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COMMENT

Sturge-Weber Syndrome without Facial *Nevus*

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متلازمة استريج–فيبر دون حدوث وحمة الوجه

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In this edition of SQUMJ, Koul *et al.* present a rare manifestation of Sturge-Weber syndrome (SWS; Online Mendelian Inheritance in Man 185300) with parieto-occipital leptomeningeal angiomatosis and seizures, but without facial *nevus* or eye involvement.[1]

SWS is a rare, sporadic, and congenital neurocutaneous disorder with an incidence of 1 in 50,000 live births.[2] It is characterised by venous-capillary abnormalities which affect the skin in the distribution of the trigeminal nerve (*nevus flammeus* or port-wine stain [PWS]), leptomeninges and the eye. For these reasons, it is often referred as encephalotrigeminal angiomatosis.

The distinctive feature of SWS is a facial cutaneous venous dilatation in the distribution of the ophthalmic (V1) and maxillary (V2) branches of the trigeminal nerve. They are present at birth and, in contrast to capillary haemangiomas, do not resolve with age. SWS is referred to as complete or type I when both the central nervous system is affected and facial angiomas are present.[3] A child born with a PWS on the face has approximately a 6% chance of having SWS;[4] this risk increases to 26% when the PWS is located in the distribution of the V1 division of the trigeminal nerve.[4] Reports of patients with SWS and central nervous system (CNS) manifestations but without a PWS *nevus* do exist in literature but these are rare.[5,6] Between 5–15% of patients with SWS have leptomeningeal angiomatosis without cutaneous lesion or ocular abnormalities, and are referred to as type III encephalofacial angiomatosis.[3]

In the brain, the angiomas are typically unilateral and located in the pial vessels of the parieto-occipital lobes of the brain on the same side of the head as the port-wine birthmark. The slow flow of blood through these vessels leads to hypoxia, cortical atrophy and subsequent calcification resulting in the characteristic gyriform hyperdensity seen in neuroimaging. Consequent neurological manifestations include seizures, local neurological deficits including contralateral stroke and hemianopsia, behavioural anomalies and progressive intellectual impairment. Seizures are often the presenting neurological symptom secondary to facial angioma and occur in nearly 75% of patients, with 75% of the seizures appearing in the first year of life.[7] In the eye, choroidal vascular malformations (haemangiomas) are common, and may lead to degenerative changes of the overlying retina and serous retinal detachment. However, the principal sight-threatening complication is glaucoma which occurs in 58–71% of cases.[8] The proposed mechanisms for glaucoma in SWS include mechanical obstruction of the angle of the eye, increased episcleral venous pressure caused by episcleral arteriovenous shunts or hypersecretion of fluid by either the choroidal angioma or a ciliary body. Congenital glaucoma in SWS is almost always associated with the involvement of both eyelids by the PWS.

It is worthwhile discussing the pathophysiology of the neurocutaneous manifestations of SWS as this can shed light on the underlying basis of the development of SWS with CNS manifestations without skin lesions. This requires an understanding of the normal pattern of the primitive cephalic venous *plexus* in gestation. During the end of the first trimester, there is a division of the primitive vascular system into an external portion that feeds and drains the facial skin and scalp, a middle portion investing the meninges and a deep portion that feeds and drains the brain. The proximity of the ectoderm, destined to form the upper portion of facial skin, to the portion of the neural tube that will form the parieto-occipital area of the brain during this early stage of vascular development may explain the noted association between parieto-occipital leptomeningeal angioma and the facial PWS in SWS.[9] Spontaneous somatic mutations occurring during this period of embryonic development and disrupting vascular development offer an explanation of the association of facial angioma and the abnormal vascularity of the

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ipsilateral brain. It is likely that a smaller defect, involving only the developing pial vascular structures of the occipital lobe, can result in an occipital leptomeningeal angioma without the facial PWS in a small subset of patients with this syndrome. There have been reports of SWS patients without a facial *nevus* with a frontal location of the leptomeningeal angioma.[6,10] The lack of a facial *nevus* may be attributed to the noncontiguous nature of the more anterior vascular *plexus* with the developing upper facial ectoderm.[6]

A recent development has been the discovery of a somatic mutation in patients with SWS confirming a long-standing hypothesis about the pathogenesis of this condition. Whole-genome sequencing of DNA from three patients with SWS, followed by targeted sequencing in skin samples from 50 patients with SWS, revealed a somatic mosaic-activating mutation in *GNAQ*,[11] which encodes a G-protein receptor for endothelin that has important roles in vasculogenesis.

A review of the literature revealed isolated case reports pertaining to SWS from the Middle East,[12,13] and one study from Saudi Arabia investigating the characteristics of glaucoma in patients with SWS.[14] The interesting medical image in this issue of SQUMJ is important in this respect as it brings to attention a rare presentation of SWS in an Omani patient. Efforts to characterise the neurological, ophthalmic and cutaneous features of SWS in the indigenous population of Oman through larger studies is likely to provide additional insights into this rare disease and will have important implications.

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