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Chronic Active Herpes Simplex Type 2 Encephalitis in an Asymptomatic Immunocompetent Child

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Abstract

A unique form of chronic, active, granulomatous herpes simplex type 2 encephalitis is described in an asymptomatic, immunocompetent 8-year-old girl who acquired the virus as a neonate. The extensive, bilateral cerebral parenchymal involvement was discovered incidentally. Diagnosis was confirmed by a combination of serial neuroimaging, brain biopsy, and quantitative polymerase chain reaction targeted to DNA sequences in the glycoprotein G gene, allowing differentiation between herpes simplex virus types 1 and 2. The clinical course over a 5-year period, treatment with intermittent intravenous steroids, and daily valacyclovir, diagnostic imaging, and laboratory studies are reviewed in detail. This form of herpes simplex virus type 2 encephalitis hasn't been described previously and is significant because of its prolonged indolent course, absence of neurological findings or suggestive history, and benign behavior in this child, who is now 14 years old. The authors believe this entity can be unsuspected and underdiagnosed in the general pediatric population, especially in those with a prior maternal history of herpes simplex virus type 2 infection.

Keywords

herpes simplex virus; molecular pathology; quantitative polymerase chain reaction; encephalitis; viral infection; granulomatous; MR imaging

Encephalitis caused by herpes simplex virus can take a chronic recurring form characterized by intractable seizures and progressive neurological deficits in a small proportion of patients weeks, months, or years after initial infection.^{1–6} Three clinical forms are recognized: delayed symptoms caused by the initial infection, immune-mediated inflammation similar to those observed in postinfectious encephalitis, and resumption of intracerebral viral replication.⁷ When recurrence occurs in the pediatric patient, the illness tends to be biphasic, with the initial classical triad of seizures, fever, and focal neurological symptoms followed several weeks later by the appearance of choreiform movements after apparent recovery.⁸

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Declaration of Conflicting Interests

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We present an unusual case of an immunocompetent 8-year-old girl who acquired herpes simplex virus type 2 encephalitis as a newborn and was found to have a chronic, active form of the same infection 8 years later in the absence of clinical, neurologic, or overt cognitive deficits.

Case History

An 8-year-old third-grade girl was incidentally found to have multiple intraparenchymal cerebral calcifications, extensive bilateral white matter hypodensities, and encephalomalacia of the right temporal lobe when computed tomography was ordered after a minor head trauma complicated by headache (Figures 1A and 1B). Mental status and comprehensive neurologic examinations were entirely normal.

Past medical history was significant for a persistently patent ductus arteriosus requiring surgical closure at age 4 and focal clonic seizures involving the left face, arm, and leg at 14 days of age, associated with a fever of 101.6°F. She had been delivered at term by normal spontaneous vaginal route with a birth weight of 3380 grams after an uncomplicated pregnancy. There was a long maternal history of genital herpes simplex virus type 2, with no active lesions noted during the pregnancy. Evaluation included normal brain computed tomography (CT) and magnetic resonance imaging (MRI) scans, an abnormal electroencephalography (EEG), peripheral white blood cell count of 12 500/μL, and xanthochromic cerebrospinal fluid with 334 800 red blood cell/μL, 360 white blood μL (64% neutrophils, 31% lymphocytes, and 5% monocytes), cerebrospinal fluid protein of 297 mg/dL, and cerebrospinal fluid glucose of 36 mg/dL. Bacterial and viral cultures of cerebrospinal fluid were negative. Polymerase chain reaction (PCR) for herpes simplex virus was not performed and lumbar puncture was not repeated.

EEG showed recurring right midtemporal spike and sharp forms. Phenobarbital easily controlled the clinical seizures and was continued until 18 months of age when it was discontinued without return of seizures. Intravenous acyclovir was given for 2 days then discontinued.

Subsequent neurodevelopment was normal: she sat at 6 months, was standing and walking by 9 months, and speaking in sentences to strangers by 2 years of age. Some academic difficulties were noted as she entered first grade, but she was in regular third-grade classes in a public school at the time of presentation.

