

Juvenile Neuronal Ceroid Lipofuscinosis: A Rare Case Report with Literature Review in a Siblings Pair Having Cardiac Involvement

Mousa Suhail Abu Ghoush^{1,*}, Mahfoud El. Bashari², Amani Alzaabi³, Mohammed Aboelnaga⁴

¹Zayed Military Hospital, Internal Medicine Resident, Abu Dhabi, United Arab Emirates

²Zayed Military Hospital, Consultant Neurology, Abu Dhabi, United Arab Emirates

³Zayed Military Hospital, Consultant and Head of Department Neurology, Abu Dhabi, United Arab Emirates

⁴Zayed Military Hospital, Specialist Neurology, United Arab Emirates

*Corresponding author: mousasuhail@hotmail.com

Received July 07, 2020; Revised August 09, 2020; Accepted August 18, 2020

Abstract Neuronal ceroid lipofuscinosis (NCL) are a group of genetically mediated neurodegenerative disorders affecting children and young adults. They are characterized by progressive vision, cognitive deterioration and epilepsy ultimately resulting in death. Of the various types, late infantile variety is the 2nd most common form of NCL. Here we report a case of an 18-year-old boy along with his elder sister who presented to the neurology clinic with progressive mental and social deterioration since the age of 5-6 years. As the disease progressed, he developed progressive vision loss, cognitive decline, behavioral changes and epilepsy. Skin biopsy from the thigh revealed characteristic curvilinear and fingerprint inclusion bodies suggestive of NCL. This case highlights a rare entity of neurodegenerative disorders with cardiac involvement.

Keywords: epilepsy, neuronal ceroid lipofuscinosis, skin biopsy, vision loss, infiltrative cardiac myopathy

Cite This Article: Mousa Suhail Abu Ghoush, Mahfoud El. Bashari, Amani Alzaabi, and Mohammed Aboelnaga, "Juvenile Neuronal Ceroid Lipofuscinosis: A Rare Case Report with Literature Review in a Siblings Pair Having Cardiac Involvement." *American Journal of Medical Case Reports*, vol. 8, no. 12 (2020): 443-446. doi: 10.12691/ajmcr-8-12-2.

1. Introduction

Neuronal ceroid lipofuscinosis (NCL) are a group of progressive neurodegenerative disorders which are autosomal recessively inherited. They are characterized by the intracellular accumulation of autofluorescent lipopigments in neurons and other tissues. At least 13 different genetic forms of NCL have been identified. Depending on the age of onset, they are classified into 4 types: Infantile, late infantile, juvenile and adult forms. Collectively, NCLs are the most prevalent neurodegenerative disorders of childhood [1]. However, the individual NCLs are rare conditions, epidemiologic studies are limited, and prevalence estimates vary from country to country. [1] Collectively, NCLs have an estimated prevalence of 1 per 1 million people in the United States [2], 1.2 per 1 million people in Italy [3], and as high as 1 per 100,000 people in Scandinavian regions [3]. The characteristic features include mental retardation, progressive visual loss at age 4-7 with blindness within 2-10 years, progressive myoclonic epilepsy, decline in motor skills resulting in premature death, psychiatric symptoms in 74 % of patients including aggression [4]. According to a clinical and epidemiologic study done in Newfoundland Seizure was the presenting

feature in the majority of patients (29/51, 57%). Other patients presented with developmental delay (10/51, 20%), developmental regression (5/51, 10%), unsteady gait (4/51, 8%) and visual failure (3/51, 5%). The median age at presentation was 3 years (range 0.7-15 years), and median age at death was 9.5 years (range 4.6-41 years). [5] Infantile and late infantile onset NCL have a poor prognosis with early deaths while juvenile and adult onset forms have a relatively better prognosis. Usually cardiac involvement is rare in such cases [2]. We report this case of an 18-year-old boy with his elder sister who had characteristic clinical features but a rare cardiac infiltrative myopathy. Histopathology confirmed the diagnosis.

2. Case Description

An 18 year old male was brought in to the neurology clinic along with his elder sister, 19 years old for evaluation of progressive visual impairment and cognitive degeneration. They are the children of consanguineous parents, with no antenatal or perinatal complications. They were born at term with good birth weight, approximately at 5-6 years of age they were able to name colors, pictures, read simple word, and perform some activities independently. At 7 years of age it was noted

that they have visual problems and progressively lost vision within two months and their growth was at best slowly progressing. Unlike his sister, he didn't have epilepsy or any psychiatric manifestations.

