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Review

Neurocutaneous syndromes: Behavioral features

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Abstract

Neurocutaneous syndromes are disorders charactertized by a neurological abnormality and cutaneous manifestations. Three of the more common neurocutaneous syndromes are Sturge–Weber syndrome, tuberous sclerosis, and neurofibromatosis. This review focuses on the cognitive and behavioral features of these syndromes.

Keywords: Neurocutaneous; Tuberous sclerosis; Sturge–Weber; Neurofibromatosis; Epilepsy; Cognitive; Autism

1. Introduction

Neurocutaneous syndromes, or phakomatoses, were first discussed as a clinical entity by the ophthalmologist Van der Hoeve in 1932. Van der Hoeve included neurofibromatosis, tuberous sclerosis, Sturge–Weber syndrome, and von Hippel–Landau syndrome. Currently, 20 to 30 disorders are grouped under the neurocutaneous rubric. The disorders typically consist of abnormalities of the brain and skin, and may also involve the peripheral nervous system and other organs. This review focuses on the behavioral features of three of the more common syndromes: Sturge–Weber syndrome, in which a cutaneous vascular anomaly is associated with central nervous system dysfunction, and tuberous sclerosis and neurofibromatosis, which share hamartomatous formations as a disease mechanism.

2. Sturge–Weber syndrome

Schirmer probably provided the first report of Sturge–Weber syndrome in 1860 when he described a patient with bilateral facial nevus and unilateral buphthalmos [1]. In 1879 Weber presented another case of a 6-year-old girl with bilateral facial nevus. Prevalence is currently estimated at one per 50,000 live births [2], although identification of milder forms of the disease will likely increase prevalence estimates. Males and females are equally affected. Familial cases are rare, and the lack of clinical similarity in monozygotic twins has pointed to somatic mutation as a possible means of disease transmission.

The vast majority of those with Sturge–Weber syndrome present with a cutaneous vascular abnormality at birth, typically affecting the upper part of the face (although most children with a facial cutaneous vascular malformation do not have the disorder). The cutaneous vascular malformation typically affects the face in a manner consistent with the ophthalmic division of the trigeminal nerve. The proximity of the portions of the ectoderm destined to form the facial skin and the parieto-occipital area of the brain has been postulated as cause for the combination of the facial nevus and leptomeningeal angiomatosis [3,4].

The main cerebral finding in Sturge–Weber syndrome is leptomeningeal angiomatosis, which can be diffuse and bilateral but most often affects occipital and posterior parietal lobes unilaterally [5]. Bilateral intracranial

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involvement, which is uncommon, is associated with poorer clinical outcome [6,7]. Calcifications in meningeal arteries and in cortical and subcortical veins underlying the leptomeningeal angiomatosis are often associated with cortical atrophy and severe hypometabolism [8]. In infants, accelerated myelination in tissue underlying the leptomeningioma has been reported [8].

The etiology of the leptomeningeal angiomatosis is unknown. It has been theorized that superficial cortical veins fail to develop appropriately or thrombosis of such veins early in development causes a redirection of blood to the developing leptomeninges and into the deep venous system [9]. Progressive venous stasis and vessel dilation due to insufficient drainage then lead to chronic hypoxia.

Partial seizures, which may occur in up to 90% of those with the disorder in early childhood, typically occur contralateral to the neurocutanous sequelae, although infantile spasms are also observed. A general pattern of worsening seizures with age is common, at times necessitating surgical intervention. Headache and transient ischemic phenomena such as hemiparesis are also commonly reported. When present, hemiparesis and hemianopia occur contralateral to the brain abnormality. Hemiparesis may or may not be directly associated with seizures, as strokelike episodes can precede seizure onset and hemiparesis can occur in the absence of epileptiform activity on electroencephalography [10].

Few large studies of cognition and/or behavior in Sturge–Weber syndrome exist. Mental retardation rates of 50 to 60% have been reported [7,11]. In a sample of 40, 60% were mentally retarded and nearly one-third of the sample fell in the severely mentally retarded range [7]. Even in those without frank cognitive impairment, intellectual skills are often lower than expected. Chapieski and colleagues noted a mean intelligence quotient (IQ) of approximately 75 and a range from 42 to 127 in 32 individuals for whom IQ scores were available [12]. In a study of 15 children, all of whom had seizure onset in the first year of life, none of the 6 individuals with normal intelligence had an IQ score greater than 100 [13].

No prospective studies of development in Sturge–Weber syndrome have been conducted. Studies of development and cognition often investigate the role of epilepsy factors. The presence of a seizure disorder is associated with poorer clinical outcome [12]. However, the correlation between age at seizure onset and intellectual functioning is less clear in this population than in others. Kramer and colleagues did not find a correlation between cognitive level at follow-up and the age at seizure onset, presence of ongoing seizures, or degree of hemiparesis, although a connection between seizure intensity and cognitive outcome was noted [13]. A study of families identified through the Sturge–Weber Foundation used questionnaires and available medical records [14]. All subjects without seizures had normal intelligence, and ~85% with seizure onset at 4 years of age and older had normal intelligence. However, whereas 25% of those with seizure onset before age 1 had normal intelligence, none of those with onset between 1 year and 3 years 11 months had normal intelligence (although the latter group tended to do better academically than the group with onset before age 1). Thus, it is possible that the combination of vascular and electrophysiological abnormalities may provide a more detrimental impact on development at a later age, in comparison with children with a more selective electrophysiological deficit earlier in life.

Hemispherectomy is a common surgical approach in individuals with Sturge–Weber syndrome and medically refractory epilepsy, particularly in children. Reviews of the literature have noted an overall 80% rate of seizure freedom following hemispherectomy [15]. The effect on cognitive and behavioral functioning has rarely been studied in a systematic fashion. Kossoff and colleagues used mailings to examine the effects of hemispherectomy in a sample of 32 individuals with seizure onset before 1 year, the majority of whom had frequent seizures and hemiparesis [15]. Surgery was performed at a mean age of 2 years 7 months. Postoperatively, 2 patients were felt to be normal cognitively, whereas 10 were noted to have only circumscribed learning difficulties. Fourteen were rated as "moderately disabled" and 6 were rated as "severely disabled." The percentage of children with no or mild learning disability did not differ between those operated before or after 1 year of age. However, interpretation of the statistical significance of such results may have been limited by sample size. The mean age at surgery was just after 2 years of age for the group with at most mild disability, compared with just after 3 years of age for those with moderate to severe disability. Erba and Cavazzuti noted a connection between later age at surgery and mental retardation [16].

One area of concern in Sturge–Weber syndrome is developmental deterioration. Ito et al. reported a progressive neurological syndrome that in at least one case was not resolved with epilepsy surgery [17]. In some individuals, an abrupt deterioration is temporally correlated with worsening of seizures and EEG abnormalities [18,19]. However, it is believed that venous occlusions and hypoxia may be responsible for neurological deterioration outside of overt seizure activity. Vascular and electrophysiological factors may combine to cause greater damage then when either factor is operating independently. Theoretically, a lack of increase in blood flow during seizures would compromise an already ischemic cortex. Additionally, the underlying brain abnormality also plays a role in development. Mental retardation has been correlated with the extent of unilateral calcification and atrophy, and bilateral leptomeningeal angiomatosis is associated with more seizures and focal deficits [6,7].