WYBURN-MASON SYNDROME

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Introduction

Wyburn-Mason's syndrome is a rare neurocutaneous disorder characterised mainly by: (1) usually unilateral arteriovenous malformations of the (mid)brain; (2) vascular abnormalities of the retina, optic nerve, orbit, optic chiasm and tract; and (3) multiple cutaneous nevi consisting either of faint reddish-bluish discoloration or dilated enlarged superficial veins involving the trigeminal region (Younge 1987).

Historical perspective and terminology

Magnus (1874) first described the retinal component of the malformation in 1874: however, that was regarded for many years as an ophthalmologic curiosity. A few patients with this retinal lesion developed signs suggesting more extensive vascular involvement of the head, and in 1930 *Yates* and *Paine* reported an extensive vascular malformation in the ipsilateral cerebral hemisphere, mid-brain, choroid plexus, sylvian veins and retina of a patient who died from an intracerebral haemorrhage.

The clinical association of retinal and cerebral arteriovenous malformation however was first reported in the French literature by the French ophthalmologist **Paul Bonnet** (1894–1959) along with the French neurosurgeons **Jean Dechaume** (1896–1968) and **Eugene Blanc** (1888–1961) (Bonnet et al. 1937). In the European literature this condition is still known as the *Bonnet-Dechaume-Blanc syndrome* (Younge 1987).

Northfield (1941) early in the era of angiography demonstrated the first retinocephalic arteriovenous malformation by this technique. However it was **Wyburn-Mason**, a British neurologist working at the National Hospital of Queen Square in London, who in 1943 described the association of retinal and intracranial vascular malformations in detail (Younge 1987). He reviewed the world literature on retinal arteriovenous malformations up untill 1943 and showed that of 27 cases, signs of intracranial arteriovenous malformations were present in 22 (Wyburn-Mason 1943). He surveyed 20 cases of midbrain arteriovenous malformations and found 14 instances of associated retinal arteriovenous malformations helping to initially categorise this condition which he regarded as a syndrome (Bidwell 2006, Brown et al. 1973, Rizzo et al. 2004). He described the "curious association of lesions, consisting of arteriovenous aneurysm of one or both sides of the mid-brain, arteriovenous aneurysm or some similar congenital vascular abnormality of the retina on the corresponding side and cutaneous naevi with physical changes" and stressed the fact that "sometimes the mid-brain or retinal lesions occurs alone, so that examples of arteriovenous aneurysms of the retina have been recorded without other abnormalities, but none of these cases have been followed for any length of time" (Wyburn-Mason 1943). Most of the reviewed cases however were not documented by contrast studies, operation, or autopsy and the diagnosis was made in the majority by clinical examination alone (Brown et al. 1973).

Shira and Guernsey (1965) first reported the extracranial vascular lesions and Archer et al. (1973) revealed by means of fluorescein the basic nature of the retinal lesion: one or more abnormal communications between arteries and veins, with a wide clini-

cal spectrum. This has led to various descriptive names, but the primary defect is an arteriovenous communication (Younge 1987).

The entity is known also as mesencephalon-oculo-facial angiomatosis.

Incidence and prevalence

Wyburn-Mason's syndrome is considered one of the rarest neurocutaneous syndromes (Taybi and Lachman, 1996, Younge 1897) with no calculated frequencies so far (Bidwell 2006) and no predilections of age and gender (Bidwell 2006, Edelstein et al. 2005). Approximately, 90 cases have been described so far in the literature.

Clinical manifestations

Wyburn-Mason usually presents in childhood, occasionally at birth. Specific symptoms and signs vary with location and size of the arteriovenous malformation (Edelstein et al. 2005). Larger arteriovenous malformations causing visual or neurological impairment generally are diagnosed earlier in life, whereas smaller lesions may not be diagnosed until later in life (Bidwell 2006). Archer et al. (1973) subdivided the arteriovenous anastomoses of Wyburn-Mason's syndrome into three groups (Bidwell 2006, Edelstein et al. 2005, Younge 1987):