At the time of presentation to the clinic they were able to recognize their family members, perform simple addition or subtraction and memorize passages with auditory memory.

Clinical examination showed overweight teenagers with no dysmorphic features. No neurocutaneous stigmata were present. They showed appropriate social responses and could make appropriate verbal responses. Their gait was slightly broad based, but there was no clear ataxia. Tone was normal and the deep tendon reflexes were normal and equal in all limbs. Plantar reflexes were down going bilaterally. Power was grade 5 in all limbs and there was no scoliosis. Eye movements could only see light only. Pupils were 4 mm in diameter and sluggishly reactive to light. Cranial nerve examination was otherwise normal. Proprioception, vibration sense, temperature and

touch were grossly normal. There was no organomegaly and other systems examinations were unremarkable.

MRI brain at the time was normal, fasting lipid, lactate, vitamin E and very long chain fatty acid levels were normal. EEG was normal. An electroretinography was done as both patients were exhibiting poor vision; it showed evidence of mild optic nerve atrophy, marked attenuation of the inner retina. There was blunting of the whole retinal appearance along with macular degeneration, there was no response to either flash or flicker stimulation, suggesting attenuated cone and rod function, picture of which is indicative of retinitis pigmentosa.

At one point the younger male sibling was admitted with palpitations and was found to have elevated troponin levels with an ECG tracing showing inverted T waves in lateral leads (Figure 1). Upon further evaluation with Echocardiography it showed an interesting finding of thickened pericardium suggestive of infiltrative myopathy (Figure 2, Figure 3).

