Rapid Progressive Subacute Sclerosing Panencephalitis in a 2-Year-Old Child with Congenital Athyreosis

We present the unique case of a 2-year-old girl with congenital athyreosis who acquired primary measles virus infection at the age of 18 months, coincidentally with an Epstein-Barr virus infection. First neurologic symptoms of subacute sclerosing panencephalitis appeared 5 months later, and the girl died within 6 months after a rapid progressive illness. Factors possibly predisposing to this extraordinary disease course—primary measles virus infection at an early age and lack of evidence for immunodeficiency—are discussed.

Subacute sclerosing panencephalitis (SSPE) is a rare subacute infection of the CNS caused by measles virus (MV) [1]. The invariably fatal disease occurs several years after primary MV infection [2] and is characterized by uncontrolled replication of mutated and defective MV in neuronal and glial cells [3]. MV infection that occurs before 2 years of age is associated with a risk for SSPE that is 16 times as high as the risk associated with infection after 5 years of age [4]. SSPE that occurs before 2 years of age is extremely rare; we only found 2 cases in the literature [5, 6]. Although the characteristic course of the disease is slowly progressive, rare fulminating cases also have been reported [6, 7]. Most of these children had primary MV infection at an early age or coincidentally with a second viral infection. We report on the case of a 2-year-old girl with congenital athyreosis who suffered primary MV infection coincidentally with an Epstein-Barr virus (EBV) infection at 18 months of age and who developed fulminating SSPE 5 months later.

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Figure 1. MRI from the brain of a 25-month-old patient with subacute sclerosing panencephalitis, showing increased signal intensity of the complete right hemisphere and the left frontal lobe.
The patient was the second child of healthy, consanguineous Turkish parents. Neonatal biochemical screening revealed hypothyroidism, and definitive reassessment of thyroid status showed complete athyreosis. The parents’ compliance for giving replacement medication was poor, and the patient showed pathologically high thyroid-stimulating hormone values at nearly each control.

Although weight gain, growth, and development were within the normal range, the patient suffered recurrent bacterial bronchopneumonias during the first 2 years of life. Extensive diagnostic measures, including several sweat tests, serologic testing for HIV and other microbes, determination of immunoglobulins and IgG subclasses, and a granulocyte function test (chemotaxis and spontaneous migration of polymorphonuclear leukocytes), all gave normal results. At the age of 18 months, the patient suffered a serologic proven EBV infection (quantitative immunofluorescence). Three weeks later, she acquired MV infection that was established by typical clinical findings and an increasing serum titer of specific MV IgM antibodies.

Five months later, a first generalized tonic-clonic seizure occurred. Serologic testing showed elevated MV IgG and IgM antibodies (ELISA). CSF was normal, with the exception of elevated MV IgG antibodies. Electroencephalographic examination by a pediatric neurologist showed a generalized nonspecific slowing with spike-and-wave activity over the right hemisphere. MRI of the brain demonstrated a small right-side, occipital focal area of increased signal intensity on T2-weighted images that was interpreted as an ischemic lesion or localized encephalitis. A 5-day course of acyclovir was started. Anticonvulsive therapy was initiated because of recurrent generalized seizures, and the patient was discharged 4 weeks later in apparently good health.

At the age of 25 months, the patient was admitted to our hospital because of progressive mental deterioration. Physical examination revealed a moderate apathy and marginally delayed psychomotoric development. MRI of the brain now demonstrated markedly enlarged areas of increased signal intensity on T2-weighted images in the right hemisphere and left frontal lobe (figure 1), as well as brain atrophy and hydrocephalus internus. Ophthalmoscopic investigation showed central and peripheral chorioretinitis (figure 2). We found normal values for all biochemical serum markers of inflammation, immunoglobulins, and IgG subclasses. Immunophenotyping of peripheral blood mononuclear cells showed 4% natural killer cells, 25% T cells (with a CD4-to-CD8 ratio of 6, 3% HLA-DR/CD3+ cells, and <1% CD3/CD56+ cells), 18% B cells, 8% mono-

