Diphtheric encephalitis and brain neuroimaging features

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Abstract
We report a rare case of paediatric diphtheria complicated with encephalitis. A 6-year-old boy who did not receive his scheduled diphtheria–tetanus–pertussis vaccination presented with one episode of generalised convulsive seizure. His illness was preceded by a 3 day history of fever associated with enlarged exudative tonsils with a pseudomembrane. He was commenced on intravenous penicillin and oral erythromycin. However, he developed progressive encephalopathy with focal neurological deficit which required intubation on day 5 of illness. Throat swab polymerase chain reaction for diphtheria toxin A and B were positive and diphtheria antitoxin was given. Magnetic resonance imaging (MRI) of brain showed T2-weighted hyperintensities over the anterior cingulate gyri, insular cortex and cerebellum. This is the first reported MRI finding of diphtheric encephalitis. Our report highlights the importance of neuroimaging in diagnosing diphtheric encephalitis particularly in cases with unremarkable cerebrospinal findings.

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1. Introduction
Diphtheria is an acute, toxin-mediated disease caused by the Gram positive bacillus Corynebacterium diphtheriae, which primarily infects the throat and upper airways producing a toxin affecting other organs. It is fatal in 5–10% of cases, with a higher mortality rate in young children [1]. Vaccination against diphtheria has, however, reduced the mortality and morbidity of diphtheria dramatically. Diphtheria cases reported worldwide steadily declined from 11,625 in 2000 to 4489 cases in 2012 [2]. In Malaysia, diphtheria is a notifiable disease. Diphtheria vaccination was introduced in this country in 1958 and vaccination coverage with diphtheria-pertussis-tetanus toxoid routinely had increased over the years to more than 90%. Despite good coverage cases of diphtheria still occur sporadically and in small numbers among the non-immunised population.

Apart from respiratory complications, symptomatic diphtheria is often complicated by myocarditis and toxic damage to peripheral nerves. The most commonly reported neurological complication of diphtheria virus is polyneuropathy [3]. Whilst diphtheric encephalitis is a recognised neurological complication, to our knowledge there are only 6 published cases to date with no reports showing its related brain neuroimaging features [4,5]. Previous published reports on diphtheric encephalitis were reported between 1930 and 1950 prior to the availability of brain neuroimaging. The description of these cases were restricted to only clinical and autopsical pathological findings [4].

With the resurgence of vaccine-preventable diseases, due to anti-vaccination movement, immigrants, and waning efficacy of vaccine, there is a reported increased incidence of diphtheria [3]. We describe a case report and brain magnetic resonance imaging (MRI) findings of a 6-year-old previously well child with diphtheric encephalitis. This particular case occurred during the most recent outbreak of diphtheria cases starting in epid week 25 of 2016 and involved three clusters in three states in the peninsula of West Malaysia.

2. Case report
A previously healthy 6-year-old boy was transferred to our tertiary institution at day 5 of illness for invasive ventilatory support. He had no significant past medical history, however review of his
vaccination records showed that he had not received his scheduled diphtheria, tetanus and acellular pertussis (DTaP) vaccination. He presented to the local district hospital in a northern state at day 3 of illness with an episode of generalised tonic clonic seizure preceded with a 3 day history of fever and sore throat. Physical examination upon presentation revealed enlarged exudative tonsils with a pseudomembrane. He was initially started on intravenous (iv) penicillin and oral erythromycin while throat swab sample was sent for culture and polymerase chain reaction (PCR) specifically for \textit{Corynebacterium diphtheriae} toxin.

At day 5 of illness, he became increasingly lethargic with acute onset cerebellar signs of dysdiadochokinesia and dysmetria, and was subsequently intubated and ventilated due to progressive encephalopathy. He was then commenced on iv ceftriaxone and acyclovir for possible meningococcal meningitis. Urgent computed tomography (CT) of brain reported areas of ill-defined hypodensities involving the cerebellar grey matter, in keeping with cerebel- litis. There was no focal enhancing brain parenchymal lesion or abnormal leptomeningeal enhancement. At day 6 of illness, it was reported that toxin-A and toxin-B producing strain of \textit{Corynebacterium diphtheriae} was isolated from the throat swab obtained earlier. Diphtheria antitoxin was then initiated.