(1) *Group 1* is characterised by a (less severe type of) interposing arteriolar capillary bed between arteries and veins (small arteriole-venule anastomoses), which is usually localised to one sector or quadrant of the retina (often involving the macula) and may be subtle and difficult to detect clinically. It was their impression that these vascular retinal lesions were stable and not associated with cerebral anomalies;
(2) *Group 2* represents direct arteriovenous communications without intervening capillary or arteriolar elements. This group may represent an exaggerated form of the abnormalities included in group 1, and is likewise geographically segmented within the fundus. There is the tendency to higher flow rates and pressures, and some decompensation of the involved vessel walls and surrounding tissues. Shunting of highly oxygenated blood past poorly perfused capillary beds may be evident. Haemorrhages, leakage of fluid with oedema, and exudates may cause decreased vision in some of these cases. With a few exceptions these, too, seem unassociated with cerebral lesions;
(3) *Group 3* includes malformations with more severe retinal involvement and a higher likelihood of intracranial and other site involvement. In these, the retinal vessels are very large communications; they are of large caliber and are interwined, convoluted, and highly arterialised in blood content. The abnormalities are extended throughout the entire fundus and there is a considerable retinal degeneration and generally poor vision. Varying amounts of exudation and pigmentary migration occur, and there are often ghost vessels and sheathed vessels in parts of the retina. This is the group that corresponds more closely to those reviewed by Wyburn-Mason in his original paper of 1943 (Wyburn-Mason 1943).

The expanded spectrum of Wyburn-Mason syndrome now includes variants with orbital arteriovenous malformations that spare the retina, bilateral orbital or retrolental arteriovenous malformations, and arteriovenous malformation of the cerebral hemisphere, basal ganglia, thalamus, optic nerves/chiasm, mandible and maxilla. At present, thus, unilateral and/or retinal arteriovenous malformation is not required for diagnosis.

Skin abnormalities

Dermatological signs are subtle and detectable in less than 50% of cases. The facial naevi are generally present from birth and vary from faint reddish-bluish discoloration containing scattered punctate red spots to dilated enlarged superficial veins involving the trigeminal region (Fig. 1) or extensive angiomatous naevi. They are usually unilateral, infrequently bilateral. Cutaneous vascular nevus, port-

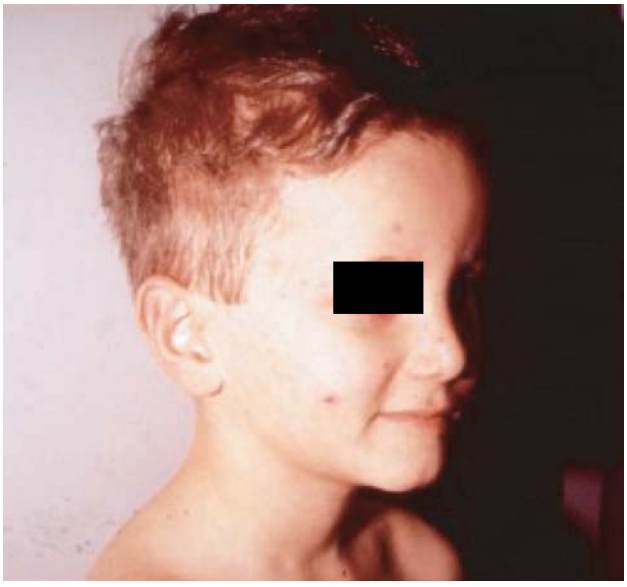

Fig. 1. Dilated enlarged superficial veins involving the trigeminal region of the right face in a child with Wyburn-Mason syndrome.