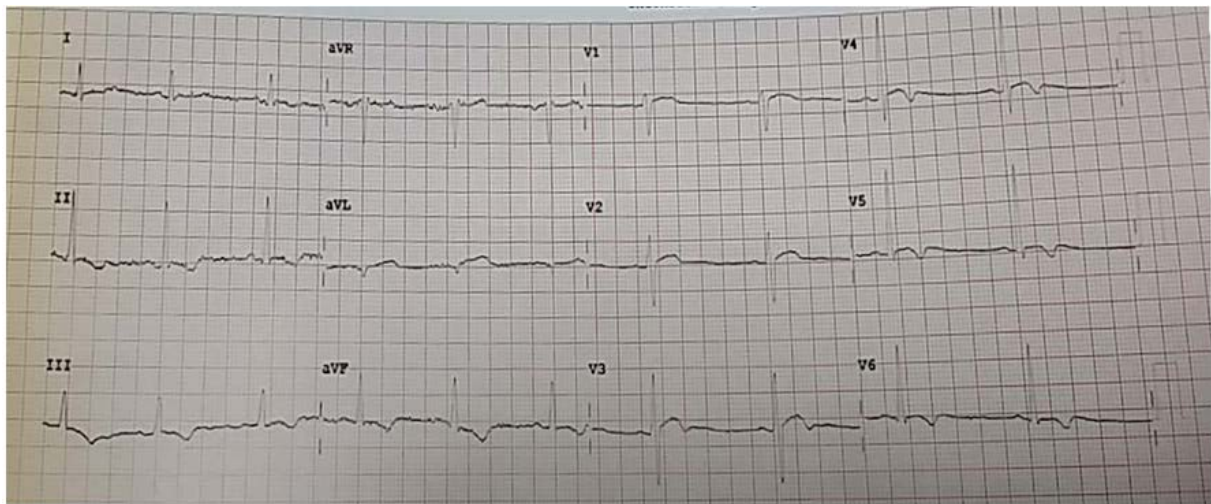


Figure 1. A 12 Lead ECG showing inverted T waves in leads V3-V6

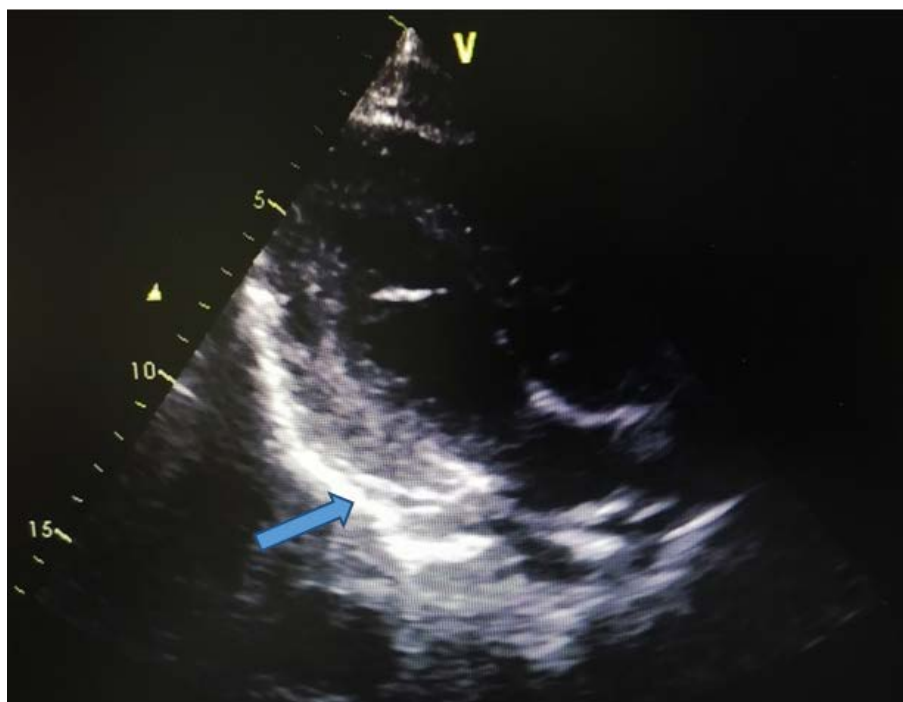


Figure 2. A Transthoracic Echocardiogram, two-Dimension long axis view showing thickening of pericardium

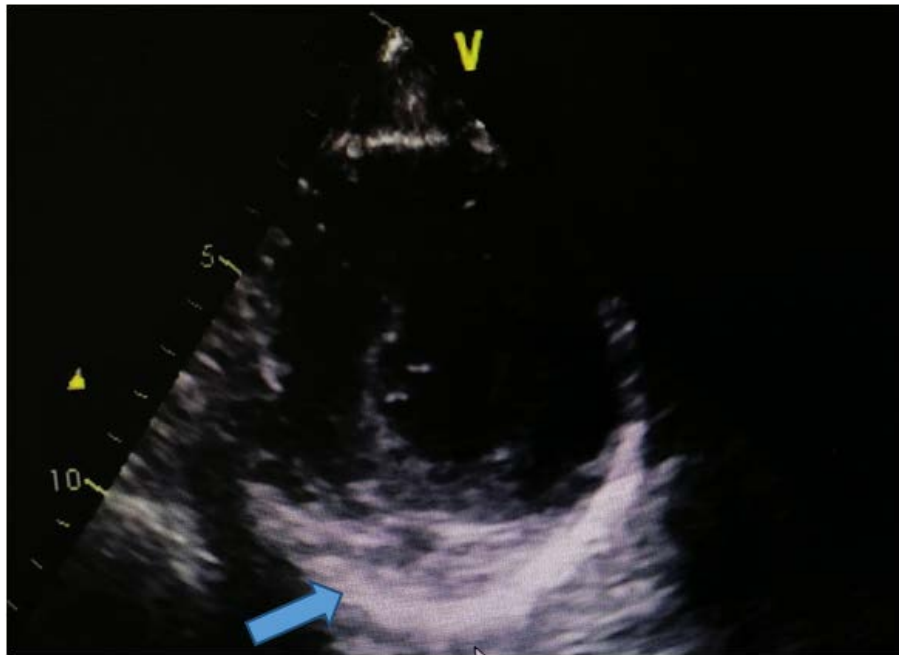


Figure 3. A Transthoracic Echocardiogram, two-Dimension short axis view showing thickening of pericardium

Given the predominant clinical features of visual loss, progressive epilepsy and psychiatric disturbance with psychomotor degeneration. It is likely that the siblings might have a variety of inherited neurodegenerative disorders. The most common of these is either neuronal ceroid neurodegenerative disorder (NCL) or mitochondrial cytopathy. They were sent abroad for further evaluation.

Genetic testing for CLN3 gene was normal for both siblings, thus a skin biopsy was done to confirm the diagnosis as the genetic test was inconclusive. It showed curvilinear and fingerprint inclusion bodies in the eccrine glands, in addition there were vacuolated lymphocytes seen on peripheral blood film suggestive of storage disease.

