Case Report

Niemann-Pick Type C disease: A case report

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Abstract

Niemann-Pick type C disease (NP-C) is a rare (1 in 120,000 live births), neurovisceral disorder due to massive lysosomal lipid storage. The mode of transmission of NP-C is autosomal, recessive with mutations most often in the NPC1 genes and sometimes in the NPC2 genes. The clinical findings vary from neonatal period to adulthood and the severity of the disease depends on the neurological involvement. The most characteristic signs are vertical supranuclear gaze palsy, cerebellar ataxia, dysarthria, dysphagia, and progressive dementia. Other common features include cataplexy, epilepsy and dystonia. Comprehensive neurological, ophthalmological evaluations and primary laboratory investigations are essential to diagnose the condition. The prognosis depends on the age of onset of the neurological manifestations. Symptomatic management of patients is most essential in these cases. This case report aims at profiling the characteristic features of the disease in a female child of 9 years and emphasizes on the utility of augmentative and alternative modes of communication.

Introduction

Niemann-Pick disease type C (NP-C) is a progressive, neurovisceral, genetic liposomal lipid storage disorder caused by mutations in the NPC1 gene and the NPC2 gene (Patterson et al., 2010). This is a very rare disease estimated to occur one in every 120,000 live births (Vanier, 2010). Approximately 95% of cases have mutations in NPC1 gene and 4% in NPC2 gene. This mutation affects individual's intracellular lipid metabolism in several tissues, including those in the brain. The age of onset, clinical presentation and the level of sphingo-myelin storage in tissues of the disease vary (Crocker & Farber, 1958). Due to varied clinical presentation, Crocker (1961) classified the disease into four types; A to D. Severe, early CNS deterioration along with substantial sphingomyelin storage in both viscera and cerebrum is considered as Type A whereas Type B exhibits a chronic course with sphingomyelin storage in only the visceral system. Types C and D demonstrates a slower course with sub acute nervous system involvement. Type D patients included those with homogenous Nova Scotia Acadian origin (restriction to a genetic isolate).

Clinical description of Niemann Pick disease type C varies including the age of onset ranging from the perinatal period to adult age. Most of the cases are reported to expire between 10 and 25 years of age, however, the lifespan of the patients can be anywhere between a couple of days to greater than 60 years of age (Vanier & Millat, 2003).

Infants with Niemann Pick disease can present with ascites (collection of fluid in the abdominal region) and liver disease and/or respiratory failure. Other neonates, without such problems of liver or pulmonary disease, exhibit hypotonia and developmental delay. The typical presentation of this disease take place in mid-to-late childhood with the slight onset of ataxia, vertical supranuclear gaze palsy (VSGP), and dementia. Gradually, child presents with dysarthria and dysphagia which disables the child making oral feeding impossible leading to aspiration pneumonia in late second or third decade of life. Adults with Niemann Pick disease present with dementia and psychiatric problems (Imrie et al., 2002; Sevin et al., 2007). Other common features include cataplexy (sudden falls), epilepsy and dystonia.

When a client presents with the most common symptoms, such as combined splenomegaly (enlargement of spleen), ataxic features, and vertical supranuclear gaze palsy (VSGP), diagnosis of Niemann-Pick disease type C can easily be made. However, clinical presentations often vary widely and hence detailed clinical investigations should be per-

formed. Abnormal saccadic eye movements (SEM), one of the earliest neurological signs in NP-C warrants an ophthalmological assessment. The initial SEM deficit is reported to be in the vertical plane (downward, upward, or both) (Abel, Walterfang, Fietz, Bowman & Velakoulis, 2009; Wraith et al., 2009). Subsequently, horizontal gaze is also affected. The neurological evaluation must include muscle tone and strength tests, motor reflexes, assessment of movement (ataxia and dystonia) and swallowing testing (Wraith et al., 2009). Psychometric assessment is also important. Wraith et al. (2009) reported that "cataplexy ranges from subtle signs (minor head-drop or falls, often confused with seizures) to full collapse in response to humorous stimuli". Audiological evaluations are reported to reveal abnormalities as may be evidenced in an audiogram and/or brainstem evoked potentials. While histological studies are reported to provide strong support to the diagnosis of the disease, MRI and CT scans are limited in their usefulness for diagnosis of NP-C. Further, specific laboratory analyses like the "filipin" test and genetic testing may be useful in identifying NP- C (Walkley & Vanier, 2009).

Miglustat (Zavesca®; Actelion Pharmaceuticals) was first approved in Europe in 2009 as a substrate reduction therapy for both children and adults with NP-C with progressive neurological deterioration. Published data on this treatment suggest that therapies that help improve swallowing function reduce the risk of aspiration pneumonia thereby reducing mortality risk of an individual. Wraith et al. (2010) reported that miglustat therapy helped in stabilizing major neurological symptoms of the disease in both adults and children.

Case Report

A nine year old female child was brought to the Speech and Hearing Center with the complaint of slurring of speech and inability to walk independently since four months. The child was reported to have developed normally till four years of age when she developed clumsiness of gait and frequent falls while walking along with inability to judge and walk over obstacles. The gait problems gradually progressed and the child lost complete mobility since the past four months. She also presented with difficulty in swallowing and choking. Family history revealed third degree consanguineous marriage of parents and the child's paternal uncle was reported to have similar problem and expired by the age of ten years. Birth history revealed full term normal delivery and the birth weight of the child was 2.5 kilograms. Neonatal jaundice was present and she was medicated for the same. Developmental history revealed slightly delayed motor and speech-language milestones. Socialization skills were good.