Brain MRI on presentation was markedly abnormal, (Figure 2, column 1) with multiple intensely enhancing cortically based lesions (Figures 1C and 1D), the largest of which had a lobular, gyriform contour. Extensive signal abnormality was noted predominately within the right hemisphere, especially in the frontal and temporal lobes (Figures 2B-1 and 2E-1) with some parietal lobe involvement, along with a lesser degree of signal abnormality within the anterior left frontal lobe. (Figure 2A-1) There was some susceptibility artifact noted on gradient echo sequences that corresponded with the densities seen on computed tomography (Figures 1C, 1D, and 2). She was admitted to the hospital for further evaluation. Initial diagnostic laboratory studies included the following: hemoglobin = 13.1 g/dL; hematocrit = 37.3%; white blood cell count = 8.4 K/μL (differential lymphocytes = 40.8, monocytes = 5.7, eosinophils = 2.5, segmented neutrophils = 50.8); platelets = 376 K/μL; prothrombin time/partial thromboplastin time = 12.4/32.9 seconds; fibrinogen = 306 mg/dL (normal, 150–480); D-dimer = 0.51 μg/mL (0.00–0.80); CD3 count = 2.776 K/μL (0.900–2.400); CD4 count = 1.987 K/μL (0.500–1.800); CD8 count = 0.648 K/μL (0.250–1.100); CD19 count = 0.680 K/μL (0.080–0.600); anticardiolipin IgA antibodies <9.4 APL (<12.0); anticardiolipin IgG antibodies <9.4 GPL (<15.0); anticardiolipin immunoglobulin M = 9.4 MPL (<12.5);

C3 complement = 126.0 mg/dL (71.3–184.5); C4 complement = 30.6 mg/dL (9.4–51.4); IgG1 = 686 mg/dL (390–1190); IgG2 = 195 mg/dL (68–520); IgG3 = 64 mg/dL (9–80); IgG4 = 22.3 mg/dL (2.0–150); erythrocyte sedimentation rate = 17 mm/hr (0–20); rheumatoid factor was absent; rapid plasma reagin for syphilis was nonreactive; and human immunodeficiency virus (HIV) was negative. Cerebrospinal fluid was clear and colorless, with a red blood cell count of 3/ μ L, a white blood cell count of 2/ μ L, protein = 48.0 mg/dL (15–45), glucose = 52 mg/dL (38–85), myelin basic protein <2.0 μ g/L (0.0–4.0), cerebrospinal fluid oligoclonal bands present, cerebrospinal fluid IgG = 7.65 mg/dL (0.50–6.10), viral cultures were negative, cytology was negative, cerebrospinal fluid IgG synthesis index = 0.87 (<0.68), and cerebrospinal fluid IgG synthesis rate = 12.8 mg/day (9.9 $\pm$ 3.3). Other lab results included the following: aspartate aminotransferase = 21 international units (IU)/L (15–40); alanine aminotransferase = 13 IU/L (5–40); alkaline phosphatase = 153 IU/L (110–360); total/direct bilirubin = 0.6/0.1 mg/dL (0.6–1.4/0.0–0.3); total protein = 6.6 mg/dL (6.2–8.1); albumin = 4.0 mg/dL (3.7–5.6); calcium = 9.0 mg/dl (8.8–10.1); magnesium = 1.8 meq/L (1.3–1.9); phosphorus = 4.6 mg/dL (3.7–5.6); angiotensin converting enzyme = 38 U/L (13–100); and serum amino acids were normal. Echocardiogram, as well as abdominal and thoracic CT scans were normal. Both parents had screening brain MRIs to look for evidence of a leukoencephalopathy and both were negative.

In the absence of a specific diagnosis, a right temporal lobe brain biopsy was obtained. Microscopic tissue examination (Figures 3A and 3B) showed the presence of granulomatous inflammation with multinucleated giant cells, focal vasculitis, necrosis, microcalcifications, and hemosiderin deposition. Some small blood vessels showed focal disruption of the internal elastic lamina. Immunostaining for herpes simplex virus (types 1 and 2) showed rare punctate positivity. CD68 (a histiocytic marker) was strongly positive within macrophages and the multinucleated giant cells. Tissue PCR for varicella zoster virus was negative but was strongly positive for herpes simplex virus, though differentiation between types 1 and 2 was not immediately possible. Subsequent DNA analysis via real-time, quantitative polymerase chain reaction identified the viral DNA as herpes simplex virus type 2. In each PCR reaction tube, 5 μ L of the patient's purified DNA—standard or control—was mixed with 12.5 μ L of SYBR Green Master Mix (Applied Biosystems, Foster City, California), 25 mM of each forward and reverse sense primer, and 5 μ L of distilled water. The herpes simplex virus type 1 glycoprotein G forward sense primer 5'-CATACCCCGCTGTTCTCGTT-3' and reverse sense primer 5'-CCATCGCACCAATACACAAAA-3' were used in conjunction to produce an amplicon of 106 base pairs, while the herpes simplex virus type 2 glycoprotein G forward sense primer 5'-ACGCTCTCGTAAATGCTTCC-3' and reverse sense primer 5'-CCCACCTTACCCACAACAG-3' produced an amplicon of 118 base pairs. After 1 cycle of denaturation (95°C for 10 minutes, Foster City, California), 40 cycles of amplification were performed (95°C for 10 seconds and 60°C for 1 minute). During the 60°C phase, fluorescence was measured, and from this data the DNA concentrations were calculated using standards of known viral copy numbers (herpes simplex virus type 1 viral DNA Macintyre strain Cat# 08-921-000, herpes simplex virus type 2 viral DNA strain G CAT# 08-922-000 [Advanced Biotechnologies, Columbia, Maryland]) (Figure 4). Serum herpes simplex viral titers were also strongly positive, showing IgG titers for type 1 of 1:5120 and for type 2 of 1:10240.

