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Case Report Open Access

Severe Acute Disseminated Encephalomyelitis Following Swine Influenza Virus (H1N1) Infection in Children

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Abstract

Background: Neurological complications of influenza viral infection have rarely been discussed in current literature. In the era of recent outbreaks of this potentially serious viral illness, understanding of possible extra-pulmonary clinical manifestations is crucially needed.

Case report: We are reporting two toddler girls who have been endorsed as previously healthy. Both patients have presented with a febrile respiratory illness followed by severe encephalopathy needing intensive care unit admission. They have been found to have novel H1N1 infection. Their neuroimaging studies were consistent with severe acute disseminated encephalomyelitis (ADEM). Good response to immunotherapy has been luckily achieved.

Discussion: ADEM is an acute autoimmune encephalopathy disease which is commonly triggered by viral illnesses. However, particular correlation with novel H1N1 viral infection is not well described. Whether H1N1 triggers more severe clinical and radiological variant of ADEM is not yet precisely known, though has been observed in our study. Current knowledge in regard to neurological burden of H1N1 infection is reviewed.

Conclusion: It is likely that H1N1 can trigger a more severe form of ADEM in children. Early suspicion and isolation of H1N1 virus in children who present with acute unexplained encephalopathy in the context of any viral illness seems to be a recommended practice.

Keywords: H1N1; Influenza; Acute demyelinating encephalomyelitis; Immunotherapy

Introduction

Neurological events related to the pandemic swine-delivered H1N1 strains of influenza virus infections have gained a lot of researchers' interest recently. Over the last few years, more and more evidence of neurological injury resulting from H1N1 is accumulating. However, most of current knowledge has come from adult studies, where as quite little is known in regard to paediatric age group. Nevertheless, it is this age group who is described as more vulnerable to the most severe, occasionally lethal H1N1 infection [1]. Interestingly, neurological manifestation has been reported following the viral vaccine as well [2].

It has been noticed that most of neurological system involvement secondary to H1N1 infection is basically peripheral rather than central. Acquired peripheral neuropathy and Guilian Barre syndrome (GBS) have been the most common clinical presentation noted [3]. However, seizures, encephalitis, ADEM and immune mediated encephalopathy have occasionally been reported by various case studies [4,5]. The clinical spectrum is so variable; creating a real challenge for the disease consideration and virus isolation tests. We are reporting two toddler-aged girls with confirmed H1N1 infection complicated by very unusual severe ADEM. In spite of both clinical and radiological severity, ultimate improvement has taken place upon appropriate utilization of immunotherapy modalities.

Case Report

Case 1

A 2 ½ years old girl had been previously well, with no prior health concern. She was born at term to non-consanguineous parents with no complications. No clear history of contact with a sick patient had been elicited but she was attending a day care facility. She presented with background history of fever and flu-like symptoms for four days prior to admission, evolved to progressive sleepiness and concerning drowsiness. She had then developed a single generalized tonic colonic seizure for few minutes. She arrived to the emergency department in a post-ictal state. She was noticed to be unresponsive with laboured breathing, so she was subsequently intubated and ventilated and shifted to intensive care unit (PICU). There was no other focal neurological sings though. Initial assumption of central nervous system infection was made, thus the patients was commenced on antibiotics and antiviral agents after doing a spinal tapping. Results of cerebro-spinal fluid (CSF) analysis, came back with normal ranges of sugar, protein and cell counts.

Her routine infection workup was negative as well. CSF was negative for both bacterial cultures and viral polymerase chain reaction (PCR) studies. She had a positive result for H1N1 PCR in respiratory secretions, using direct florescent assay (DFA). Therefore, she received a five days course of oral oseltamavir. Initial computed tomography (CT) scan for her brain was remarkable for subtle thalamic

hypodensity. Magnetic resonance imaging (MRI) study had been arranged thereafter, showing extensive white matter changes with minute hemorrhages and necrosis as below (Figures 1-4). Clinico-radiological diagnosis of severe hemorrhagic-necrotic variant of ADEM secondary to H1N1 was ultimately concluded.

The patient was in critical status in PICU, needing ventilatory and inotropic support to maintain her vital functions. Aggressive immunotherapy was started after the MRI results were available on her third day of admission. She received five days of high dose pulse steroids (methylprednisilone), five sessions of plasma exchange then two days of immunoglobulins (IVIG). She continued to receive levetiracetam as an anti epileptic agent as well.

