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Hippocampal sclerosis, mesial sclerosis, cognitive deterioration, cherry red spots, and splenomegaly: A diagnostic challenge in an unfavorable setting

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Abstract
Background: Many practicing physicians cannot acquire adequate professional knowledge, experience and awareness of the manifestations of many rare diseases that is clearly attributed to their large number. It is generally challenging to diagnose a rare disease or disorder because it is impracticable for physicians to be familiar with thousands of rare conditions. In many geographic areas, diagnostic challenges are increased by lack of diagnostic facilities, and inability to have adequate follow of patients or to complete their diagnostic work-up. We have previously described our effective diagnostic approach which helped us in documenting the diagnosis of many rare disorders despite various limitations. The aim of this paper is to describe the approach used in facing a diagnostic challenge which was increased by the lack of information about the clinical history of the illness including family history and past history as the patient was an orphan that was transferred temporarily to Baghdad in an emergency situation from the province of Mosul following the huge turmoil associated with emergence of ISIS in Mosul.
Patients and Methods: A 17-year old orphan who had cognitive impairment, dysarthria, gait abnormalities, bilateral macular cherry red spots, mild hyperbilirubinemia, mild splenomegaly, and mild right hippocampal sclerosis on brain MRI was studied.
Results: The key in the approach to the diagnosis of this case was focusing on the presence of macular cherry red spots and considering the disorders associated with it and with other manifestations especially hippocampal sclerosis. When considering the age of the patients, clinicians with extensive clinical experience can tell confidently that the patient had a late onset (Juvenile or adult form) of Niemann-Pick disease.
Conclusion: Despite the unfavorable diagnostic setting, it was possible to document the occurrence of the first case of Niemann-Pick disease. The involvement of hippocampal involvement is well recognized, but its detection on MRI has been infrequently reported. This paper emphasized the association of Niemann-Pick disease with MRI evidence of Hippocampal sclerosis and mesial sclerosis.

Keywords: rare disease, Iraq, niemann-pick disease, hippocampal sclerosis, mesial sclerosis

Introduction

Many practicing physicians cannot acquire adequate professional knowledge, experience and awareness of the manifestations of many rare diseases that is clearly attributed to their large number. It is generally challenging to diagnose a rare disease or disorder because it is impracticable for physicians to be familiar with thousands of rare conditions. In many geographic areas, diagnostic challenges are increased by lack of diagnostic facilities, and inability to have adequate follow of patients or to complete their diagnostic work-up. We have previously described our effective diagnostic approach which helped us in documenting the diagnosis of many rare disorders despite various limitations [1, 8].

The aim of this paper is to describe the approach used in facing a diagnostic challenge which was increased by the lack of information about the clinical history of the illness including family history and past history as the patient was an orphan that was transferred temporarily to Baghdad in an emergency situation from the province of Mosul following the huge turmoil associated with emergence of ISIS in Mosul.

The patient was transferred by a non-governmental humanitarian organization, and his attendance didn't have satisfactory information about the clinical course of the patient nor any medical record, and it was possible to see the patient once.

Patients and methods

A 17-year old orphan was brought to the pediatric neuropsychiatry clinic following an emergence emergency transfer to Baghdad because his current unrelated humanitarian guardians not that he had cognitive impairment, dysarthria, and some gait abnormalities mostly in the form of awkwardness and slowness, despite he was staying in healthy orphans care house. The patient's attendance didn't have satisfactory information about the clinical course of the patient nor any medical record, and it was possible to see the patient once. However, they thought that his current illness was not of very long duration because he was kept in healthy orphans care house.

The patient had obvious difficulty in understanding ordinary talks, slow speech, and awkward gait, and it was not possible to take a satisfactory history from him. He had normal hearing and

visual acuity, but fundoscopy showed bilateral macular cherry red spots.

Laboratory tests showed normal liver function tests and alkaline phosphatase, but there was mild hyperbilirubinemia, and the total billirubin was 2.1 mg/dL (Normal: 0.3-1 mg/dL). Direct billirubin was mildly elevated at 0.8 mg/dL as the normal is less than 0.3 mg/dL. Indirect billirubin was also mildly elevated at 1.4 mg/dL as the normal is less than 1 mg/dL. Abdominal ultrasound (Figure-1) showed only one abnormality which was a mildly enlarged spleen (12.7 cm span) which had normal. The only abnormality present on brain MRI was mild right hippocampal sclerosis, mesial sclerosis.

