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STURGE WEBER SYNDROME

Developed by Miles Jaques, Dr. Jennifer Ling, Dr. Gardiner for PedsCases.com.
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Introduction

Hello, my name is Miles Jaques, and I am a fourth-year medical student at the University of British Columbia. Today I will be discussing Sturge Weber syndrome, a rare, congenital, neurocutaneous syndrome that presents most frequently in pediatric patients. Our focus will be on the ophthalmologic manifestations of the disease, but we will indeed discuss both the ocular and non-ocular manifestations. This podcast was designed with Dr. Jennifer Ling, an ophthalmology resident at the University of British Columbia, and Dr. Gardiner, a pediatric ophthalmologist at the University of British Columbia in Vancouver, BC.

Learning Objectives

By the end of this podcast, we hope you'll be able to:

1. Understand the pathophysiology of the Sturge Weber syndrome
2. Apply the pathophysiology to its broad spectrum of clinical presentations
3. Recognize clinical presentations of the disease in the brain, epidermis, and eyes
4. Describe the ocular manifestations of Sturge Weber syndrome and their treatments.

Case

To put this into perspective, let's first examine a case.

You are a third-year medical student completing your ophthalmology rotation. Jamie, a two-year-old boy, who comes into your office with his mom, is referred by his pediatrician for a port-wine stain on his right forehead for ocular evaluation. Your

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preceptor asks you to take a thorough history and focus on any symptoms of glaucoma. If you are comfortable, she says, you can perform a slit lamp examination of the patient but says to defer intraocular pressure (IOP) measurements until you are together with the patient.

You enter the room and meet Jamie and his mother. You explain that you will be starting first, completing a history and physical examination, and then will bring in your attending physician to review.

Jamie is a shy boy who you note has challenges focusing, and you suspect that he may have some developmental delay. You also notice that on the right side of his face, he has a hyperpigmented red patch around his eyelids and forehead. You palpate the patch and notice that it is non blanchable in pigmentation, and his mother reports he has had the patch since birth and that it has remained stable in size.

On examination of his eyes, you notice that that the right eye (on the same side as his bn pigmented changes) appears larger than the contralateral side and suspect that it is mildly injected; there is no associated history of pruritus or viral illness. Visual acuity is central, steady, and maintained in each eye with no fixation preference. He seems to show stereopsis on the Lang test (stereopsis is 3-dimensional vision, and is assessed via the Lang stereo test, where patients are asked to identify 3-dimensional images). His extraocular movements are full, and his Hirschberg corneal light reflex test is symmetric. You perform a handheld slit lamp examination to find increased conjunctival vascularity on the right side. His anterior segment appears normal otherwise, though you defer doing intraocular pressure at this time.

You finish your examination, and you ask if they have any other questions before you leave to discuss with your preceptor. The mom tells you that she is pregnant and is concerned that her next child might also be at risk for similar vision problems. Unsure yourself, you thank her for her questions and tell her that you will discuss with your preceptor an address her question shortly.

You leave the room and debrief with your preceptor, who says you performed a good history and physical exam and asks you what you would like to do next for Jamie and what you will tell the mother regarding how her future children may be affected.

Background

Sturge Weber syndrome is a congenital neurocutaneous syndrome (which are collectively also known as phakomatoses) involving the malformation of blood vessels that can affect the brain, skin, and eyes. In fact, its non-eponymous name is encephalotrigeminal angiomatosis; “encephalo” referring to brain, “trigeminal” referring to the 5th cranial nerve, and “angiomatosis” meaning a vascular malformation. And as we will come to learn, encephalotrigeminal angiomatosis is a name that well encompasses the pathophysiology of this disease.

Sturge Weber syndrome is a rare disease, with an incidence of 1/20,000 to 1/50,000 live births, with no sex or racial predilection. It varies widely in its clinical presentation. Patients require two of three criteria to be diagnosed: (1) facial port wine birth mark, (2) increased intraocular pressure, and/or (3) leptomeningeal angiomatosis. Leptomeningeal angiomatosis are vascular lesions of the arachnoid and dura matter; we will cover these much more in detail later. Interestingly, Sturge Weber syndrome is not really a syndrome at all, but rather has a well-studied single gene abnormality that results in its clinical presentation.

But how does one single gene cause such a wide gamut of disease presentations amongst patients? And similarly, how does it affect 3 seemingly distinct organ systems?

Let's dive into the pathophysiology of this disease process and learn how this diversity in clinical presentation results from the pathophysiology.

Pathophysiology

To fully understand this disease, we must revisit embryogenesis. The following description of embryogenesis is not for the purpose of memorizing the steps, but rather to help highlight the gene to phenotype progression of this disease. Bear with me; our journey through embryogenesis will focus on two key time points in fetal growth: week 3 of gastrulation, and week 6 of angiogenesis.