A 21-day course of intravenous acyclovir (30 mg/kg/day divided 3 times a day) was given with some neuroimaging improvement. Daily valacyclovir was then started at a dosage of 1000 mg 3 times a day and has continued uninterrupted until this day. Monthly neuroimaging showed modest reduction in the degree of signal abnormality (Figure 2); however, 6 months after initiating treatment, a new area of signal abnormality arose in the left parietal lobe extending from the surface of the posterior horn of the ipsilateral ventricle

to the gray/white matter junction (Figures 2B-2 and 2C-2). No change in her clinical appearance, physical examination, or detailed neurologic examination could be detected as the new radiographic abnormality appeared. Repeat lumbar puncture at this time and again 2 months later were normal, with negative herpes simplex cultures and PCR for the virus each time.

Intravenous methylprednisolone (initially 1.6 mg/kg/day $\times$ 4 days, divided 2 times a day) followed by a 10-day oral prednisone taper was administered for the first time 8 months after diagnosis and continued at monthly intervals for the next 8 months, accompanied by cessation of progression and incremental reversal of signal abnormality with further regression of previously observed white matter abnormalities (Figure 2, column 4). When no further improvement in the appearance of imaging was seen after the eleventh and eighth course of intravenous corticosteroids, the monthly treatments were stopped.

Nine months after discontinuation of the monthly corticosteroids, 26 months after diagnosis, she was noted to have a very mild left facial weakness in the form of decreased prominence of the left nasolabial fold, unaccompanied by any observable change in the appearance of the MRI (Figure 2C-4). Monthly corticosteroid treatments were again given for the next 3 months, with resolution of the facial weakness. Thirty-two months after diagnosis, new areas of increased signal intensity on T2-weighted and fluid attenuation inversion recovery sequences were noted in the right superior temporal lobe without any clinical correlate. Neurologic examination continued to be normal.

Forty-one months after diagnosis, the left superior frontal lesion again showed an increased degree of hyperintensity on T2-weighted and fluid attenuation inversion recovery imaging. Steroid treatments every other month for the next 6 months resulted in retreat of these new findings. Serial imaging over the next 12 months showed stable imaging appearance of the parenchymal lesions (Figure 2).

Neuropsychological testing was completed 2 and 15 months after diagnosis, showing deficits with executive control, short-term working memory, and attention with trouble sustaining focus, and rapidly shifting attention at both sessions without a significant interval difference in skills or abilities. Weaknesses in functioning persisted across assessments, but the gap from age-expected abilities did not increase.

Discussion

Asymptomatic survivors of herpes simplex encephalitis are relatively rare. Only 1 of 34 patients described by McGrath had no symptoms with a normal neurologic examination following herpes simplex encephalitis 2 or more years after their initial infection.⁹ Recurrence of herpes simplex encephalitis is, on the other hand, not that uncommon in children, occurring from 5 days to 26 months after cessation of acyclovir treatment,⁷ causing some authors to suggest that overt relapses of herpes simplex encephalitis can be a common sequence of events in children.¹⁰

Recurrence of herpes simplex encephalitis tends to appear in 1 of 3 forms. There are delayed symptoms caused by the initial infection, immune-mediated inflammation similar to those observed in postinfectious encephalitis, and resumption of intra-cerebral viral replication.⁷ Recurrent herpes simplex encephalitis is generally an ominous development, with a progressive clinical deterioration consisting of intractable seizures and progressive neurological deficits.^{1-6,11,12} When neonates survive herpes simplex encephalitis, the majority has significant neurodevelopmental disabilities, including spasticity, quadriplegia, psychomotor retardation, learning disabilities, and blindness.¹³

The clinical presentation and natural history of herpes simplex encephalitis in this child does not appear to conform with any of the 3 forms of recurrence described above, suggesting it is either not a recurrence or a new form not described previously. Serial neurologic examinations, neuroimaging, and neuropsychological testing over a 5-year period, as well as brain biopsy and molecular identification of the virus as herpes simplex type 2, differentiate this case from similar isolated cases reported previously.