Both siblings had recurrent infections, therapy was mainly supportive. Their condition progressed with time, and unfortunately both siblings expired at 27 years of age. One of them had a severe pneumonia and the other one due to seizures.

3. Discussion

NCL confirmation is usually made on the basis of histopathology, enzymatic assay and genetic testing. Biopsy can be obtained from the rectum, skeletal muscle, skin and conjunctiva. Four distinct types of membrane-bound osmiophilic profiles are classic lipofuscin, fingerprint profiles which predominate in chronic juvenile form, curvilinear inclusion bodies (curved stacks of lamellae with alternating dark and pale lines) in infantile forms and pure granular profiles which predominate in some infantile and adult type. Molecular genetic studies allow for definitive diagnosis but at times they are inconclusive. Thus, histopathological study of biopsy material is of importance for diagnosis of NCL. [6] The characteristic features are eosinophilic intra-cytoplasmic inclusions within the eccrine glands. Staining with periodic acid-Schiff stain highlights these inclusions. Genetic testing wasn't conclusive in our case and given

the high clinical suspicion the diagnosis was confirmed on the basis of skin biopsy which showed characteristic features of NCL.

Ophthalmological evaluation gives important clues to the diagnosis of NCL. Ophthalmoscopic findings can occur even before onset of vision loss. Early changes include defective macular light reflex and optic disc pallor followed by attenuation of vessels, pigmentary retinal changes. [7]

Cardiac involvement is often rare in this condition, as discussed earlier in our case there was evidence of thickened pericardium suggestive of infiltrative myopathy and inverted T-waves in the ECG. It was not until 2011 that a systematic clinical investigation of cardiac involvement in juvenile CLN3 was reported by clinicians in Denmark [8]. The Danish cross-sectional and follow-up study comprised twenty-nine children and adolescents with juvenile CLN3, and showed progressive cardiac impairment with repolarisation disturbances, expressed by abnormally deeply inverted T waves, ventricular hypertrophy, and sinus node dysfunction ultimately leading to a severe bradycardia and/or other conduction abnormalities [8]. The inverted T waves were present as early as 14 years of age and were associated with an increased risk of death during the 7½ years follow-up period. Four of seven patients beyond 20 years of age had hypertrophy of the left ventricular walls. A growing number evidence indicates that the deteriorating heart function can be a significant co-morbidity in NCL, and that correcting heart function, may enable patients to access a better quality of life. [8]

Our case initially had developmental regression followed by vision loss, myoclonus, and gait ataxia. Seizures occurred later in the course and they were of generalized tonic clonic type as discussed earlier. Based on a clinical study done in Newfoundland [5], seizures were one of the most common symptoms in this condition, both of which our patients had along with visual loss which is one of the earliest signs to develop in more than 80% of patients. [11]

Usually By the age of 10 years, the affected children are usually unable to walk and sit unsupported and

become blind. Death occurs in mid-childhood likely due to recurrent infections and loss of function [9], similar to what happened to one of our patients discussed earlier.

There is no definitive treatment till date. Bone marrow transplant, stem cell transplant and gene therapy have been tried but none have shown any long term benefit. [10]

To conclude, NCL are a group of progressive neurodegenerative disorders, in our case report there was an evidence of infiltrative cardiomyopathy which is relatively rare. Typical clinical, features can be suggestive of this rare disease preventing misdiagnosis, thus helping in genetic counseling. Skin biopsy is of critical importance for diagnostic confirmation.

4. Conclusions

Neuronal ceroid lipofuscinoses (NCL) are a group of lysosomal storage disorders characterized by progressive neurodegeneration and in rare cases have an evidence of cardiac myopathy, diagnosis is often confirmed with skin biopsy when genetic testing is inconclusive as described in this case report.

List of Abbreviations

NCL-Neuronal ceroid lipofuscinoses
ECG- Electrocardiogram

Availability of Data and Materials

All data are within the article.

Authors Contribution

We acknowledge that all the authors contributed to this case report whether in data gathering or editing

Funding

No funding was required for this work.

Ethics Approval and Consent to Participate

Consent was taken from patient's parents and approval from hospital ethical committee.

Competing Interests

The authors declare that they have no competing interests.

Acknowledgments

We would like to thank the echocardiography department technicians at zayed military hospital for assisting us in obtaining the echocardiography images.

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