Brain MRI done at day 8 of illness showed patchy high signal intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences at the cortical and subcortical white matter of anterior cingulate gyri, insular cortex, and both cerebellar hemi- sphere (Fig. 1). Diffusion weighted imaging (DWI) and apparent diffusion coefficient (ADC) map demonstrated vasogenic oedema over the cerebellar lesions. There was no focal enhancing brain lesion and abnormal leptomeningeal enhancement. Magnetic reso- nance angiography of brain was normal. Brain electroencephalogram showed features of moderate encephalopathy.

Lumbar puncture done at day 9 of illness showed normal opening pressure and normal cerebrospinal fluid (CSF) biochemistry (absent erythrocyte and leucocyte, glucose 4.9 mmol/L which was 80% ratio of the paired serum blood glucose, and protein of 0.16 g/L). CSF PCR was negative for neurotropic viruses including cytomegalovirus (CMV), enterovirus, human herpes virus (HHV)-

![Fig. 1. MRI brain in axial T2 (A1) and coronal T2 FLAIR (A2) showing high signal intensity in both cerebelli (white arrows), predominantly on the right. There are also high signal intensity in cingulate gyri on axial T2 (B1) and coronal T2 FLAIR (B2) shown with blank arrows and in both insular cortices on axial T2 (C1) and coronal T2 FLAIR (C2) shown with black arrows.](image-url)
6. HHV-7, herpes simplex virus (HSV)-1, HSV-2, parvovirus B19 and varicella-zoster virus (VZV). CSF and blood culture yielded no growth. Blood serology for VZV, Epstein-Barr virus (EBV) and mycoplasma was negative. Nerve conduction study was normal. He was extubated at day 10 of illness and completed a 2-week course of antibiotic and antiviral therapy. He was discharged at day 23 of illness with resolution of his encephalopathy. On follow-up review at day 40 of illness, he made a full recovery. Repeat brain MRI at month 8 after illness showed complete resolution of all the previously described changes.

3. Discussion

Severity and clinical course of diphtheria depends largely on mechanical respiratory obstruction from the pseudomembrane and systemic toxin produced by the organism which affects mainly the cardiovascular, renal and neurological system. Despite the affinity of the toxin to the central nervous system, diphtheric encephalitis has been rarely reported with only 6 cases to date [4,5]. To our knowledge, this is the first case report on brain neuroimaging findings of diphtheric encephalitis. Previous reports on diphtheric encephalitis were from the pre-neuroimaging era between 1930 and 1950 [4,5].

Case review by Dolgopol and Katz recorded collection of autopsial case reports from year 1900 to 1950. Wide range of central nervous complications associated with diphtheria infection were reported such as cerebral hemorrhage, meningoitis and degenerative changes of the brain and spinal cord. There were total a of 5 cases of histological diphtheric encephalitis with age range of patients between 1 and 26 years old. Histologically, cerebral oedema, perivascular cuffing (at basal ganglia, cortex, cerebellum and medulla) and cellular degeneration (at medulla and midbrain) were present in all cases with or without glial nodules [4]. In the other reported case, autopsy findings showed petechial haemorrhage over the white matter [5].

The predominant cerebellar involvement on MRI in our patient was of a similar location as described in the previous reported autopsial findings. Cerebellitis has also been reported in other viral encephalitis including VZV, HSV, EBV and enterovirus infection; whilst cingulate gyrus and insular involvement is typically reported in HSV [6,7]. The MRI findings showing cerebellar vasogenic oedema and gyriform cortical hyperintensity also correlate well with reported autopsial histological findings of cerebral oedema and glial degeneration [4].

In the reported 7 cases of diphtheria encephalitis including our case, CSF findings were only reported in 2 cases (including ours). Both of the CSF findings were essentially normal with no organism isolated from CSF culture, and in one case a slightly elevated white cell count was present [5]. Thus in patients suspected of diphtheric encephalitis, our case highlights the importance of brain neuroimaging in making the diagnosis as the CSF findings may be unremarkable.

4. Conclusion

This is the first reported MRI findings of diphtheric encephalitis. Our case report reiterates the importance of clinicians being vigilant of possible paediatric diphtheria infection particularly in unvaccinated children. Our case also highlights the importance of neuroimaging in diagnosing diphtheric encephalitis especially under circumstances whereby CSF findings can be negative.

Conflict of interest/disclosures

The authors declare that they have no financial or other conflict of interest in relation to this research and its publication.

References