There are several descriptions of progressive neuroimaging changes over time following herpes simplex encephalitis, but most have involved selected patients¹⁴ or those with progressive or clinical impairment.^{13,15,16} The most commonly invoked explanation for such changes is immune-mediated tissue damage.^{13,15–17} However, the meaning of imaging changes when they have been progressive is unclear, given that evolving signal abnormalities may not correspond with disease activity or persistence.^{15,18} Longitudinal MRI studies in 2 asymptomatic children, after herpes simplex encephalitis, have shown that self-limiting diffuse white matter lesions can be present.^{19,20}

A case with imaging changes similar to ours described without brain biopsy was described in detail by Mitsufuji and Ikuta.¹⁹ A 9-month-old girl with herpes simplex encephalitis and hemiparesis showed improvement of MRI findings after intravenous acyclovir, but then showed evolution of findings at 4 months and expansion of white matter lesions at 9 months after the onset of illness. By 14 months, lesions had reduced in size and disappeared by 2 years after the initial infection. These changes occurred in the absence of neurologic or psychomotor deficits once the initial hemiparesis had resolved 2 weeks after presentation.

Mitsufuji and Ikuta¹⁹ compared the white matter lesions of their case with those of 4 similar cases^{20–22} and classified them into 2 types: lesions with delayed perivascular focal myelin destruction in patients with subacute evolution²¹ and widespread lesions with no relation to gray matter lesions seen in the acute stage.^{20–22} The latter lesions were noted to disappear spontaneously from 7 weeks²⁰ to 2 years¹⁹ of onset without treatment or clinical findings. Histologic findings, when herpes simplex encephalitis recurs months to years after infection, show perivascular clusters of lymphocytes and macrophages, nonnecrotic granulomas, granulomatous giant cells without necrosis, multinucleated giant cells, and calcifications,¹ while chronic granulomatous inflammation with foci of calcification has been described years after the first episode of herpes simplex encephalitis.^{2,12} Microglial nodules, perivascular lymphocytic aggregates, and rare neuronophagia without inclusion bodies seen in a patient with nonprogressive spasticity and epilepsy suggested an active and ongoing disease process.⁵

Pathologic descriptions of chronic progressive herpes simplex encephalitis are few and generally described as a necrotizing inflammatory process resembling active herpes simplex encephalitis.^{1,23–25} While microglial nodules, astrocytic proliferation, and chronic inflammation of parenchyma and leptomeninges characterize the chronic progressive form of herpes simplex encephalitis, giant cells and granulomatous features are not common.^{1,2,5,6}

Immunohistochemical findings in recurrent herpes simplex encephalitis are strong positivity for CD68 (giant cells, macrophages), CD3 (T cells) in leptomeninges, and CD20 (B cells) in the granulomas.¹ In recurrent herpes simplex encephalitis, viral DNA can be recovered from the site of infection,²⁴ though no viral antigen can be identified, even 10 years after infection.⁵ Viral DNA has been detected in the brain long after herpes simplex encephalitis when the causative agent is herpes simplex virus type 1,^{1,26,27} but the meaning of this is uncertain, since herpes simplex DNA can be found in the brains of people without a history of encephalitis.^{1,28,29} Whether the herpes simplex virus type 1 DNA fragments detected by

PCR in long-term survivors of herpes simplex encephalitis are nonviable residual fragments of viral DNA or intact transcriptionally active virus is unknown.²⁶

The majority of reports of relapsing recurrent herpes simplex encephalitis are more commonly associated with herpes simplex virus type 1,^{2,30–31} rather than type 2, but the neurologic complications of infection with type 2 herpes simplex encephalitis may not be as severe as with type 1, since complications tend to subside within 6 months of initial infection³¹ and rarely have been associated with an unexpectedly mild clinical course.^{30–31}

The natural history of the neonatally acquired herpes simplex encephalitis in our patient was similarly benign, with no clinical symptoms, no abnormal findings on neurologic examination, and a featureless clinical course over the 5-year follow-up period. During this time, there was considerable variability in the degree of imaging abnormalities, with distinct episodes of waxing and waning involvement of brain parenchyma suggesting an active pathologic process responsive to initial intravenous acyclovir and later methylprednisolone infusions. The histological observations of granulomatous inflammation with multinucleated giant cells, focal vasculitis, microcalcifications, and necrosis also suggest a chronic, active inflammatory process, rather than the end result of a remote infection or ongoing immune-mediated tissue injury.