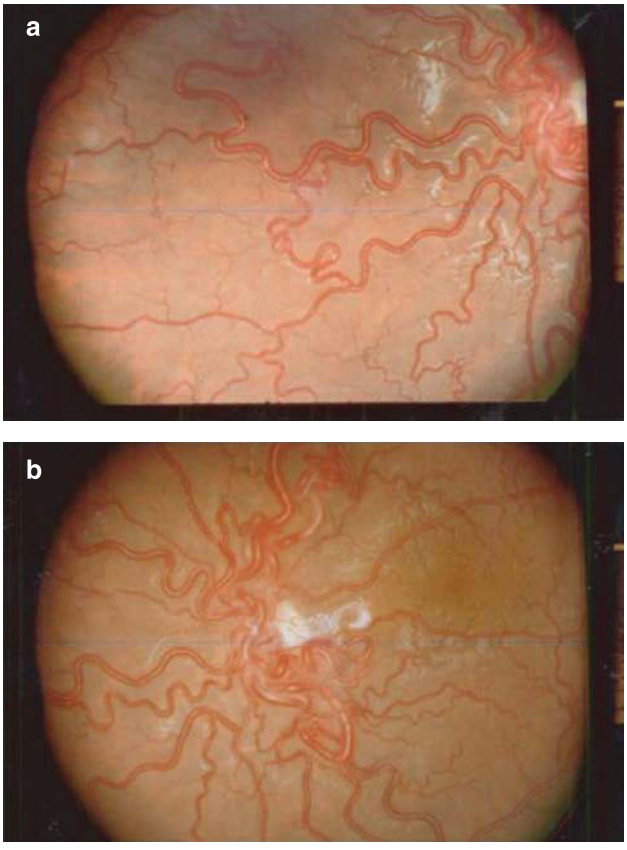

Fig. 2. (**a**) and (**b**) Fundi examination showing mixed angiomatous/large masses of tortuous and dilated vessels covering almost the entire retina in a cirsoid/aneurismal pattern ("bag of worms") in a patient with Wyburn-Mason syndrome.

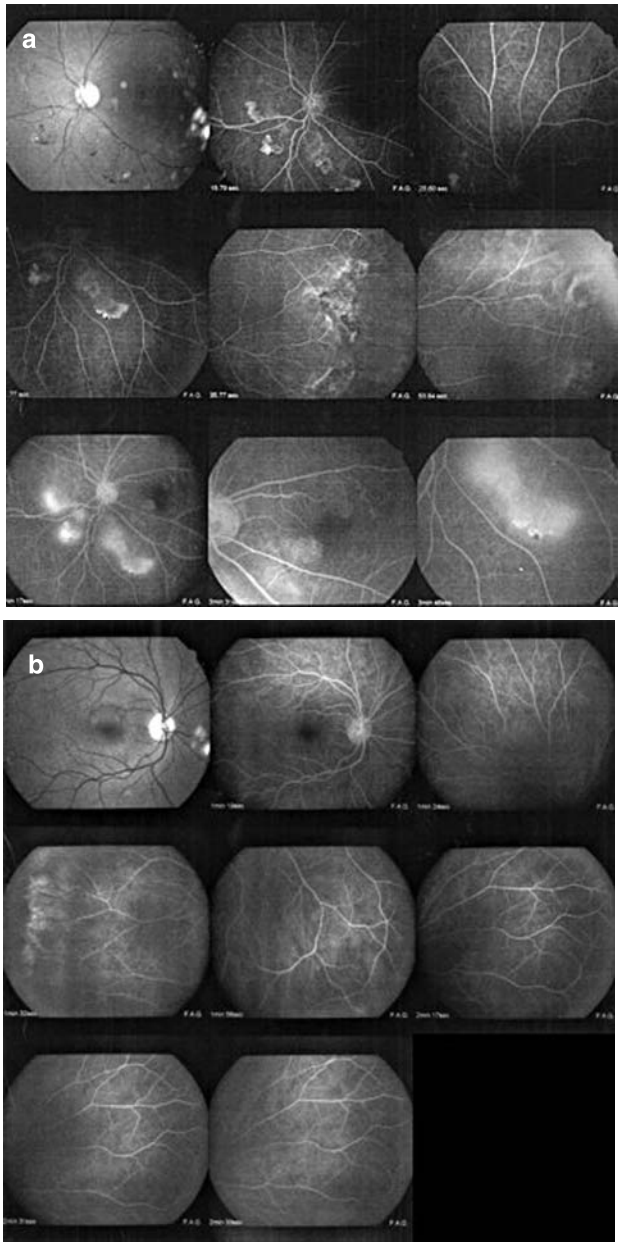

Fig. 3. Fluorescein angiographic examination of the eyes in a child with Wyburn-Mason's syndrome: the right eye (**a**) shows tortuos and dilated retinal vessels in a cirsoid pattern with spot haemorrhages (white dots); the left eye (**b**) shows only minimal spot haemorrhages (courtesy of Professor S. Li Volti, Department of Pediatrics, University of Catania, Italy).

wine nevus, or dilated veins involving the eyelids have also been reported.