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<th>Table 1</th>
<th>Results of serologic testing for measles virus (MV) antibodies in serum and CSF of our patient at the age of 25 months.</th>
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<td>Method</td>
<td>Serum</td>
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<tr>
<td>Complement fixation</td>
<td>1:320</td>
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<tr>
<td>Hemagglutination inhibition</td>
<td>&gt;1:65,536</td>
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<tr>
<td>Enzyme immunoassay IgM</td>
<td>400,000 mg/dL</td>
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<td>Isoelectric focusing</td>
<td>&gt;20 oligoclonal bands of specific MV IgG</td>
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cytes, and 43% polymorphonuclear granulocytes. CSF contained no cells, and its total protein and glucose values were within the normal range. CSF-IgG was increased to 6.7 mg/dL. High antibody titers against measles virus were detected in serum and CSF by various techniques including complement fixation, hemagglutination inhibition, and enzyme immunoassay (table 1). Measles-specific oligoclonal bands in serum and CSF were visualized by isoelectric focusing and immunoblot techniques, as described by Dörries and ter Meulen [8]. There were >20 distinct bands in CSF that indicated specific intrathecal antibody synthesis.

After confirmation of early-onset SSPE, the patient’s condition deteriorated rapidly. Within 3 weeks, she became stuporous, with frequent seizures, generalized muscular hypertonia, and periodic myoclonic jerks. She died of pulmonary infection with respiratory failure at the age of 29 months. Post-mortem examination was refused by the parents.

Despite the refusal of necropsy in the present case, the diagnosis of SSPE could be certainly confirmed on the basis of the impressive results of virologic studies (table 1), as well as its agreement with the diagnostic criteria proposed by Dyken in 1985 [9]. Brain biopsy today is rarely necessary for establishing a proper diagnosis [2]. Imaging procedures are also not required for diagnosis. Unspecific MRI lesions of high signal intensity on T2-weighted images, as in our patient, are the most common finding, although the extent and location of these lesions do not correlate with the neurologic status of the patients [10].

The only other type of persistent MV infection of the CNS that may arise within weeks to months after MV infection, measles inclusion body encephalitis, is confined to immunocompromised patients as an opportunistic infection [11] and therefore can be ruled out in the present case. Although congenital hypothyreosis has been associated with a variable degree of impaired immune function, there were no clinical signs of immunodeficiency in our patient. Molecular-biological investigations have revealed that the persistence of MV in the CNS is associated with and most likely caused by a defective viral replication, which allows MV to survive intracellularly during incubation period while remaining inaccessible to host immune surveillance [3, 12]. The susceptibility of the host, as well as the host’s age and immune status, at the time of infection also constitute significant factors for disease progression [12]. Although EBV is known to produce marked and long-lasting disturbances of immune functions [13], the coincidental EBV infection obviously has not yet contributed to the rapid development of SSPE in the present case. This, especially, seems to be true, because our patient was able to fight this infection, and no clinical signs of a lymphoproliferative disorder were present.

From an epidemiologic view, it is reported that MV infection that occurs before the age of 2 years carries the highest risk of SSPE [4]. Therefore, some age-dependent immaturity of the host at the time of measles infection may contribute to subsequent SSPE. In animal models, the age-related susceptibility to neurotropic viruses during the first few postnatal weeks has been well documented [14]. Moreover, it has been indicated that the age-related virulence of neurotropic viruses depends on maturation of neuronal systems itself [15]. The only 2 patients with neonatal MV infection and development of SSPE reported thus far exhibited an early-onset and rapid progressive course of the disease [6, 9]. Intratuberculosis absence or insufficiency of thyroxin results in impaired RNA and protein synthesis, reduced size and number of cortical neurons, retarded myelination, and ~30% of infants with congenital hypothyroidism have neurological abnormalities [16]. In the present case, neuronal developmental delay due to congenital athyreosis may have predisposed our patient to a rapid progressive form of SSPE, otherwise predominantly seen in children with neonatal MV infection.

Overall, the present case of a 2-year-old patient with rapid progressive SSPE and congenital athyreosis offers some new hypotheses for the etiology and natural course of early-onset and rapid progressive SSPE following MV infection beyond the neonatal period. This report should address further investigations toward the influence of coincidental viral infections and neuronal development on the susceptibility to neurotropic pathogens, especially MV.

