagnostic image being it CT[2] (including CT Angiogram), MR[3] (including MR angiogram) or catheter angiogram. Patterns of intervention were then monitored including both observational and surgical treatment. Any complications noted at the time of diagnosis or subsequently were then documented and analysed.

3 Results

82 patients were included in the study of which 47 had AVMs and 35 had a cavernoma as shown in Table 1. The incidence of newly diagnosed AVM in the Maltese Islands between 2008 and 2016 was 0.01% whilst that of cavernomas was 0.008%.

The mode of presentation of both AVM and cavernoma are as shown in Fig. 1. The commonest presentation with regards to AVMs was with headaches (28%), followed by neurological deficit (21.3%) and seizures (17%). 26% of AVMs were diagnosed incidentally in comparison to 43% of cavernomas. Symptomatic cavernomas presented mostly with seizures (20%) and neurological deficits (20%) with only 17% presenting with headaches.

MRIs were the commonest imaging modality used at the time of diagnosis of an AVM (47.8%) followed by MR Angiography (23.4%) and CT Scans (including CT Angiogram). 51% of patients diagnosed with an AVM, had a cerebral angiogram of which 87.5% took place prior to therapeutic interventions, be it excision, radiosurgery or embolization. 61.7% had follow-up imaging within a year since diagnosis. 70.2% of AVMs were lobar with the commonest areas affected being the frontal as can be shown in Fig. 2. 23.4% of AVMs were deep and 6.4% were cerebellar. Size was documented in 46.8% of cases where an AVM was detected.

82.8% of cavernomas were diagnosed on MRI (including MRA) with only 8.5% being diagnosed using a CT (including CT Angiogram). 54% of the cavernoma were lobar (as shown in Fig. 3), 43% were deep and 3% were cerebellar. In 80% of cases, dimensions of the

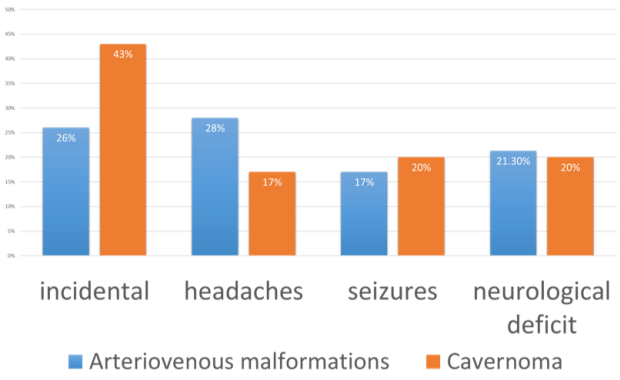

Figure 1: Mode of presentation of ICM. Headaches were the commonest complaint in the AVM subgroup whilst most cavernoma were diagnosed incidentally.

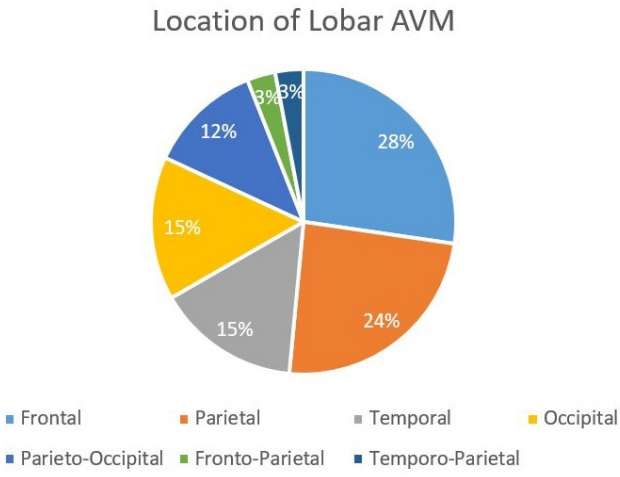

Figure 2: Location of lobar AVM. 70.2% of AVMs were lobar with the commonest areas affected being the frontal as can be shown in Fig. 2. 23.4% of AVMs were deep and 6.4% were cerebellar. AVMs in deep locations were located in the thalamo-capsular region over the corpus callosum, brainstem, floor of the fourth ventricle, basal ganglia, thalamus, the splenium of the corpus callosum and the floor of the middle cranial fossa.