Eye abnormalities

Ocular manifestations involving both the retina and orbits are diagnostic for the disease. An important sign is the presence of a vascular malformation in the bulbar conjunctiva as this can be easily detected at examination. The retinal lesions are usually unilateral and range from visible vascular malformations of the angiomatous type to large masses of tortuous and dilated vessels covering a substantial portion of the retina, a so-called (cirsoid) aneurismal pattern or "bag of worms" (Figs. 2 and 3) (Bidwell 2006). Normal acuity and normal disk do not exclude the presence of a malformation. In the original series of Wyburn-

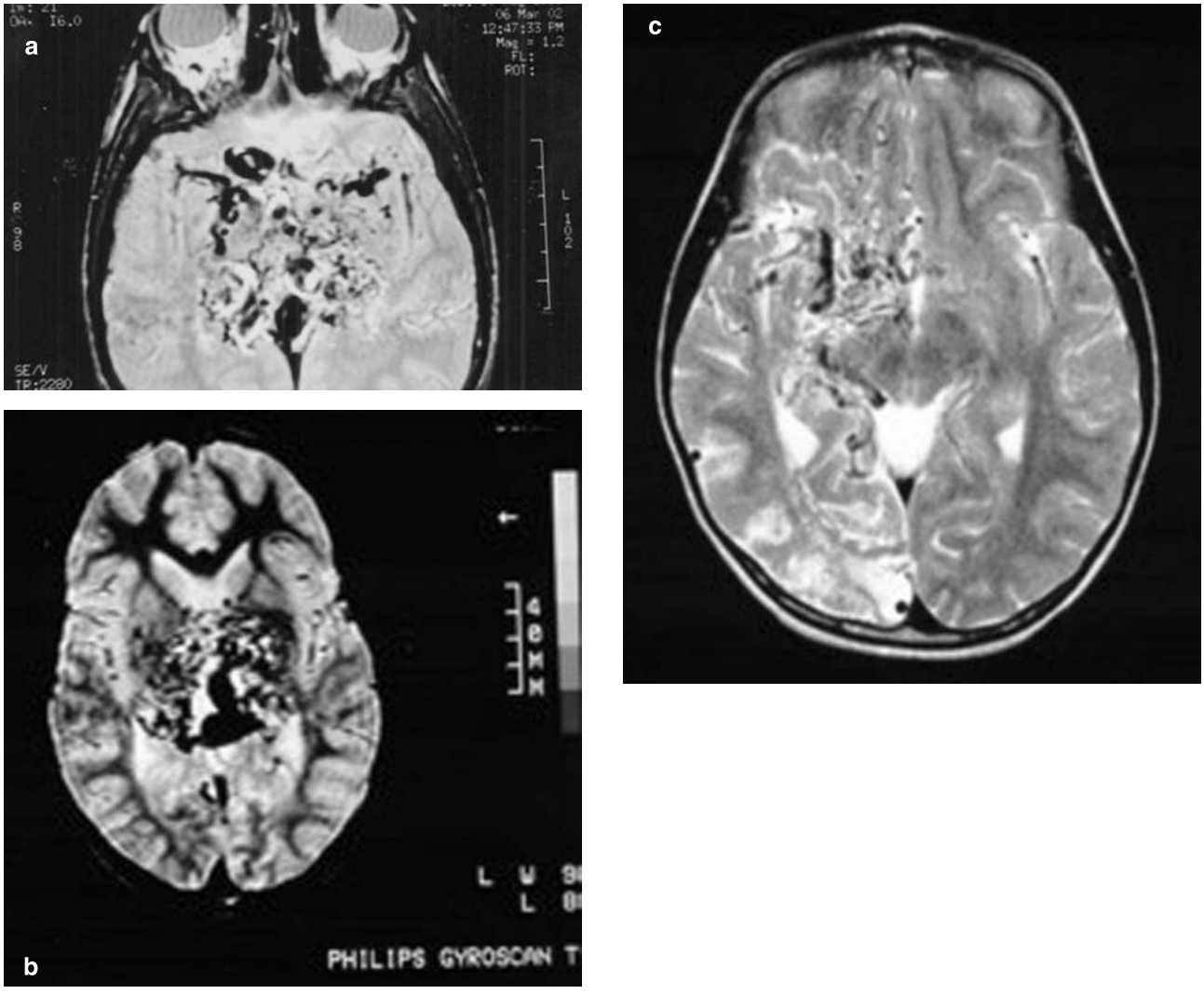

Fig. 4. Axial T1-weighted (**a–b**) and T2-weighted (**c**) magnetic resonance images of the brain showing typical vascular malformations: deeply located in the midbrain and brainstem (**a**) in a woman who had acute headache as presenting symptom at age 22 years; (**b**) deeply located in the entire thalami and basal ganglia regions in a 44-year-old woman who had hemiparesis at onset; (**c**) located in the entire right hemisphere with high signal areas in the posterior regions in a 6-year-old child (same child shown in Fig. 1) who had headache and later progressive cognitive deterioration (Figs. a and b are courtesy of Professor G. Pero, Institute of Neuroradiology, University of Catania, Italy).

