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VZV SPINAL CORD INFARCTION IDENTIFIED BY DIFFUSION-WEIGHTED MRI (DWI)

We present a case of spinal cord infarction due to varicella zoster virus (VZV) vasculopathy identified by diffusion-weighted MRI (DWI) and confirmed virologically.

Case report. An 84-year-old Caucasian woman with a history of breast cancer and essential thrombocythemia developed the apoplectic onset of severe low back pain, numbness and paralysis of both legs, and bowel and bladder incontinence. Initial CSF exam was acellular with protein of 31 mg%. She was treated with oral prednisone (10 mg qid) without improvement and was hospitalized 4 days later. On admission, she was afebrile, blood pressure was 162/73 mm Hg, and heart rate 111 beats/min. Physical exam revealed hepatosplenomegaly and bilateral lower extremity edema. There was flaccid lower extremity paralysis. Proprioception and vibratory sensation were absent in the feet, although vibration was perceived at the knees, and there was a T7 sensory level to light touch, pinprick, and temperature. Deep tendon reflexes were absent in the legs, and there was no response to plantar stimulation bilaterally.

There were 41,000 white blood cells (WBCs) and 550,000 platelets. Flow cytometry of blood WBCs revealed no clonal populations. Serum lactate dehydrogenase and uric acid levels were elevated; blood urea nitrogen was 66 and creatinine was 1.1. Hematologic analysis revealed a JAK2-positive, BCR/ABL(9,22)-negative myeloproliferative disorder with iron-limited erythropoiesis, most consistent with essential thrombocythemia.

Brain MRI revealed chronic white matter disease without diffusion restriction. Cervical and lumbar spine MRI indicated mild to moderate degenerative disease without root or spinal cord compression. Thoracic spine MRI showed abnormally increased T2 signal within the mid- and distal thoracic spinal cord; from T7 to T12, there was prominent diffusion restriction, with apparent diffusion coefficient (ADC) correlation consistent with spinal cord ischemia (figure). Three days later, she developed left T7 tot T8 distribution zoster. CSF was acellular with protein 62 mg%; gram stain, bacterial and fungal cultures, cytology, and flow cytometry were negative. CSF PCR revealed no amplifiable Epstein–Barr virus, cytomegalovirus, herpes simplex virus (HSV), or VZV DNA. CSF did not contain IgG antibody to HSV but was positive for anti-VZV IgG antibody by ELISA. The serum/CSF VZV IgG ratio was 42, compared with ratios of 395 for total IgG and 185 for albumin, consistent with intrathecal synthesis of anti-VZV IgG antibody. Despite treatment with IV acyclovir (500 mg twice daily for 14 days) and prednisone (50 mg daily for 5 days), there was no neurologic improvement after 2 months of follow-up.

Discussion. This patient with VZV spinal cord infarction presented with abrupt onset myelopathy followed by zoster. Virologic analysis detected anti-VZV IgG antibody, but not VZV DNA, in CSF with a reduced serum/CSF VZV IgG ratio consistent with intrathecal synthesis of VZV IgG. The virologic findings are the same as described in most cases of VZV vasculopathy in the brain, where the detection of anti-VZV IgG in CSF was more sensitive than detection of VZV DNA in indicating VZV vasculopathy. Like other cases of VZV vasculopathy, neurologic disease preceded rash. Infarction was likely due to VZV vasculopathy and may have been compounded by essential thrombocytosis. Based on a PubMed search that reviewed thousands of articles back to 1950, which did not reveal a single case of isolated spinal cord infarction in patients with polycythemia vera or essential thrombocytosis, it is unlikely that essential thrombocytosis was the sole cause of spinal cord infarction.

Most reported cases of VZV myelopathy have been inflammatory or demyelinating, as determined by conventional spinal cord MRI combined with CSF findings. Disease is usually subacute to chronic, rarely recurrent, and often coexists with cerebral disease; in such cases, the CSF usually contains VZV DNA, with or without
anti-VZV IgG antibody. Rare cases of putative spinal cord infarction produced by VZV vasculopathy have been diagnosed based on the acute onset of myelopathy associated with zoster or on virologic evidence of VZV infection in acute myelopathy cases without rash. Only a few cases of VZV spinal cord infarction have been verified pathologically. Before DWI, postmortem spinal cord necrosis secondary to VZV vasculitis with productive VZV infection was the only way to establish the diagnosis of VZV vasculopathy in the spinal cord. DWI has proven superior to conventional MRI in detecting spinal cord ischemia and infarction. Our case specifically illustrates this superior utility and suggests that DWI, in conjunction with virologic analysis of CSF, should be used to evaluate patients with acute myelopathy, even in the absence of zoster rash.