[1] AV – arteriovenous
[2] CT – computed tomography scan
[3] MR – magnetic resonance

Table 1: Demographic data of patients participating in the study. The AVM and Cavernoma subgroups showing the number of male and female participants. The mean age at the time of diagnosis based on the gender is shown.

	AVM	Mean age at diagnosis of AVM	Cavernoma	Mean age at diagnosis of cavernoma
Male	29	44.89	12	56.42
Female	18	40.44	23	42.00

cavernoma/s were included in the radiological report. 65.7% of patients were followed-up with some form of imaging modality within one year of the diagnosis.

Management of IVM is made on a case-by-case basis. Fig. 4 shows a summary of the interventions offered to patients diagnosed with an ICM.

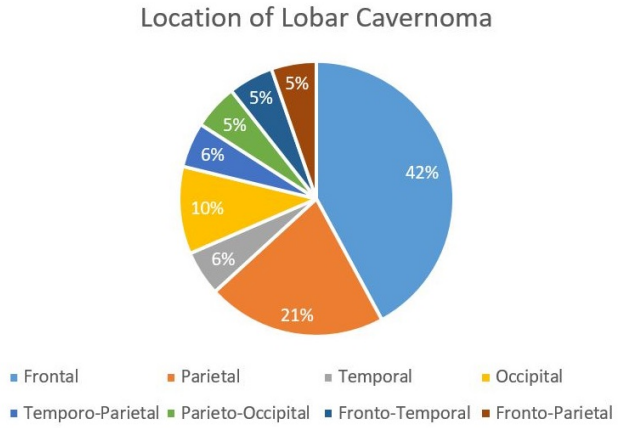

Figure 3: Location of lobar cavernoma. 54% of the cavernoma were lobar, 43% were deep and 3% were cerebellar. Deep seated cavernoma were located in the centrum semiovale, pons, lentiform nucleus, adjacent to the ventricles, basal ganglia, midbrain, thalamus, periventricular area, hippocampus and medulla.

The most common complication in both subgroups is haemorrhage with 36.2% of patients with an AVM suffering a bleed either at the time of presentation or during the period of follow-up. In comparison, 37.1% of patients with a cavernoma had a bleed wither at presentation or thereafter. Seizures and progressive neurological deficits were commoner in the AVM subgroup in comparison to the cavernoma subgroup, as can be seen in Fig. 5. Interestingly, no statistically significant increase in complications was noted between patients who were regularly followed-up with imaging but never received a therapeutic intervention and those who received some form of intervention. A p-value of 0.09 was obtained when comparing haemorrhage rates between the afore mentioned sub-groups, a p-value of 0.48 when comparing seizures and a p-value of 0.62 when comparing the rates of progressing focal neurological signs.

Out of the 35 individuals who were diagnosed with a cavernoma, 8.6% were diagnosed with multiple lesions affecting both sides of the brain.

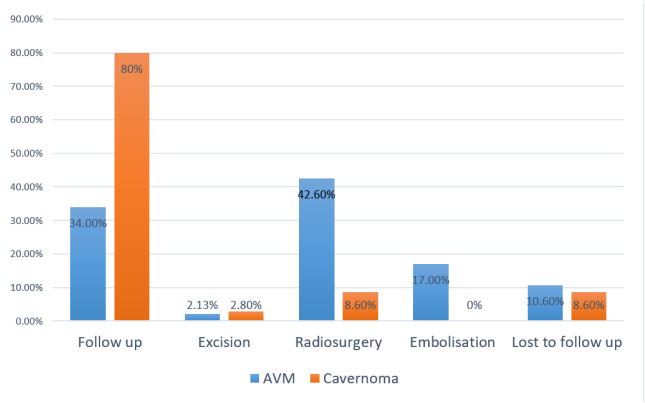

Figure 4: Management of ICM. 42.6% of patients with an AVM had radiosurgery with the commonest modality used being Gamma knife. Cyberknife and stereotactic radiosurgery where other modalities used. This is in contrast to the cavernoma subgroup where a minority of 8.5% were treated with Gamma knife radiosurgery. A single patient was offered debulking surgery.