Mason, six patients had normal fundi; visual impairment was reported in 50% of them (Wyburn-Mason 1943). Orbital manifestations include optic atrophy, involvement of the retrobulbar soft tissue by vascular malformations, or varying amounts of gliosis leading to mild, non-pulsating exophthalmos. The eye vascular malformations usually remain stable and generally do not demonstrate leakage on fluorescein angiography (Fig. 3) (Bidwell 2006). Rare associated ocular complications have been reported which include macular hole, central retinal vein occlusion, neovascular glaucoma, macroaneurysmal abnormalities, retinal haemorrhage and vitreous haemorrhage.

Nervous system abnormalities

The vascular malformation of the central nervous system are deeply located (Figs. 4–6) and frequently related to the optic pathways, extending sometimes to the occipital lobe. Extension into the vermis is not frequent. Other sites of involvement are the hypothalamus, thalamus, basal ganglia, midbrain, temporo-occipital and fronto-temporo-parieto-occipital

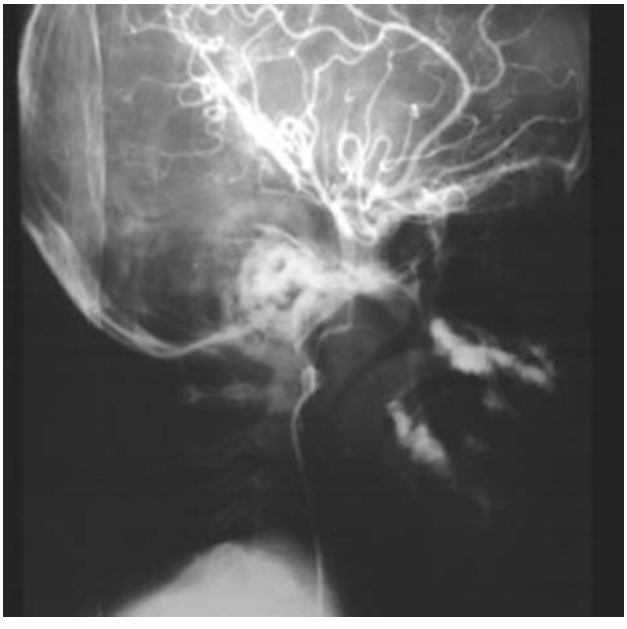

Fig. 5. Brain angiography showing the complex arteriovenous malformation in the left parieto-temporal region of a woman with Wyburn-Mason syndrome (courtesy of Professor G. Pero, Institute of Neuroradiology, University of Catania, Italy).

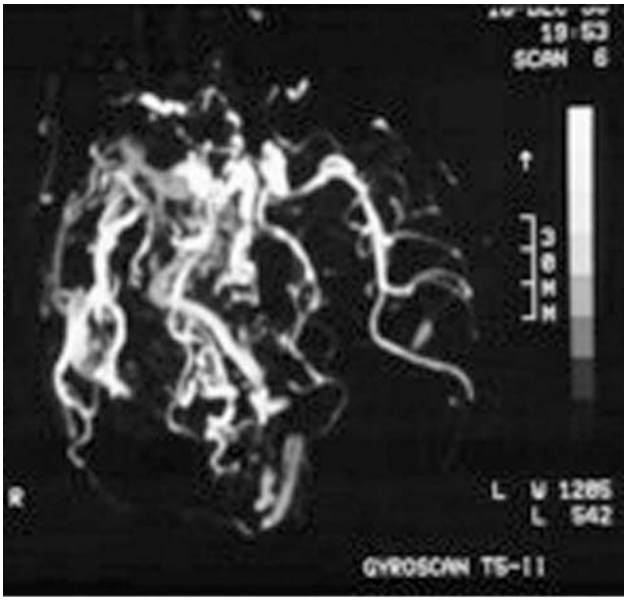

Fig. 6. Axial magnetic resonance angoiography showing the right arteriovenous malformation seen in Fig. 4c.