During the 3rd week of embryogenesis, gastrulation occurs, which is the formation of the trilaminar disk which contains the ectoderm, endoderm, and mesoderm. We will focus here on the subsequent development of the ectoderm. The ectoderm undergoes neurulation to form the neural tube. Specific neural tube cells differentiate to neural crest cells and migrate away from the neural tube to form the central and peripheral nervous system, the epidermal layer of the skin, various parts of the anterior segment of the eye including corneal stroma, corneal endothelium, ciliary body stroma, iris stroma, and trabecular meshwork.

During the 6th week of development, vascular plexuses develop starting at the cephalic region of the ectodermal neural tissue. The development of these vascular plexuses is regulated by the activation of gene GNAQ at Chromosome 9q21. Expression of GNAQ occurs until approximately week 9, after which it is turned off and the vascular plexus regresses.

In 90% of non-syndromic Sturge Weber syndrome, a single-point somatic mutation of the GNAQ gene occurs. Simplistically, this results in continued expression beyond week 9. As a result, the vascular plexus does not regress, and the affected regions have excess capillaries.

Now, previously we said that the ectodermal neural tissue goes on to form the brain, components of the anterior segment of the eye, and the epidermal skin layer starting in

week 3. Both the time and location in which the sporadic GNAQ mutation occurs will determine the presentation of the disease. If the mutation occurs prior to neurulation, then we would expect all 3 of these organ systems to be affected and it may present with bilateral 'complete' manifestations. The later the mutation occurs, the more likely it is to affect neural crest cells post-migration and be unilateral and confined to fewer of these organ systems.

So, as a quick recap:

- The ectoderm forms the central and peripheral nervous system, epidermis of skin, and the anterior segment of the eye.
- GNAQ is a gene expressed in ectodermal tissue that stimulates vascular plexus formation, and is tightly regulated in fetal development.
- In Sturge Weber syndrome, there is an "activating" mutation of the GNAQ gene that results in continual expression.
- Therefore, depending on the location and time that the GNAQ point-mutation occurs during development – since all the cells that divide from the initial mutated cell will share that mutation – the extent of organ involvement will vary from one to all 3 of the organ systems.
- Of note, since this is a spontaneous somatic, non-germline, mutation, this disease is not heritable.

Clinical Presentation and Management

Now, the rest of this podcast should be very straightforward, as the clinical manifestations, diagnosis, and management logically follows. We will focus on the ocular manifestations and management, and briefly touch on the involvement of the other systems.

In the brain, Sturge Weber syndrome results in vascular leptomeningeal malformations which can be viewed on CT or MRI as so-called tram tracking. These leptomeningeal malformations may present unilaterally – with ipsilateral ocular and cutaneous manifestations - or bilaterally. As the lesions enlarge, they can cause increased intracranial pressure and brain atrophy. Increased ICP can present with headache, nausea, vomiting, and diplopia from an associated compressive cranial nerve VI palsy. Studies have shown up to 80% of patients may have at least 1 seizure related to Sturge Weber syndrome, and this syndrome is often associated with intellectual disabilities. Seizures have varying presentation, and often present in infancy or early childhood. They are usually focal on the contralateral side to the brain involvement (or contralateral to port-wine staining), although some may still be generalized seizures. Intellectual disability is not ubiquitous to SWS patients, but for those affected it ranges from mild to severe and can lead to subsequent lower cognitive function.

On the skin, it classically presents with a unilateral nevus flammeus, also called a port-wine stain, seen as a purple patch on the face. Nevus flam meus is a non-regression

of the vascular plexus from embryonic development. It can be distinguished from trauma by the non-fading nature of the lesion and the remarkable unilateral cut-off (if present). Port wine stains can be treated with laser therapy. If left untreated can hypertrophy and become nodular over time. A referral to dermatology should be made to consider pulse laser therapy for regression of the nevus flammeus.

With regards to ocular manifestations, several parts of the eye can be affected, and we will cover them one by one.

Over the anterior segment, Sturge-Weber may present with increased conjunctival vascularity, producing a red eye. There is often an associated abnormal plexus of the episcleral vessels, and this more commonly presents when the port-wine stain involves the skin over the eyelids.

The retina may likewise show an abnormal plexus, with arteriovenous communications. This results in a choroidal hemangioma - a benign vascular neoplasm of the choroid. This is usually asymptomatic in children, but in adulthood, can result in macular thickening and degeneration or detachment of the overlying retina. The diagnosis is usually made on clinical exam, fluorescein angiography, or ultrasound. Treatment is focused on slowing the natural history of the disease processes. Laser photocoagulation, photodynamic therapy, and radiation therapy are current techniques that are used to treat choroidal hemangiomas.