Parenchymal herpes simplex virus PCR documenting the presence of viral DNA, the markedly elevated but nonspecific serum viral titers (1:5120 type 1, 1:10240 type 2), and the subsequent molecular identification of the DNA as type 2 virus are consistent with prior reports of viral DNA persistence within lesions, as such persistence occurs with either herpes simplex encephalitis type 1 or 2.^{2,30–32}

We believe this to be a unique case of chronic, granulomatous, herpes simplex virus type 2 encephalitis in an asymptomatic pediatric patient. Our patient's clinical course was characterized by the absence of clinical signs, normal neurologic examination, remote history of neonatal exposure to herpes simplex virus type 2, neuroimaging showing chronic and acute metamorphic changes to parenchyma, and elevated IgG synthesis rate and index with otherwise normal cerebrospinal fluid. She was clinically asymptomatic with a normal neurologic examination at a time when extensive white and gray matter changes were present in both cerebral hemispheres, raising difficult questions when considering to what extent this entity can be underdiagnosed in the general pediatric population and whether clinical follow-up alone in the absence of additional neuroimaging, months or years after initial exposure, is sufficient. She has had no change in the appearance of her neuroimaging abnormalities in the last 12 months, at the end of a treatment period extending over 5 years while she remains on 3000 mg/day of valacyclovir. Whether this will continue to be the case, or when discontinuation of the valacyclovir can be considered, is unknown because of the protean nature of herpes simplex encephalitis. We propose a new entity called "chronic active herpes simplex encephalitis," characterized by a chronic, disseminated encephalitis resulting from untreated or partially treated neonatal herpes simplex virus type 2 infection. Patients with this entity can be asymptomatic and have no history of recurrent disease or relapses, no history of cutaneous lesions, a normal or near-normal neurologic examination, and normal or near-normal academic performance. This entity may be associated with unique host variances in cellular immune responses yet to be described.

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Figure 1.

Axial computed tomography (CT) (A and B) and magnetic resonance imaging (MRI) scans (C and D) at initial presentation showing extensive right hemispheric white matter abnormalities with bilateral frontal (A) and right temporal (B) calcifications. Postcontrast T1-weighted MR images showing postcontrast enhancement (C and D). Compare Figure 1D with Figure 2A-1.

Figure 2.

Selected serial axial fluid attenuation inversion recovery magnetic resonance images (MRIs) showing evolution of herpes simplex virus type 2 encephalitis over a 48-month period. The number of months since initial diagnosis is shown in the lower right-hand corner of each image. The first column of images represent the appearance of the brain at the time of diagnosis. Each row of images A through E depicts the brain at the same anatomical level: (A) superior to the body of the corpus callosum, (B) lateral ventricles at the splenium and genu of the corpus callosum with bifurcation of the fornix, (C) through the thalamic nuclei and genu of the internal capsule, (D) through the basal ganglia and superior cerebellar cistern, and (E) temporal lobes and mesencephalic red nuclei.

Figure 3.

(A) Lesion biopsy site showing diffuse, chronic, granulomatous inflammation. Scattered areas of necrosis are present (arrows). Many multinucleated giant cells are seen—representative examples being highlighted with arrowheads. Hematoxylin and eosin stain $\times 100$. Scale bar 100 μm (B) higher-power view of the lesion biopsy site showing chronic granulomatous inflammation and large, multinucleated giant cells (arrows). Hematoxylin and eosin stain $\times 600$. Scale bar 100 μm .

Figure 4.

Detection and quantification of herpes simplex virus types 1 and 2 by quantitative polymerase chain reaction. DNA oligo primers are targeted to sequences in the glycoprotein G gene, which are highly specific for each virus and easily differentiates between the two. (A) Linear view of SYBR Green fluorescence PCR amplification of target DNA in the patient's sample and in herpes simplex virus DNA standards. (B) The standard curve used to calculate the number of herpes simplex type 2 DNA copies in the patient's sample is derived from a 10-fold serial dilution of a known herpes simplex type 2 DNA concentration provided by Advanced Biotechnologies. (C) The final products after 40 cycles of amplification on the ABI 7500, separated by electrophoresis on a 1% agarose gel.