(Luo et al. 2006). The malformation is supplied either by the vertebral or the carotid system or both.

Arteriovenous malformations are dynamic structures that change over time. Substantial remodelling of an arteriovenous malformation has been observed in the retina and is evident on pathological analysis of intracranial lesions. Within the same lesion one can find atrophy of some vessels and dilatation of other vessels. These changes are most likely directed by vascular dynamic forces caused by spontaneous thrombosis and might account for the progression of neurological signs.

Clinically, the intracranial vascular malformation causes central nervous system signs in more than 80% of patients. The onset is generally sudden during puberty and adolescence. Affected individuals may present with acute headache, hemiplegia, and homonymous hemianopsia in 50% of cases. Seizures, cerebellar dysfunction, acute psychiatric signs, hallucinations and temporal/spatial disorientation are reported more rarely. Mental impairment is rarely present at onset but it becomes evident later in about 30% of cases. Arteriovenous shunting and steal may cause progressive neurological deficits and optic nerve atrophy.

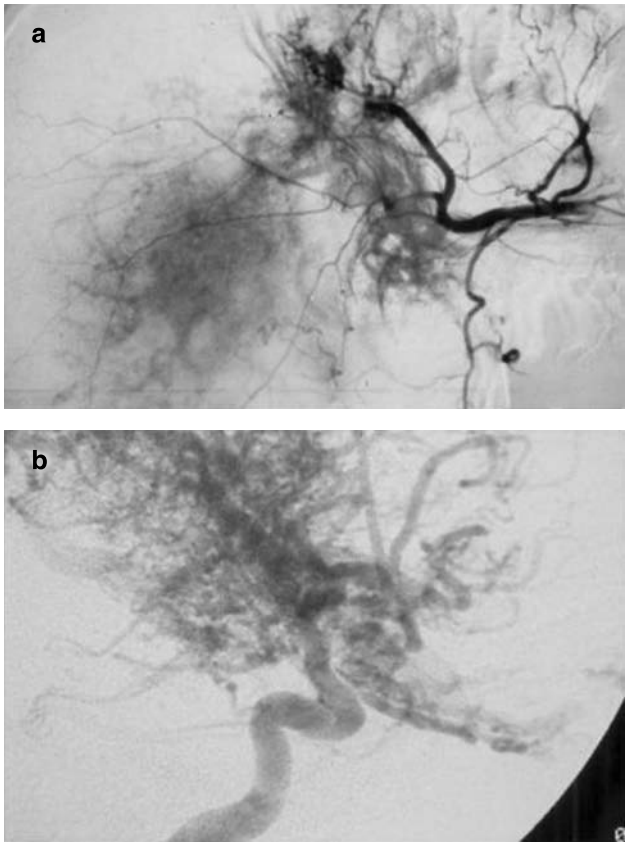

Fig. 7. Angiography (vein phase) (**a**) and (**b**) showing the arteriovenous malformation in the carotid and vertebral regions (courtesy of Professor G. Pero, Institute of Neuroradiology, University of Catania, Italy).

Neuroimaging studies

The imaging findings reflect the primary vascular lesions and secondary complications (Edelstein et al. 2005). Thus, CT, MRI and angiography (Figs. 4–7) reveal arteriovenous malformations within the orbits, retro-orbital region, cerebral hemispheres and brainstem, any associated subarachnoid or intraparenchimal haemorrhage and any optic nerve atrophy that result from direct compression or chronic ischemia (Fig. 4c). The retinal arteriovenous malformation varies from tiny angiographically occult lesions to large, tortuous and dilated vessels covering much of the retina (Edelstein et al. 2005). Arterial supply to the arteriovenous malformations arises from the internal carotid artery more often than from the vertebrobasilar arteries or the external carotid artery. Venous drainage is primarily via the cavernous sinus or the vein of Galen.

Extracranial/systemic involvement

The intracranial and retinal vascular malformation in Wyburn-Mason's syndrome can (occasionally) extend to the jaw, nose and mouth and to the thyroid (Brown et al. 1973, Lee et al. 2007, Shira and Guernsey 1965). Severe bleeding from the gingiva and tonsils, following chewing hard foods or during dental extraction is frequently reported and recurrent bouts of nose bleeding has been also described. Lung and spinal involvement has also been recorded (Bidwell 2006).