Finally, Sturge Weber syndrome is most frequently associated with glaucoma secondary to increased intraocular pressure (IOP), occurring in up to 70% of patients. Increase IOP presents with a watery, light-sensitive eye. The cornea might look cloudy due to corneal edema, which can occur when the intraocular pressure is very high and ruptures Descemet's membrane, allowing fluid to leak into the cornea. Increase IOP is almost always ipsilateral to the side of the cutaneous manifestations. The increased vascular plexus leads to elevated IOP due to raised episcleral venous pressure, resulting in impaired venous drainage. Additionally, hyperemia – that is to say, increased blood in the vasculature – of the ciliary bodies induces hypersecretion of aqueous humor. The hyperemia also engorges the ciliary bodies and thereby puts mechanical pressure to close the anterior chamber angle. Thus, there is increased IOP from increased production and impaired drainage of aqueous humor. If left uncontrolled, the increased IOP can lead to buphthalmos – a physical enlargement of the eye – and associated myopia.

Treatment of Sturge Weber syndrome induced elevated IOP is often challenging and can start with medical management before progressing to surgical management. Topical prostaglandin inhibiting eyedrops such as latanoprost can decrease aqueous humor production to stabilize IOP, and are often first line choice. Beta blockers, such as timolol, are a second-line agent that is also be effective in lowering IOP, but can be associated with the usual systemic side effects of B blockers. For pediatric patients, without a history of cardiovascular disease, this is often well tolerated.

Other medications that can be used include oral and topical carbonic anhydrase inhibitors, topical alpha-adrenergic agonists, and topical parasympathomimetic agents. However, these require more frequent dosing regimens and have potential systemic side effects and are considered as second or third-line therapies.

When medical management alone is not sufficient to manage IOP, which can often be the case in Sturge Weber syndrome, surgical management may be considered. In general, there are 4 surgical options available: Goniotomy, trabeculotomy, trabeculectomy, and drainage implant valves. We will not go over the details of these procedures, but essentially, they are all designed to facilitate easier and more effective drainage of the aqueous humour. Considerations for surgery vary from patient to patients and are made by specialists in the field. Overall, these complex patients benefit from longitudinal care from a Pediatrician who can monitor and help manage the systemic manifestations of Sturge Weber syndrome.

Now, let's return to the case.

Case

While discussing with your preceptor, you recall that the developmental delay that you suspected is related to some leptomeningeal malformation that may accompany his disease presentation.

You enter back into the examination room with the preceptor and the preceptor examines the patient with the portable slip lamp. His right intraocular pressure measures at 28 mm Hg and his left at 16 mm Hg with an iCare tonometer (the normal range 12-22 mm Hg). Your preceptor tells you the fundoscopic examination shows a cup-to-disk ratio 0.5 on his right and 0.3 on his left. Cycloplegic refraction is also performed, after instilling cyclopentolate 1% to each eye. This paralyzes the ciliary muscles and prevents accommodation. Cycloplegic refraction revealed the right eye to be -1.25 diopters and the left as +1.75 diopters: a relative myopia in the affected right eye.

Together, you start Jamie on latanoprost eyedrops 1 drop to his right eye every evening. You also reassure Jamie's mother that although Sturge Weber syndrome is a genetic condition, it is not heritable, and her next child is not at an increased risk of having this disease.

She thanks you but says is still worried about Jamie's vision. You let her know that we are starting with the conservative treatment options which will likely manage his pressure, but there are more medical and surgical options available if needed. You reassure her that with adequate management of Jamie's intraocular pressure and any subsequent manifestations of Sturge Weber syndrome, as well as with possible corrective eyeglasses, Jamie can have healthy vision for many years to come. You also let her know that it is important to follow up with their pediatrician and that referrals to dermatology and neurology are needed, so that he can be followed for any cutaneous or neurologic concerns.

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Summary

That's everything we have for you today. Hopefully, you now feel equipped to diagnose a patient presenting for ocular evaluation in the setting of Sturge Weber syndrome, and understand the fundamentals of management for the potential sequelae of this disease. As a quick recap, Sturge Weber syndrome is a genetic disease of spontaneous origin that causes excess small vascular plexus formations which can manifest in the brain, eyes, and skin. In the eyes, it most commonly presents as increased intraocular pressure and can lead to glaucoma. It can also result in choroidal hemangiomas. Indeed, its most classical presentation is a triad of facial port-wine stain, intracranial angiomata, and glaucoma. Ocular management of the disease is specific to the phenotype of presentation, and includes medical management or surgery for glaucoma, or photocoagulation, photodynamic therapy, or radiation therapy for choroidal hemangiomas. As well, it is important to adopt a multidisciplinary approach when managing these patients. While their care is usually coordinated by their primary care provider or pediatrician, ophthalmology, dermatology and neurology are often involved.

Thank you for listening today, and we look forward to seeing you again for another episode.

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