Viral Encephalitis and acute Cerebellar Ataxia Due to Late Reactivation of Varicella- Zoster Virus in an Immunocompetent Child.

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Abstract

Reactivation of latent Varicella-Zoster virus may cause various neurological complications including meningitis, encephalitis, myelitis, vasculopathy resulting in stroke and pseudotumor cerebri. It occurs mainly in elderly or immunocompromised patients and is very rare in children. We report a 4-year and 6-months old immunocompetent boy who developed encephalitis and cerebellar ataxia, due to reactivation of latent Varicella-Zoster virus (VZV). Characteristic skin lesions of varicella were absent. Varicella-Zoster virus DNA was weakly positive in cerebrospinal fluid and serum Varicella-Zoster virus immunoglobulin G was positive while immunoglobulin M remained negative. Although rare, Varicella-Zoster virus may reactivate to cause significant central nervous system disease even in immunocompetent children. We highlight the importance of keeping a high degree of suspicion as the typical rash may not associate the disease. The key for correct diagnosis is the temporal relationship between the symptom appearance and elevated anti-VZV antibodies in serum (immunoglobulin G) or the presence of VZV DNA (PCR) in cerebrospinal fluid.

Keywords : Varicella-Zoster virus; Meningoencephalitis; Acute Cerebellar Ataxia

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Introduction

Varicella or chickenpox is a contagious disease caused by the virus Varicella Zoster, primarily affecting children. [1] The eruption and the presentation of the disease are generally typical, so the diagnosis is mainly based on clinical examination. The virus is spread by the respiratory route and disseminates to lymph nodes and then via lymph back to the skin, resulting in the rash of chickenpox. The virus infects the neurons of the dorsal root ganglia and cranial nerves. It remains latent there and may reactivate years later, usually to produce shingles [2]. The most common complications of Varicella are secondary bacterial infection, Varicella pneumonia, and neurologic complications.

The neurological complications may be categorized into those caused by primary infection including post-infectious encephalitis (commonest), acute disseminated encephalomyelitis (ADEM), acute cerebellar ataxia, facial nerve palsy, optic neuritis [3], sinovenous thrombosis, acute transverse myelitis and Reye's syndrome, and those associated with virus reactivation. [4] The latter is more frequent among elderly individuals and immunodeficient patients and include mainly meningitis, encephalitis, myelo- litis, vasculopathy of both large and small vessels resulting in stroke. Neurological involvement in immunocompetent children following Varicella-Zoster virus reactivation is exceptionally rare and has been described previously in only 4 cases with Aseptic meningitis / encephalitis [5-8], and in another 4 patients with pseudotumor cerebri. [9, 10]

We report a 4-year and 6 months boy who developed Varicella- Zoster virus encephalitis and acute cerebellar ataxia after 3 and ½ year of presumed primary chickenpox infection caused by exposure to household contact diagnosed with chickenpox. To the best of our knowledge, this is the first patient reported from Saudi Arabia in whom encephalitis and acute cerebellar ataxia developed secondary to reactivation of latent Varicella-Zoster virus post upper respiratory tract infection (URTI) with no previous vaccination or clear evidence of primary chickenpox infection (typical characteristic exam-thema).

Case Report

A previously healthy 4-year and 6- months old boy was admitted because of 3 days duration of excessive lethargy and difficulty in walking. He had prior history of URTI
for two weeks after contact with his brother who had mild cold with no history of Varicella eruption. He had minor head trauma 4 days before presentation with no vomiting or loss of consciousness. On the morning of admission his parent found him sleepy, more tired and weak than usual. He had excessive salivation, reduced appetite and walked with a staggering, wobbly gait. There was no history of aspirin, analgesic or any drug injection. No nausea, vomiting, headache, agitation, loss of consciousness or seizures were noted. He was fully vaccinated except for varicella. His past medical history was unremarkable except for mild bronchial asthma and of exposure to his two sibs and his father having chickenpox at one year of age. Parents were consanguineous with no history of neurological disorders. His mother had pervious history of celiac disease.

Physical examination revealed a temperature of 36.8°C, a heart rate of 100/min, and a respiratory rate of 32/min. He had no rash or vesicles and no hepatosplenomegaly. He was drowsy; he knew his name and recognized his parents easily, but quickly feel asleep, if not stimulated.