Pathology/pathophysiology

Arteriovenous anastomoses are characterised by variable alterations in capillary and arteriolar networks. Small anastomoses may have only minor alterations within the capillary system and can be subtle, whereas large, racemous aneurysms are characterised by direct artery-to-vein communication, without interposing capillary or arterioral elements (Bidwell 2006). At pathology, most of the vascular malformations in Wyburn-Mason's syndrome are a grossly tangled mass of convoluted vessels that histologically are neither arteries nor veins, with direct continuity from the arterial side to venous side (Brock and Dyke 1932, Krug and Samuel 1932, Younge 1987). The vessel walls are ectatic and have a fibromuscular media of varying thickness with wide fibrohyaline adventitial coats showing hyaline degeneration, haemorrhage, and calcification; and may be of such size to occupy more than the entire thickness of the retina. Nearby tissues are often gliotica and have loss of neurons. This is evident in the retina (Cameron and Greer 1968, Younge 1987), presumably because of the great mechanical distortion and compression of the neurons, although optic atrophy can occur from compression elsewhere on the optic nerve or chiasm, even in the absence of the retinal lesion (Danis and Appen 1984). Thrombosis and organisation may be present to a variable degree.

Natural history

The natural history of the syndrome is unpredictable, the long-term outcome largely depending on the extensiveness of the lesions (Rizzo et al. 2004, Younge 1987). The arteriovenous malformation could remain asymptomatic throughout the patient's life. In the literature, the presenting symptoms were reported at the mean age of 20 years. The risk of haemorrhage is not higher in children than in adults (Iizuka et al. 1992).

Bilateral involvement of the midbrain and early onset of symptoms are usually regarded as poor prognostic factors. However, a precise correlate between the size of the lesions and the haemorrhage does not exist. It seems that venous drainage is responsible for neurological and haemorrhagic symptoms. In our experience, slow, progressive cognitive impairment was evident in children whilst acute neurological symptoms (e.g., headache, focal neurological deficits) were the typical symptoms/sings at presentation. If the vascular malformation remains untreated, progressive deficits related to congested cerebral veins owing to ischaemic or to limited episodes of bleeding bring additional functional impairment.

Diagnostic work-up

Imaging studies should include fluorescein angiography (Fig. 3), which may further demonstrate the abnormal retinal vascular communications; most arteriovenous aneurysms are stable nonleaking processes (Bidwell 2006). MRI studies of the brain (Fig. 4) (and the spine) and MR angiography (MRA) (Fig. 6) of the ipsilateral orbit and the brain may be considered. Additionally angiographic evaluation of the affected regions (Fig. 7) could be obtained.

Pathogenesis and molecular genetics

The anomaly is considered to be the result of a persistent primordial stage of vascular development without separation of arteries from veins in that part of the circulation shared by the optic cup and prosencephalon. The various systems that are affected in the head likely represent the effect on the particular stage of differentiation at the time of the insult (Danis and Appen 1984, Younge 1987). No instance of familial transmission are known and no genetic mechanisms have been invoked so far to explain the syndrome.

Treatment

The therapeutic strategies in Wyburn-Mason's syndrome are extremely challenging. In most cases, complete eradication of the arteriovenous malformation is not feasible. Partial or targeted surgical resection was undertaken to either decrease the symptoms or eradicate obvious dangerous portions of the lesions (Berenstein and Lasjaunias 1992, Lasjaunias et al. 1995). Endovascular management of arteriovenous malformations seems to be the best form of treatment (Lasjaunias et al. 1995). In a few cases, complementary radiosurgical treatment might follow the partial embolisation with bucrylate (Iizuka et al. 1992). Partial treatment performed with a permanent agent such as bucrylate is an acceptable therapeutic objective when complete eradication of the vascular lesion cannot be obtained due to the elevated risks. Partial removal of the most dangerous portions of the intracranial vascular anomaly might progressively minimise the deleterious affects to the adjacent brain (Lasjaunias et al. 1995).

Because of the stability of the retinal lesions, treatment from an ophthalmologist usually is not necessary beyond routine, periodic ophthalmic examination (Bidwell 2006).

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