Acknowledgments

We are indebted to V. ter Meulen and B. Weißbrich (Institute of Virology and Immunobiology, Julius-Maximilians University, Würzburg, Germany) for the serologic investigations for specific measles virus antibodies of our serum and cerebrospinal fluid samples.

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Cutaneous Leishmaniasis following Local Trauma: A Clinical Pearl

Cutaneous leishmaniasis is acquired from the bite of an infected sand fly and can result in chronic skin lesions that develop within weeks to months after a bite. Local trauma has been implicated as a precipitating event in the development of skin lesions in patients who have been infected with *Leishmania* species. Here we report a case series and review the literature on patients who developed cutaneous leishmaniasis after local trauma, which may familiarize clinicians with this presentation.

New World cutaneous leishmaniasis is acquired from the bite of infected female sand flies. The skin lesions typically evolve over weeks to months from papules to nodules to ulcers with raised, indurated borders [1]. The time from the bite to the development of a lesion varies; incubation periods range from days to months [2]. The ulcerative skin lesion seemingly precipitated by local trauma is a clinical pearl associated with this disease. In 1974, Walton and Valverde reported a series of 4 American soldiers in Panama who had a defined history of exposure to *Leishmania* species in an area of endemicity, followed by an extended period living in a nonendemic location. After sustaining relatively minor trauma (a puncture wound of the hand, an eyelid struck by a small piece of gravel, a pimple that was manipulated, and a repeatedly abraded elbow) each patient developed a leishmanial lesion at the site of trauma [3]. In a different publication, Walton presented a dramatic photograph of a leishmanial lesion that developed along the margins of the length of a laceration [4].

In addition to these reports, cutaneous leishmaniasis that developed at the site of an injury has been reported after a bump on the forehead sustained after striking a low hanging beam [5], a coral cut on the palm [6], a creosote burn on the nose [7], and after a cat scratch [8]. This phenomenon does not appear limited to New World disease, however, as cutaneous leishmaniasis has been reported following submucous nasal resection (*Leishmania major*) [9], in the herpes zoster lesions of an HIV-infected patient in Spain (species not reported) [10], and after a skin snip biopsy of a patient with visceral disease (*Leishmania infantum*) [11]. After evaluating a patient who developed cutaneous leishmaniasis at the site of a recently placed tattoo, we reviewed our experience with patients who developed cutaneous leishmaniasis at sites of local trauma.

We reviewed medical records for patients diagnosed with cutaneous leishmaniasis (defined as evaluation of a skin lesion biopsy demonstrating amastigotes on histopathology or growth of promastigotes in culture of the biopsy) who were evaluated at the Walter Reed Army Medical Center (Washington, DC) from 1994 through 1999, in order to identify physician notes stating that skin lesions occurred after local trauma. Medical histories were unstructured and this association was not specifically solicited. Seven patients were identified whose cutaneous lesions were seemingly precipitated by local trauma. Six of 7 patients acquired their disease in Panama while participating in training at the military’s jungle training school. In 6 cases, leishmanial culture of the cutaneous lesion allowed characterization by analysis of isoenzyme patterns in electrophoresis with cellulose acetate [12, 13]. All patients received treatment with iv sodium stibogluconate (Pentostam; Glaxo-Wellcome, London) with clinical cure of their lesions.

Case 1 was in a 21-year-old man stationed in Panama who developed an ulcerative lesion in the right temporal area and was given an oral antibiotic without effect. One month later, he was reevaluated because of the same lesion and was given a different antibiotic, again without effect. Several weeks later, the patient received a circumferential tattoo over the left biceps. Within 5 days of placement of the tattoo, the patient developed several ulcerative lesions at the site of the tattoo. He also developed a lesion on his right thigh, which was biopsied and cultures yielded *Leishmania (Viannia) panamensis*. 

Informed consent was obtained from the patients, and guidelines for human experimentation of the US Department of Health and Human Services and those of the author’s institution were followed in the conduct of the clinical research. The opinions or assertions contained here are the private views of the authors and are not to be construed as official or as reflecting the views of the US Department of the Army or the US Department of Defense.