Neurologic examination revealed no signs of meningal irritation, coarse end gaze horizontal nystagmus with occasional rapid upward gaze movement, and his optic fundi and cranial nerves were normal. He had mild slurred speech, intension tremors, past pointing, and truncal ataxia. Motor function was difficult to assess because of drowsiness, but there was no gross asymmetries. He was not able to stand unassisted with broad based gait and he had normal tone. Tendon reflexes at the knee and ankles appeared slightly elevated, but no pathologic reflexes were elicited.

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Two days post hospitalization, he developed three episodes of generalized tonic-clonic seizures during sleep, each lasted for few minutes with frequent eye deviation, staring episodes and worsening of slurred speech during wakefulness, with no loss of sphincter control.

Laboratory findings disclosed that leukocyte count, erythrocyte sedimentation rate, blood chemistry, electrolytes, blood glucose, and liver function test were all within normal limits. Metabolic work up including blood gas, serum ammonia, serum lactate, tandem amino acid in blood, and gas chromatography in urine for organic acids, all were unremarkable. A lumbar puncture on admission (2 weeks after URTI) revealed no pleocytosis, with a protein level of 0.17 g/L (NR 0.15-0.45 g/L), and a glucose level of 3.2 mmol/L (NR 2.5-4 mmol/L). A cerebrospinal fluid (CSF) culture was sterile. The cerebrospinal fluid polymerase chain reaction (PCR) for viral multiplex including Herpes simplex virus type 1, Influenza, Parainfluenza, Enterovirus, and Varicella-Zoster virus were negative except for Varicella-Zoster virus was weakly positive. No sample was send for oligoclonal IgG band and a second CSF analysis was refused by parents. Other screen for viruses include IF (immunoflurscents ) test of nasopharyngeal aspirate for respiratory syncytial virus, influenza A and B antigen , and parainfluenza 1, 2, 3 antigen, all were negative as well as throat swab culture. Stool for Rota virus antigen, Astrovirus antigen, and Adenovirus antigen all were negative as well as the culture. Serum serology for anti-Cytomegalovirus IgM, anti - Epstein Barr virus IgM, anti-Herpes IgM type 1, and anti-Herpes IgM type 2, antibodies were negative for all. Anti-mycoplasma IgM antibodies was negative. Serum Varicella–Zoster virus immunoglobulin G was positive and Varicella-Zoster virus immunoglobulin M serology was negative. Screen for celiac disease revealed negative result. Thyroid function test revealed normal result of both FT4 13.58 pm/l (NR 10.3-25.8), and thyroid stimulating hormone 0.61 MIU (NR 0.25-5). Anti-streptolysin O antibodies, double - stranded DNA virus antibody, toxicology screening were normal. Electroencephalography disclosed bilateral theta slowing, mostly in temporal regions and more prominent on the left hemisphere. Computerized tomogram (CT) scan of brain, was unremarkable. Brain magnetic resonance imaging (MRI) was unremarkable with no white matter, cerebellar changes, and no enhancement post contrast. Screening for paraneoplastic syndrome cause like neuroblastoma including, CT scan of chest, abdomen, and pelvis as well as the metaiodobenzylguanidine (MIBG) scan, all revealed negative result for tumors. Later on evaluation by ophthalmologist did not support opsinclonus.

During hospitalization, he developed one episode of bradycardia with heart rate down to 50/min with no associated symptoms. ECG and Chest X-ray both were normal, Echocardiogram showed mild mitral regurgitation and
minimal pericardial effusion. He was given a follow-up by the cardiologist as there was no active ongoing problem. Treatment with 3 weeks intravenous acyclovir 30mg/kg per day and two weeks of intravenous ceftriaxone was started from day one. Clinical improvement in level of consciousness and speech with no abnormal movement or staring look was evident 5 days after initiation of therapy with slow recovery of other neurological deficits. His seizures were controlled with carbamazepine. Seventeen days post admission, he could stand unassisted with disappearance of nystagmus and mild ataxia with no evidence of skin rash. At discharge 3 weeks after admission, his clinical abnormalities had almost completely disappeared. A second CSF analysis was refused by parents. Serum Varicella - Zoster virus immunoglobulin M remained negative and Varicella - Zoster virus immunoglobulin G was again positive (sequential increase in titer was not assessed). Human immunodeficiency virus (HIV) serology was negative. Serum immunoglobulins and complement studies were normal. Total counts and functional studies of T cell were also normal. Ten months later, he was completely healthy, his EEG was normal and carbamazepine was weaned off. No relapse occurred after 24 months of follow-up.