In the second week, the patient started to show some slow improvement. The treating team was able to wean her off respiratory support till she was able to breathe normally in room air. Her cardiac support medications were stopped and she started to receive enteral feeding. She began slowly to open her eyes, track objects, move her limbs and to be consoled with family presence. She was trying to communicate using some incomprehensive sounds and letters, though no fully understood sentences were observed initially. In the third week she was able to take her meals orally without significant swallowing dysfunction. She was building up some generalized spasticity, though this had been lessened with the care of occupational therapists and physiotherapists. Luckily, she did not have fixed contractures, however she continued to need a special seating chair. She remained seizure free and her anticonvulsant medication was weaned off successfully over few weeks. Thereafter, she was transferred to a special rehabilitation hospital to complete her recovery. She did achieve a considerably excellent performance with rehabilitation sessions. Ultimately, she could walk reasonably balanced, with a barely noticed speech articulation difficulty, which is expected to get progressively better with time.

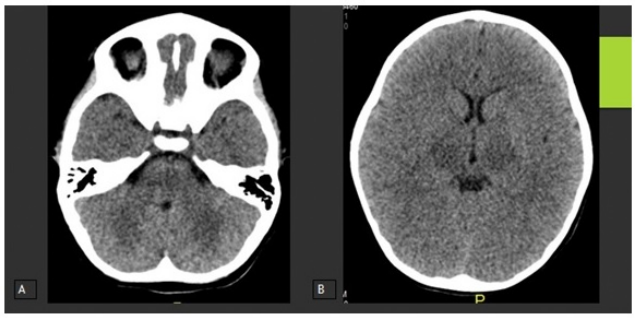

Figure 1: Axial Non-Contrast CT examination of the brain at the level of the pons (A), Basal Ganglia and Thalami (B) showing subtle hypodensity along with no gross basal ganglia or posterior fossa changes.

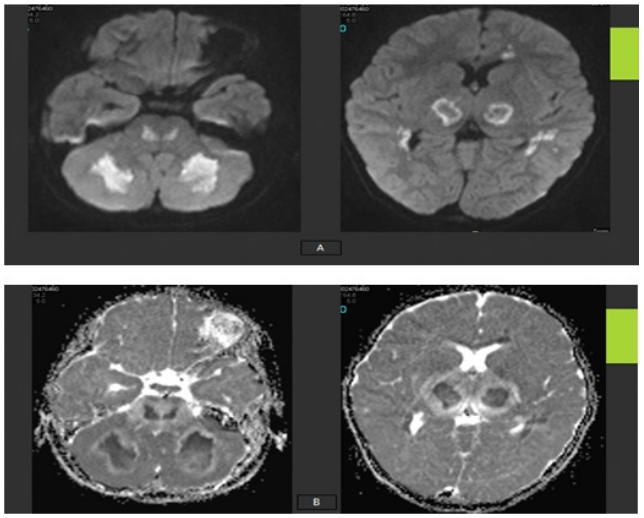

Figure 2: Axial DWI (A) and ADC map (B) MRI brain at the level of the pons, Basal Ganglia and Thalami showing bilateral rather symmetrical parenchymal areas of bright signal in DWI and low values in ADC maps denoting some element of restricted diffusion which also is seen involving the corpus callosum and the cerebellar white matter.

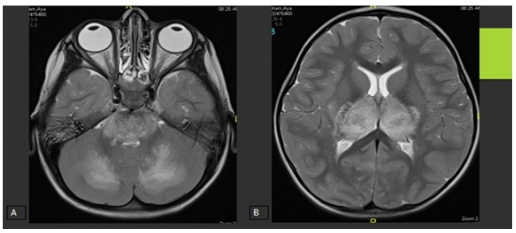

Figure 3: Axial T2 WI MRI of the brain at the level of pons (A), Basal Ganglia and Thalami (B), Showing swelling and bright T2 signal intensity with attenuated 3rd ventricle and basal cisterns.

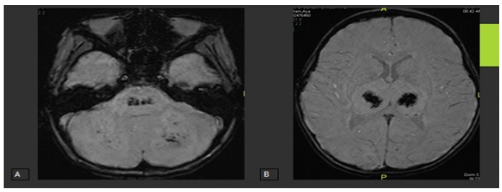

Figure 4: Axial Susceptibility weighted images(SWI) MRI of the brain at the level of the pons (A), Basal Ganglia and Thalami (B) Showing patchy dark blooming low signal intensity denoting parenchymal haemorrhages as well.

Case 2

A 4 years old girl who has been described as previously healthy apart from recurrent episodes of chest wheezes in the first few years of life, which has improved by its own. The patient who has two older

healthy siblings was born at term without concern. She presented to emergency health services with two weeks history of fluctuating fever and cough productive of non-purulent sputum. Her father was having flu symptoms the week before she started coughing. Over the last couple of days before admission the patient was noticed to be progressively ill looking with obvious tendency to sleep most of the day. On the day of admission the patient was crying that she could not see well what was in front of her. Otherwise, there was no headache, vomiting, seizures, weakness or change of behaviour.