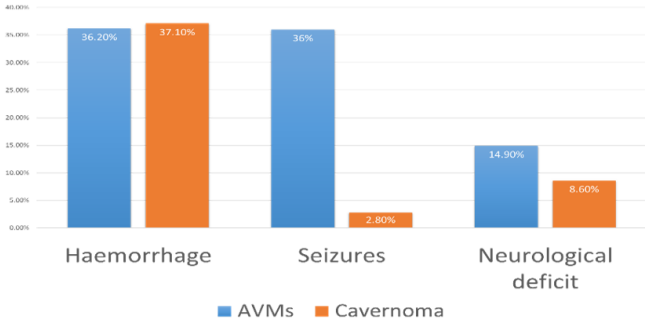

Figure 5: Complications of ICM. 36.2% of patients had haemorrhage as a complication of the AVM of which 82.4% had it at presentation and 17.6% had multiple episodes. In 11.8% of cases where haemorrhage was documented, the haemorrhage was the cause of death. This is in contrast to cavernomas where 37% of patients had haemorrhage with up to 75% of these having the bleed at presentation.

4 Discussion

4.1 Arteriovenous Malformations

Intracranial AVMs are a relatively rare occurrence and are typically congenital vascular anomalies. They are composed of complex connections between arteries and veins without any intervening capillary bed. The veins are typically tortuous and dilated secondary to the high velocity of the blood flowing through the fistula. Some conditions linked to intracranial AVMs include Sturge-Weber disease, Osler-Weber-Rendu syndrome, von Hippel-Lindau syndrome and neurofibromatosis (International RadioSurgery Association, 2009). Mohr, Kejda-Scharler and Pile-Spellman (2013) suggest an incidence of AVMs of 0.1%, whereas that in the Maltese population was found to be 0.01%.

Although the AVMs are typically congenital, patients typically present in early adulthood between the ages of 20–40 (Fleetwood IG, 2002). Seizures or brain haemorrhage may occur in the younger and elder population as an incident event. Up to 66% of adults who have been found to have an AVM might also have a history of subtle learning disorder (International RadioSurgery Association, 2009). Presentation can be varied with headaches, seizures, progressive neurological deficit or brain haemorrhage being the commonest mode of presentation. Indeed many AVMs are identified once there is sudden onset of bleeding that can merely lead to a headache with or without any neurological signs or can be fatal. Deep seated AVMs are the most likely to present with haemorrhage. Bleeding can occur into the brain parenchyma, subarachnoid space or the intraventricular space. Patients with an AVM carry an annual risk of 1–4% of getting an intracranial bleed (Fleetwood IG, 2002) with particular angiographic features, such as, small/deep venous drainage and high pressures of the arterial and venous components of the AVM nidus increasing the chance of bleeding further. Previous rupture, as well as, young age are other predictors of increased risk of bleeding. The risk of bleeding is highest in the first 5 years after diagnosis yet it remains significant for decades (Laakso et al., 2008).

Headaches are the commonest presentation of AVMs. The headaches can be typical for migraines, especially if the AVM is a subcortical lobar one, or can present with non-specific generalised headache. Seizures can be both focal or secondary generalised in nature. Progressive neurological deficits may be a presenting feature if the AVM is enlarging or if there is high pressure in the draining vessels causing a mass effect. In the absence of the mass effect, progressive neurological deficits can occur secondary to the 'steal phenomenon', where blood is syphoned away from the adjacent brain parenchyma into the AVM nidus (International RadioSurgery Association, 2009).