**Table 2: Varicella – Zoster Virus Related Central Nervous System Reactivation in Children**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Chiappini et al</th>
<th>Jhaveri et al</th>
<th>Leahy et al</th>
<th>Spiegel et al</th>
<th>Kentab A.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td></td>
<td>2</td>
<td>12</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Chickenpox</td>
<td>4/12</td>
<td>NM</td>
<td>6 yrs</td>
<td>4 yrs</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>Encephalitis</td>
<td>Aseptic meningitis</td>
<td>Aseptic meningitis</td>
<td>Meningoencephalitis</td>
<td>Encephalitis</td>
</tr>
<tr>
<td>Skin rash</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Previous reactivation</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Zoster 10 yrs</td>
<td>No</td>
</tr>
<tr>
<td>Cerebrospinal fluid cells/uL</td>
<td>590</td>
<td>285</td>
<td>434</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Cerebrospinal fluid protein (mg/dL)</td>
<td>Normal</td>
<td>86</td>
<td>158</td>
<td>59</td>
<td>Normal</td>
</tr>
<tr>
<td>Cerebrospinal fluid Varicella-Zoster virus DNA</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive</td>
<td>Positive (Positive weakly)</td>
<td></td>
</tr>
<tr>
<td>Brain MRI</td>
<td>Bilateral multi-lesions</td>
<td>ND</td>
<td>ND</td>
<td>Unilateral lesions</td>
<td>Normal</td>
</tr>
<tr>
<td>Treatment (days)</td>
<td>Acyclovir (15)</td>
<td>No</td>
<td>Acyclovir (14)</td>
<td>Acyclovir (14)+ high dose steroids (5)</td>
<td>Acyclovir (21)</td>
</tr>
<tr>
<td>Neurologic complications</td>
<td>Rt hemiparesis (mild)</td>
<td>Complete recovery</td>
<td>Complete recovery</td>
<td>Lt. high neuralgia</td>
<td>Complete recovery</td>
</tr>
</tbody>
</table>

**Note**: Yrs, Years ; 6/12, 6 months; MRI, Magnetic resonance imaging ; ND, not done; NM, not mentioned; Rt, right; Lt, left

**Discussion**

Varicella is a common contagious childhood illness, where the exposed individuals should be isolated from immunocompromised patients, pregnant women, and previously unaffected adults [11], they are infectious from 2 days prior to the exanthema until 5 days after the vesicles have crusted. [12]. Although varicella is generally a benign condition, the range of complications is extensive. Live attenuated varicella vaccine was licensed by the U.S. Food and Drug Administration in March 1995 for use in individual 12 months of age and older who have not had varicella. The Committee on Infectious Diseases of the American Academy of Pediatrics recommended universal vaccine use in early childhood and immunization of susceptible older children and adolescents. [13]

However, varicella vaccine is not available universally, and even where available, acceptance is still quite variable [14].

Central nervous system complications (CNS) occur frequently, especially the primary central nervous system complications. Of these, the most common clinical syndromes include cerebellitis and meningoencephalitis. These complications usually appear during (2-6 days after the onset of rash) or following the exanthema (after full resolution of rash). Pre-eruptive (during the incubation period) neurologic complications of varicella have been previously described but are extremely rare. In this group average time lag between the onset of symptom and appearance of rash was 11-18 days [15,16]. Early neurologic involvement in these patients may have occurred during the initial exposure and viremia [15,17,18]. The rash then followed after the usual 14-16 day incubation period [11].
In the primary type, the exact pathogenesis leading to central nervous system involvement is unknown. It may result from direct invasion of the virus, an autoimmune process, or both. In regard to an autoimmune mechanism, molecular mimicry between virus neural antigens in genetically selected individuals was postulated. Confirmation of the etiologic link between the varicella virus and the primary central nervous system complication is based on a positive history of varicella and exclusion of other common etiologies, because a direct pathologic examination of the involved area is not possible. Serologic testing for varicella and other viral factors is indicated only when the medical history is unclear or the cutaneous exanthema has not been evaluated by a pediatrician. In varicella, high levels of immunoglobulin G can be detected within a few days (usually between 10-14 days) of the acute infection. High immunoglobulin G and negative immunoglobulin M titers in the absence of recent clinical picture of varicella usually indicate a past infection. The use of steroids in treating varicella primary central nervous system complications is controversial. Because of the rapid spontaneous improvement of the disease, the current attitude is steroid abstention. Others suggest that steroid may hasten the recovery, and recommended their early use.