Initially, the patient was found to have low grade fever of 38.3 degree upon admission to PICU, with otherwise stable vital signs. The patient was sleepy though easily arousable. She was extremely irritable, far beyond her usual attitude. Mild neck stiffness was felt, so in spite of absence of other supporting signs an initial impression of meningo-encephalitis as potential diagnosis was entertained and subsequently CSF samples were taken and broad-spectrum antibiotic and antiviral therapies were started. All infectious workup was non-revealing apart from positive PCR for H1N1 in nasal secretions. MRI was arranged in the second day of admission, showing extensive demyelinating, yet haemorrhagic white matter changes compatible with severe ADEM with micro-haemorrhages and necrosis (Figures 5-8). Thereafter, the patient had been subjected to intensive immunotherapy in from five days course of high dose pulse methylprednisilone, four sessions of plasma exchange followed by two doses of IVIG, as well five days course of oseltamavir.

The patient had started showing some improvement in the second week of admission, with near full recovery of her visual impairment, resolution of irritability, disappearance of fever and progressive improvement in her overall interaction. By the third week, she was showing a steady improvement, so she had been transferred to the affiliated rehabilitation unit for intensive sessions of rehabilitative exercises; delivered through the physical therapists, occupational therapists and speech therapists. By the fourth week, she had gained most of her pre-morbid functions with the exception of mild gait ataxia.

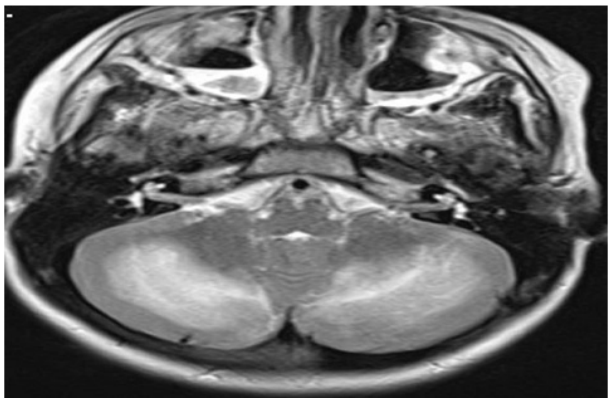

Figure 5: T2 MRI showing bilateral rather symmetrical cerebral and predominantly cerebellar patchy areas of high intensities in T2/FLAIR sequences.

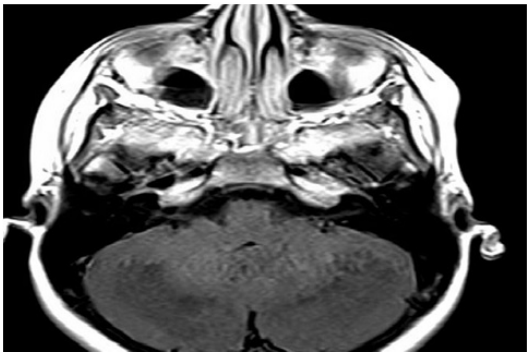

Figure 6: Faintly cerebellar low signal T1 images, indicating demyelinating process.

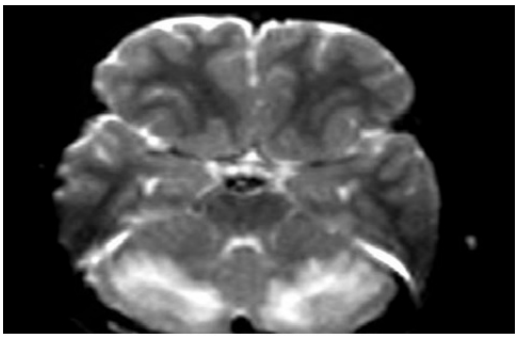

Figure 7: DWI image Patch deeply seated parenchymal areas of diffusion restriction as well as micro-hemorrhages.

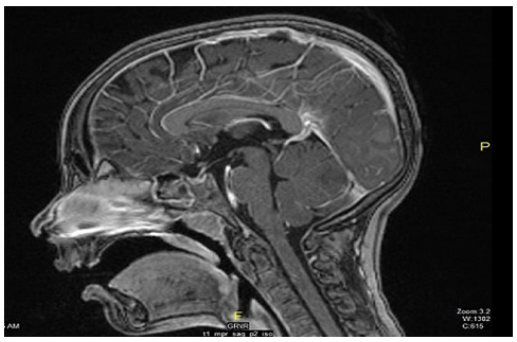

Figure 8: Sagittal post contrast view showing suspicious areas of altered signal intensity in upper cervical spinal cord, though no definitive post contrast enhancement seen.