High-resolution neurodiagnostic imaging is indicated in patients presenting with any of the symptoms common to AVMs. Magnetic resonance imaging with cerebral angiography is required to identify AVMs. Cerebral angiography helps to assess the haemodynamics and the morphology of the AVM, which are essential when planning treatment. Important features include the presence of any arterial or venous aneurysms within the nidus of the AVM, which increase the risk of rupture, the venous draining patterns and the feeding vessels (International RadioSurgery Association, 2009).

Management of the AVM depends on the nature of the AVM, risk of subsequent bleeds and any co-morbidities. There are four management strategies: observation, endovascular embolization, stereotactic radiosurgery and surgical excision. Observation may be ideal for patients with large volume AVMs, especially if there has never been an episode of bleeding. Endovascular embolization is typically used as an adjunctive therapy prior to surgery and can only be used if a part of the AVM nidus can be obliterated successfully. Stereotactic radiosurgery is recognised for AVMs that cannot be resected. Depending on the patients' age, AVM location, size and underlying comorbidities one can opt for Gamma knife radiosurgery, linear accelerators or proton beam therapy (International RadioSurgery Association, 2009).

4.2 Cerebral Cavernous Malformations

Cerebral cavernous malformations (CCMs) are a collection of atypical blood vessels through which blood flow is sluggish. They are rarer than AVMs with an incidence of 0.4–0.8% (Mouchtouris et al., 2014). In our study, the incidence was of 0.008% which was significantly less than that for AVMs and also lower than that in published data.

CCMs carry a risk of haemorrhage as blood tends to leak through the inter-cellular junctions making up the walls of the cavernoma (Samarasekera et al., 2005). Most cavernomas occur sporadically however, some have been noted to be inherited in an autosomal dominant pattern with mutations in the CCM1, CCM2 and CCM3 genes being linked to such inheritance. Studies have shown that in adults with a single cavernous malformation but with no family history the chance of a mutation is up to 1% whilst in adults who have at least one cavernoma and a positive family history, the chance of a mutation being present is between 78–94% (D'Angelo et al., 2011; D. L. Verlaan, Laurent, Rouleau & Siegle, 2004; D. J. Verlaan et al., 2004). Hence, it is recommended that in patients with a cavernoma and a positive family history, investigations are carried out to check for mutations in CCM1 - 3 genes.

Cavernomas, like AVMs, can present with intracranial bleeding, epileptic seizures and focal neurological signs.

The annual risk of an intracerebral bleed in someone who has been diagnosed with a cavernoma that has never bled is between 0.4% and 0.6%. The percentage increases to between 3.8% and 22.9% if the cavernoma has already leaked (Al-Shahi, Berg, Morrison, Awad & Angioma Alliance scientific advisory board, 2008). The risk of a second bleed decreases over time (Flemming, Link, Christianson & Brown, 2012). Patients who present with a first seizure have a risk of 94% of developing epilepsy in the first five years from the time of diagnosis (Samarasekera et al., 2005).

Diagnostic imaging using T1-weighted and T2-weighted MRI together with haem-sensitive sequences is recommended in order to diagnose cavernomas and assess whether they are solitary or multiple. It is also recommended that in patients who have a brain mass accompanied by substantial amount of blood and vasogenic oedema an assessment for the presence of a CCM is carried out. Decisions regard whether patients should be followed up with imaging or whether to refer for radiosurgery should be done on a case-by-case basis as there are currently no guidelines (Samarasekera et al., 2005).

5 Conclusion

IVMs can cause significant morbidity and mortality in patients and hence, their detection and follow-up is essential. Data from this study suggests that incidence in Malta is comparable to that overseas and that patients are managed in a similar fashion albeit decisions are taken on a case-by-case basis. A limitation of the study was that death certificates were not looked into and thus any IVMs that might have caused sudden death were missed.

Documentation of size is essential as well as details regarding the feeding and draining vessels and the location of any malformation as these might affect the clinicians' decision to offer therapeutic intervention and might affect prognosis. While the studies performed in the area indicate the potential dangers of these ICMs, there is a lack of consensus among clinicians on how to proceed once an ICM has been detected. This raises the need for a guideline, which would help direct clinicians as to when follow-up scans should be undertaken and at which point interventions should be offered to their patients.

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