In general varicella - zoster reactivation have been reported in pediatrics where it is usually associated with the appearance of characteristic skin lesions. This was found among cancer patients especially leukemia and those receiving immunosuppressive therapy. [19] Also among immunocompetent children like those under severe stress admitted to intensive care units, in whom prolonged duration of fever have been found [20], and also very rarely among previously vaccinated children.[21] While reactivation of latent Varicella-Zoster virus to produce specific neurological complications usually occurs in absence of typical exanthem. It occurs mainly in elderly or immunocompromised patients and is very rare in children.

Extensive workup was done to cover all the differential diagnosis of this patient’s presentation taken in consideration the sudden onset of symptoms and eventual recovery, which could be consistent with an infectious etiology or stroke or paraneoplastic syndrome or episodic metabolic disorder; however, the neuroimaging study excluded any structural abnormality or cerebrovascular event or tumors as well as the metabolic cause was ruled out by initial screen (Table 1) [22]. Reye syndrome was unlikely without an elevation in liver enzyme activities. As in this case, in some instances of varicella encephalitis or cerebellar ataxia the CSF can be normal [9,17,23-25].

Our patient is noteworthy because reactivation of latent Varicella- Zoster virus resulting in encephalitis and cerebellitis is likely, though not absolutely certain, diagnosis in our patient given the history of previous exposure to varicella at one year of age, absence of past or recent history of infection, absence of pathognomonic varicella rash , fever , or any other sign of recent infection, and finally the presence of the temporal relationship between symptoms appearance (i.e. encephalitis manifested by the altered sensorium, seizures and abnormal electroencephalogram and concomitant cerebellar ataxia, manifested by nystagmus, truncal ataxia, and gait unsteadiness) and positive serum Varicella-Zoster virus IgG antibody combined with negative Varicella-Zoster virus IgM serology. Our patient had a weakly positive VZV DNA (PCR) in the cerebrospinal fluid, confirmation by another CSF sampling was not feasible . This patient did not receive virus vaccine. In addition, when he was exposed to chickenpox at one year of age, and he did not develop the typical skin rash and even he did not misbehave despite the presence of three members affected at home. The exact reason is not will clear for us. It might be that he reacted before to such exposure and developed mild respiratory infection with no characteristic skin lesions and that was missed by his mother. There was no history suggestive of immunodeficiency such as frequent infection or multiple admissions and he had no problems with his growth or development. His complete immunological work-up revealed negative results.

The pathogenesis of varicella reactivation - related neurologic complications is not clearly defined but has been attributed to immune-mediated post infectious demyelination or direct viral invasion. [26] We do not know which of these 2 mechanisms is more likely in our patient. It is of interest to know that in contrast to herpes simplex virus reactivation , which can occur many times during life, Varicella-Zoster virus reactivation usually occur once in a lifetime [27] The reasons for this low tendency of varicella-Zoster virus to reactivate are poorly understood , but are assumed to include viral causes such as low degree of viral replication to enable reactivation, low amount of latent viral load in the dorsal root ganglia, and the modulating role of the host immune response. The latter is supported by the increased frequency of syndromes caused by Varicella- Zoster virus reactivation such as herpes zoster and post herpetic neuralgia among immune-deficient patients and elder individuals [27].