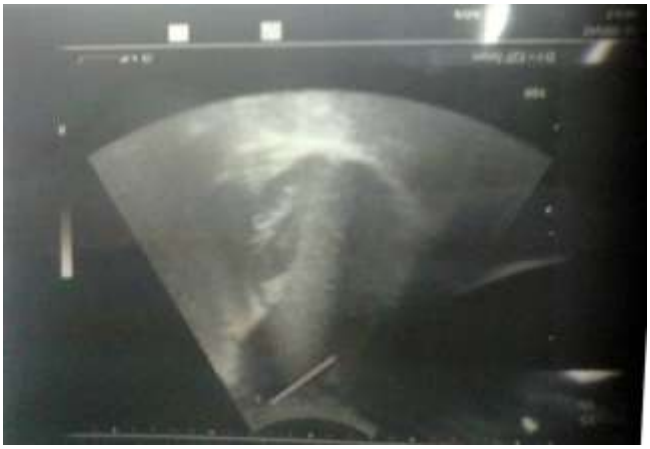

Fig 1: Abdominal ultrasound a mildly enlarged spleen (12.7 cm span) which had normal

Results

The key in the approach to the diagnosis of this case was focusing on the presence of macular cherry red spots and considering the disorders associated with it and with other manifestations especially hippocampal sclerosis. When considering the age of the patients, clinicians with extensive clinical experience can tell confidently that the patient had a late onset (Juvenile or adult form) of Niemann-Pick disease.

Discussion

Niemann-Pick disease is a rare autosomal recessive neuro-visceral lysosomal lipid storage disease of various forms with extremely heterogeneous clinical manifestations, age of onset, clinical course and progression. Late onset forms which are sometimes called “Intermediate forms) can be associated with dysarthria, progressive cognitive deterioration (Dementia), gait problems, falls, and clumsiness, splenomegaly with or without hepatomegaly, hyperbilirubinemia, and macular cherry red spots. The clinical diagnosis can be easily and practically confirmed by finding foam cells in the bone marrow examination. The condition was first described by Albert Niemann (Figure-2) in 1914, while Ludwig Pick (Figure-3) described the pathology of the condition in a series of papers during the 1930s [9, 15].

Fig 2: Albert Niemann (1880-1921), a German pediatrician

Fig 3: Ludwig Pick (1868-1944), a German pathologist

Neurologic involvement in Niemann-Pick disease has been linked with brain involvement in the hippocampal gyrus dentatus (Conte *et al*, 2019), hippocampal volume reductions (Walterfang *et al*, 2013) and reductions in neurons and synapse in the hippocampus (Byun *et al*, 2011) have been attributed in cognitive deficits especially in late onset forms. Hippocampal neuronal involvement in Niemann-Pick disease is similar to what has been reported in Alzheimer's disease which is associated with hippocampal sclerosis with a severe loss of neurons and gliosis in the CA 1 sector of hippocampus (Mahieux *et al*, 2003). Hippocampal sclerosis and mesial temporal sclerosis may occur with fronto-temporal lobar degeneration and Alzheimer's disease (Joshi *et al*, 2014) [16, 21].

Elleder and Cihula (1983) reported three families with five patients with late onset, chronic course Niemann-Pick disease who had mental deterioration, cherry red spots, splenomegaly and hepatomegaly, and numerous foam cells in the bone marrow. Elleder and Cihula There emphasized a striking variability in the clinical manifestations in three siblings. The first sibling was a girl who died at the age of seven years from visceral involvement which included the lung, and without showing of clinical

neurologic deterioration. One of her younger brothers had significant neurological deterioration by the age of 22 years, while the second younger brother was showing no neurological changes at the age of 18 [11].

Sévin, *et al* (2007) reported 13 unrelated patients with late onset form of Niemann-Pick disease diagnosed in France who had dysarthria, cognitive impairment, splenomegaly, and of evidence of brain atrophy on MRI [12].

The occurrence of Niemann-Pick disease Iraq has not been reported or documented before [22, 25], and this paper presents the first Iraqi patient with Niemann-Pick disease.

Conclusion

Despite the unfavorable diagnostic setting, it was possible to document the occurrence of the first case of Niemann-Pick disease. The involvement of hippocampal involvement is well recognized, but its detection on MRI has been infrequently reported. This paper emphasized the association of Niemann-Pick disease with MRI evidence of hippocampal sclerosis, and mesial sclerosis.

Acknowledgement

In most of our previous publications, we keen in enhancing our reports with photos, but in this, the patient and guardians were unable to provide consents. Therefore, only an ultrasound image was included.

Conflict of interests: None.

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