Earlier investigations carried out by neurologists three years prior to evaluations at the Center revealed a diagnosis of Niemann Pick Disease (Type C). Clinical examination showed positive vertical supranuclear gaze palsy, Romberg sign, bilateral finger to nose incoordination, soft and tender pelvis suggestive of no hepatosplenomegaly. Bone marrow aspiration showed normocellular marrow with normal marrow elements, and good number of large cells, with abundant foamy cytoplasm (soap bubble appearance) and peripherally pushed nucleus suggestive of Niemann Pick cells. Brain MRI and Electroencephalography showed normal study. She is under medications including Parkiledine (100mg), Evion (200mg) and Inderal (10mg) on a regular basis. Various evaluations were carried out at the Speech and Hearing Center. The details of the same are listed below.

Speech and Language Evaluation

Detailed speech and language evaluations were carried out. Kannada Language Test (Shyamala, Vijayashree & Jayaram, 2003) was administered and the language age was found to be between 4 and 5 years of age for both reception and expression. Scores for semantic language was found to be higher than syntactic language skills. However, she found it difficult to perform receptive language tasks that involved judgement (correct/incorrect responses). The child could respond correctly when the same stimuli were presented in the form of simple questions. To illustrate, in the Semantic Similarity subsection under Semantics, the stimuli to assess reception skills required the child to respond in the form of right/wrong or correct/incorrect [E.g.: anna : kudi (rice : drink) - The child was expected to say wrong/incorrect]. The child did not respond to these stimuli. However, when the same concept was asked in the form of a question [E.g.: ni:nu annana kuditi:ya? (Do you drink rice?)], she responded by saying 'No'. Similarly, in the Morphophonemic Structures subsection under Syntax, the child was unable to respond when the stimuli under reception was presented for judgment. [E.g.: manejalli : manedalli - Here, the child was expected to identify the first stimuli as correct, but was unable to do so. However, she was able to use the correct morphophonemic structures during conversation or picture description task (E.g.: akka manejalli idda:Le). She had a mean length of utterance of around 3-4 words. On informal assessment, pragmatic language abilities were found to be intact.

On oral motor and feeding evaluation, lip seal was found to be poor. Accuracy of spreading and rounding of the lips was fair. Reduced contribution of the upper lip observed for both speech and non speech tasks. Mild drooling was present. She was able to build up fairly good intra-oral breath pressure but was unable to sustain the same. Sucking was possible through neck type straw but not with other type of straws. Tongue movements were limited for bolus formation and she chewed food only on the left side

of the mouth. Hyperextension of the neck was observed during the act of swallowing. Liquids posed greater difficulty than solid food items for swallowing, thereby increasing the risk for aspiration. On administration of the Com-DEALL Oro Motor Checklist (Archana, 2008), it was found that the oro motor abilities of the child was in the age range of 1-2 years with a total score of 29, suggesting poor oro motor skills. Further, the scores obtained in individual sub sections of the checklist indicate greater difficulties in the jaw movements when compared to that of lips and tongue.

Psychological Evaluation

Psychological evaluation revealed borderline intelligence with an Intelligence Quotient (IQ) of 71. Results of Developmental Screening Test revealed a developmental age of 3 years to 3 years 6 months.

Physiotherapy/ Occupational Therapy Evaluation

Observations by Physiotherapist/ Occupational therapist support the earlier findings of ataxic dysarthria with features including wide based gait, swaying while walking, incoordination, dysmetria, difficulty in maintaining the head in the midline while performing any given task, low muscle tone and fair voluntary motor control. Activities of daily living like bowel/bladder indication were also found to be inconsistent in nature.

Neurological Evaluation

On neurological examination, vertical supranuclear gaze palsy was present (absent upward and downward movement of the eye ball) whereas, lateral eye ball movements were spared. History of frequent falls to sudden stimuli was reported by parents, which is suggestive of cataplexy. No drugs were prescribed and only supportive therapy was suggested.

Summary

To summarize, this study profiled a child diagnosed with NP-C with complaints of slurring of speech and inability to walk independently since four months. This case report offers us an excellent opportunity to study the speech-language and feeding issues in a child with NP-C. As the condition is degenerative in nature, symptomatic treatment was the only available option of management. Similarly, speech and language therapy focussed on slowing down the deterioration in communication abilities. Further, it was speculated that use of augmentative and alternative communication may help the child and the family members maintain basic communication in the course of deterioration of the disease. On these lines, three sessions of demonstration speech and language therapy were given. The major focus in speech and language therapy was introducing augmentative and alternative modes of communication. The mother was demonstrated to prepare a picture communication book for the child depending upon her interests and needs at present. The child was encouraged to use both verbal and picture book to communicate with others. Simple signs for communicating basic needs were also demonstrated. In addition, guidelines to improve swallowing function were provided in terms of food consistency, placement of food in the mouth and quantity of food for each swallow.

Speech Language Pathologists (SLP) play a key role in assessment and management of issues related to swallowing in clients with NP-C. The role of an SLP is also crucial in referring such clients to medical/paramedical professionals. Whenever swallowing through oral modes is difficult due to aspirations or the food intake is limited leading to compromised nutrition in the body, then an SLP may refer such clients to the concerned medical professionals for considering other modes of food intake (e.g.: tube feeding). SLPs may further refer them to a physiotherapist in order to maintain mobility as long as possible. Frequent follow up with a paediatrician may be suggested to deal with risks of pulmonary diseases due to increased rate of aspirations and problems with bowel movements. Genetic counselling may also be advised to gain information regarding risks to siblings, offspring and to know if the other family members are carriers of the affected gene etc. However, the effectiveness of these management options remains to be seen. Further, it may be of interest to study whether speech and language intervention, in particular, in the early stages of the disease may help maintain better communication abilities in cases with NP-C for a longer duration.

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