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PROGRESSIVE MEGALENCEPHALY DUE TO SPECIFIC EIF2B MUTATIONS IN TWO UNRELATED FAMILIES

We report four patients, from two unrelated families, affected by an infantile form of childhood ataxia with central hypomyelination syndrome or vanishing white matter disease (CACH/VWM) with large megalencephaly in the three children with a protracted disease course.

Case reports. Patient 1. A girl, born in 1990 from unrelated parents, presented two acute episodes of neurologic deterioration during viral infections at ages 10 and 14 months, followed by a progressive decline. Brain MRI showed severe white matter abnormalities. At age 3, a cerebral biopsy was performed and was complicated by a subdural hematoma that did not explain the persistence of an excessive head growth (figure, A and B). Neuropathologic analysis showed an increased oligodendrocyte density but no Rosenthal fibers. Head circumference (HC) reached 58 cm, and she died at age 8.5.

Patient 2. Her brother, born in 1997, presented with a coma during a viral infection at ages 14 months. MRI showed a diffuse involvement of white matter with hemispheric cystic degeneration. He recovered partially, but subsequently, neurologic deterioration occurred with an abnormal increase in HC. At age 5, he was bedridden. MRI showed a complete disappearance of hemispheric white matter (figure, C); the cerebral cortex appeared laminated, and the lateral and third ventricles were slightly enlarged. His HC reached 71 cm at age 9 despite corticosteroids, CSF evacuation, and acetazolamide therapies (figure, D). Corticosteroid therapy only relieved acute episodes of irritability and vomiting.

Patient 3. A girl, born in 1962 from unrelated parents, became comatose during a viral infection at age 18 months and died 1 month later. No HC data were available. An autopsy showed preserved gray structures and massive hemispheric white matter necrosis with increased oligodendrocyte density but sparse astrogliosis.

Patient 4. Her sister, born in 1965, had similar neurologic symptoms at age 2, but she recovered.

Six months later, she declined progressively. At age 4.5, she fell into coma, and a macrocephaly was noticed. Cranial radiographs showed increasing suture disjunction. She died at age 8.5 with an impressive macrocephaly (HC: 88 cm) (figure, G). At autopsy, brain weight was 850 g (50% of normal for age) and the neuropathologic findings were similar to those of her sister (figure, E and F).

Molecular genetic and biochemical analysis. Patients 1 and 2 carried two homozygous EIF2B mutations: p.R315H/p.F56V (c.944G→A/c.1666T→G), as already reported (Patients 571-1 and 571-2). Their guanine nucleotide exchange factor (GEF) activity of EIF2B measured in lymphoblasts had decreased to the range found in severe infantile forms (Patient 1 = 40 ± 3%, Patient 2 = 50 ± 5%). For the second family, the diagnosis was reconsidered in 2005 when a healthy brother asked for genetic counseling. No DNA was available from the affected dead children. Each parent carried a heterozygous EIF2B mutation, p.R315H and p.F56C (c.167T→G) respectively, suggesting that Patients 3 and 4 were compound heterozygotes (p.R315H/p.F56C).

Discussion. In this study, we have identified compound heterozygous EIF2B mutations in four patients with classic signs of severe, infantile-onset CACH/VWM. The three patients that survived infancy developed an unusual large macrocephaly. This macrocephaly had a late onset, 2 years after the first clinical signs, with progressive suture disjunction suggesting intracranial hypertension. The latest neuradiologic and neuropathologic studies showed a complete disappearance of hemispheric white matter but no hydrocephaly. Surprisingly, the vanishing white matter did not collapse but appeared swollen and compressed the cortex. Among the large number of patients with CACH/VWM reported, only one had a HC above the 98th percentile. Nevertheless, the swollen aspect of vanishing white matter has been described previously in CACH/VWM. These observations suggest that altered brain water balance is a feature of CACH/VWM.
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