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Vanishing White Matter Disease and Genetic Association

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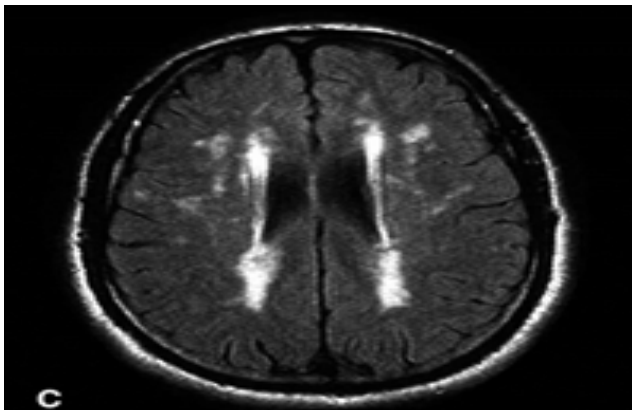

Courtesy of Dr. Asia Filatov

Literature Review of Vanishing White Matter Disease

Vanishing White Matter disease (VWM) is a genetically inherited condition usually arising from abnormal genetic makeup. Children born with VWM have a non-typical gene that inhibits the body from producing a substance known as myelin [1]. Myelin is a white fatty tissue that insulates nerve fibers, called axons, protecting them from damage. Consequently, axions interconnect neurons from the brain to the spinal cord and aid nerve cells in sending signals that enable them to communicate [2].

'White matter' is thus a term used to refer to nerve fibers covered by myelin sheaths; hence, in the event of the degeneration of the white matter, nerve fibers all over the body are more likely to disappear and deteriorate. Deterioration of the nerve fibers will hinder any transmission within the brain or from the brain to the spinal cord, causing cognitive and neurological disorders in the affected individual. Symptoms associated with cognitive impairment include mood changes, poor vision, memory loss, and difficulties in problem-solving [2]. On the other hand, individuals suffering from VWM are likely to present neurological impairment symptoms such as muscle stiffness, seizures, and impaired mental awareness [3].

Diagnosis of Vanishing White Matter disease is usually based on factors such as presenting symptoms, results of an MRI (magnetic resonance imaging) brain scan, or DNA (Deoxyribonucleic acid) tests [3]. DNA tests are typically carried out because VWM disease is a genetically inherited disorder, and both parents carry a mutated gene that the offspring can inherit. Mutated genes that cause VWM disease are referred to as EIF2B. EIF2B genes are five in number (EIF2B 1, EIF2B 2, EIF2B 3, EIF2B 4, and EIF2B 5); hence, a mutation of one of the given genes cause the VWM disease [4]. Parents are carriers of the disease, and when both parents experience a mutation on the same EIF2B gene, the offspring will be infected with VWM disease. However, each parent experiences a unique set of mutations they pass on to the child. Therefore, the child experiences a different type of combined mutation that determines the severity of the VWM disease.

The life expectancy of an individual born with the Vanishing White Matter disease relies on the stage of the disease, its progression rate, and the kind of complicacy it causes [2]. There are several stages of VWM disease- antenatal onset, infantile-onset, early childhood onset, juvenile-onset, and adult onset [5]. Antenatal onset refers to detecting VWM disease during the last three months of pregnancy. Infantile onset describes VWM disease that occurs within the first year of the infant's life and progresses for at most two years before its death [5]. Early childhood onset illustrates VWM disease that is unnoticeable until age 1-5,

whereby individuals experience varying progression rates. Juvenile onset refers to VWM disease that is noticeable at the ages of 5 to 15 years; hence, symptoms of persons with the condition at this stage progress slower than those in the infantile and early childhood stages. Finally, the adult-onset describes VWM disease that primarily affects an individual's behavioral patterns due to cognitive impairment rather than neurological impairment.

The progression rate of Vanishing White Matter disease varies between individuals because each patient has a unique genetic makeup. However, patients can experience rapid progression between the ages of 1 and 5, which is later followed by death [5]. In contrast, a much slower disease progression is usually associated with death several years after its onset.

The complications generated by VWM disease also determine an individual's life expectancy. Some of the complications likely to be experienced during the disease progression include minor headaches, fevers, seizures, and anesthesia. Additionally, motor skills can be hindered. Motor skills involve walking, sitting, or even moving hands [5].

Treatment for VWM disease involves medications and physical therapy. Currently, there is no known cure for VWM disease; however, anti-seizure medications help manage seizures, whereas physical therapy involves aiding patients with walking challenges [6].

Genetic Mutations Associated with Vanishing White Matter Disease in Children

Vanishing White Matter disease is associated with several genetic mutations in children. Some genetic mutations arising from VWM disease are leukodystrophies and developmental delays.

Leukodystrophies

Leukodystrophies are hereditary neurological disorders that lead to the degeneration of myelin sheaths, thereby hindering effective communication in children due to the destruction of peripheral nerves [5].

Leukodystrophy diagnosis involves a range of clinical examinations, such as the age of onset, general physical features, neurologic features, and electrophysiology [7]. The age of onset involves a close scrutinization of the progress of symptoms; hence, unexplained symptoms that hinder mental and motor development may indicate the disease [7]. Examining an infant's physical features involves inspecting abnormalities such as a large head or other deformities. Neurologic features entail observing symptoms such as muscle stiffness, speech difficulty, and seizures. Finally, electrophysiology is used in the diagnosis by measuring nerve velocity. Thus, patients displaying abnormal nerve conduction velocities are likelier to be infected with leukodystrophy.

Treatment of leukodystrophies involves using antispasmodics and gabapentin [7]. Antispasmodics are used to relieve pain caused by muscle contractions, especially in infants, while gabapentin is utilized in the treatment of seizures and neuropathic pain.

Developmental Delay

Developmental delay (DD) is a concept referring to the challenges that infants encounter in achieving growth. Such challenges are usually faced in social communication, motor development, and visual problem-solving [8]. Furthermore, DD in children usually arises due to challenges in normal brain development. Consequently, such challenges may be due to interference in processes such as myelination. Children affected with DD have decreased myelin volume [8].

Diagnosis of DD involves an imaging test such as the MRI (magnetic resonance imaging) scan, which checks the volume of white matter in the brain [8]. Treatments for DD involve physical therapy and speech and language therapy [9]. Physical therapy is helpful in children with motor skills difficulties, whereas speech and language therapy assist children in formulating speech and understanding language.

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