Discussion

Most CNS neurological complications of H1N1 involve a picture of clinical encephalopathy and often tend to affect patients at the extreme age groups, making children among the high risk categories [6]. The direct viral tropic effect on growing children has been always a theoretical justification for such an observation; however this has not

been supported by definitive evidence. Fortunately, advanced laboratory techniques are now helping to facilitate H1N1 isolation from CSF samples and postmortem brain tissues [7-9]. In our study we could not technically manage to isolate the virus from CSF. It has been isolated from respiratory secretions though. The associated inflammatory reaction to the virus is the sole harmful pathogenic mechanism responsible of the neurological injury is an assumption that has been argued by some researchers as well [10].

ADEM is an acute, probably autoimmune demyelinating inflammatory disorder of CNS affecting multifocal patches of predominantly white matter, and rarely grey matter and spinal cord. Being usually preceded by a minor illness, it is not quite surprising that it can follow H1N1 infection in the recent few years [11]. Nevertheless, only few studies have been available on current literature. A little is known about whether the specific viral treatment has been contributing to the improvement of these patients` cohort, the practice that we have followed in our reported patients.

It is not fully understood why some children went into full blown picture of severe encephalopathy, while others did not. Possible genetic mutations or metabolic disorders might be ultimately to be unraveled [12]. Calitri and his group have estimated that up to 5% of children hospitalized for H1N1 infection had encountered neurological complications, mainly encephalitis and ADEM [13]. The overall risk of developing ADEM with H1N1 infection might be as high as 5% in infants and small children [14]. Clinical correlation of ADEM with the severity of the respiratory compromise caused by H1N1 is poorly understood. Some patients had severe clinical ADEM with minimal respiratory symptoms, making a conclusive statement in regard to the exact pathogenesis a little challenging [15,16].

The clinical spectrum of post-H1N1 ADEM is within the common clinico-radiological scenarios of ADEM variants. Reports from both adults and children have shown variable clinical severity, radiological lesional distribution and prognostic outcomes [17-20]. Occasionally ADEM behaves as a multi-phasic disease with close proximity to multiple sclerosis. The disease might have either a chronic or a relapsing/remitting course in this rare context. Very rarely H1N1 infection might cause severe recurrent ADEM [21]. ADEM tends to be associated with other extra-pulmonary complications of H1N1; putting more burdens on the possible treatment options and making the future outcome more gloomy [22].

The most worrisome neurological sequale of H1N1 is a rare variant of H1N1 called acute necrotizing encephalopathy (ANE), or acute hemorrhagic encephalomyelitis; which is the most morbid form of ADEM [23-26]. The pertinent radiological features in this rare category are the extensive white matter changes and presence of small sized haemorrhages [27]. The disease, which is occasionally named Hurst disease, is usually fatal or at least severely devastating. Most of the patients who have survived Hurst disease have done so with major neurological deficits [28]. However, with early recognition and proper utilization of intensive care support and aggressive immunotherapy, some cases have almost reached to a complete recovery [29,30].

Another emerging related hot topic is post H1N1 vaccine neurological complications [31]. Classical clinical and radiological ADEM has been described following H1N1 vaccine without overt precise understanding of the underlying patho-physiologic basis [32]. More unique radiological features have been reported as well, including unusual extensive thalamic involvement in the context of post-vaccine ADEM [33]. Interestingly, severe hemorrhagic ADEM variant was initially thought to be linked to H1N1 vaccine, possibly the same way as the principal infection [34]. Very rarely, H1N1 vaccine might lead to severe involvement of the spinal cord alone rather the classical brain changes. In one report, severe transverse myelitis; a disease with obscure etiology and similar triggers to ADEM, has flared soon after H1N1 vaccine [35]. These case reports, though represent complete rarity, do still raise a major concern about safety profile about H1N1 vaccine, especially among the public community. Hopefully, our understanding of such complex correlation is expected to improve in the near future.

Conclusions

ADEM as a potential diagnosis is to be considered for all children who present with acute encephalopathy in the context of a recent febrile illness. Early recognition of such diagnostic possibility is crucial to ensure early commencement of appropriate immunotherapy. Entertainment of possible H1N1 as a viral trigger is advised, as possible anti-influenza treatment might be helpful in containing the unwanted clinical deterioration. We have reported the first couple of children with H1N1 induced severe hemorrhagic ADEM in the region. Our cases have stressed on the importance of early diagnosis and directed management for such case scenarios. Both of our patients have ended with exceptionally near normal outcome in spite of the overwhelming nature of clinical and radiological manifestations.

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