Spiegel R. et al suggested that minor immunological abnormalities such as altered T cell responses which may not be discovered by traditional studies may predispose certain individuals to a more severe course of the disease and to an increased tendency to reactivate [5]. While certain genetic deficiencies such as mutations in 2 novel genes TLR3 and UNC-93B have been reported as predisposing factors for herpes virus encephalitis in otherwise healthy patients , there are no reported data of certain genetic deficiencies that might predispose to Varicella-Zoster virus central nervous system involvement [28,29].
In addition to our patient there were four previous cases of Varicella-Zoster virus associated central nervous reactivation in immunocompetent children reported in the literature (Table 2). In all cases, diagnosis was confirmed by the detection of Varicella-Zoster virus DNA in cerebrospinal fluid. The presence of abnormalities on magnetic resonance imaging (MRI) or computed tomography (CT) scan especially ischemic lesions is the most consistent conventional criterion supporting the diagnosis of Varicella-Zoster vasculopathy [30].

In these cases two patients had no MRI and the other two with non-specific findings. Their Clinical presentation ranged from uncomplicated self-limited aseptic meningitis to a more severe encephalitis/meningitis with neurologic sequels of interest, in all cases the preceding vesicular exanthema, which is usually considered the leading clue to the correct diagnosis, was absent. From these cases we can conclude that absence of viral exanthem is more common than previously thought and dose not rule out the possibility of Varicella-Zoster virus reactivation.

Recently, Esposito S. et al reported a 14-year-old immunocompetent boy who developed meningitis due to varicella zoster reactivation. His cerebrospinal fluid analysis revealed lymphocytic pleocytosis with 1400 lymphocyte/µL, normal glucose and high protein (95 mg/dL). Varicella-zoster DNA was detected in the cerebrospinal fluid by PCR. His brain MRI was normal. This case was not included in our comparison (Table 2) because this patient had herpetic zoster skin lesion and was on oral acyclovir two days before his presentation. These lesions resolved in about one week and his symptoms resolved after a 10-day treatment with acyclovir [31].

Our patient received a total course of 21-days of intravenous acyclovir. His initial motor improvement was noted at 14-days from the onset, and that is why other extensive investigations were done to rule out serious disorders like opsonoclonus myoclonus syndrome, especially in the presence of high amplitude coarse nystagmus and the high intensity of the truncal ataxia. He did not receive any immunosuppressive therapy either corticosteroids or intravenous immunoglobulin to halt the proposed ongoing inflammatory process.

In the literature, there are no controlled treatment trials available regarding the treatment of Varicella-Zoster virus associated central nervous system complications and the efficacy of antiviral therapy in immunocompromptent children remains to be established. Because Varicella-Zoster virus is present in cerebral arteries, most authors agree that patient should be treated with intravenous acyclovir in the context of CNS complications [32,2]. Corticosteroids are commonly added to decrease the inflammatory reaction presumed to further contribute in the pathophysiology of the disease [33]. The use of corticosteroids was supported by the study reported by Nagel et al who found out that 66% of patients improved or stabilized with acyclovir alone, while 75% improved or stabilized when treated with both acyclovir and steroids [30]. Future prospective controlled trials can define the optimal treatment. Spiegel R, et al suggested that acyclovir should be given in all cases and high-dose steroids should be considered in the more aggressive severe cases and in those with prolonged clinical manifestations especially when inflammation seems to play a major role [5].

In conclusion, primary Varicella-Zoster virus CNS infection should be suspected in association with appearance of typical exanthem either before the onset of symptoms or during the course of illness. While Varicella - Zoster virus reactivation should be included in the differential diagnosis of unexplained meningitis/encephalitis, cerebellitis, stroke or pseudotumour cerebri in immunocompetent children with previous history of exposure to chickenpox or vaccination, even if specific MRI abnormalities are absent. A systematic workup for potential viral infection, regardless of cerebrospinal fluid pleocytosis, is warranted. To establish the diagnosis, one should search for the temporal relationship between the onset of clinical symptoms and positive Varicella-Zoster PCR (DNA) in CSF analysis or the rising titer of VZV IgG antibodies in the serum (to be tested initially during the acute phase and repeated during the convalescence phase of the illness), in the absence of characteristic lesion of varicella. Once diagnosis is confirmed, specific antiviral therapy like acyclovir should begin immediately to improve the functional neurological outcome. An adjuvant high-dose steroid treatment should be reserved for those with severe intense course in order to lessen the duration of inflammation and improve the future prognosis of such patients. Further work-up for immunodeficiency such as serum immunoglobulins, complement, total count and functional studies of T cells, and Human immunodeficiency virus (HIV), should be considered with CNS complications secondary to latent activation of virus.

References

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