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Case Report

Siblings with nemaline myopathy: a case of rare genetic mutation

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ABSTRACT

Nemaline myopathy (NM) is a rare, congenital myopathy with varied clinical presentation. This case report talks about varied manifestation of this condition among siblings from same couple with a rare specific mutation at molecular level among the known mutations reported for NM. The subsequently mentioned patient had severe respiratory distress and recurrent respiratory tract infections since infant, which led to meticulous investigations and relevant family history charting. Such methods proved to be fruitful for suspecting and subsequently led to successful diagnosis of NM in the patient and aforementioned siblings. The diagnosis of NM was made with proper genetic testing, and patient was put on ventilatory support and appropriate physiotherapy for muscle weakness. Lower respiratory tract infections were treated with appropriate antibiotics and medications as and when required. To conclude this case report, advising adequate pre-conceptional genetic counselling to the couple having affected siblings with dire outcomes, which helps avoid the psychological, financial and medical demands of managing such conditions.

Keywords: Congenital myopathy, Nemaline myopathy, Nemaline rods

INTRODUCTION

Nemaline myopathy (NM) is a non-dystrophic, most common congenital myopathy with an incidence of about 1 in 50,000.[1] Nemaline myopathy is characterized by rod/thread like cytoplasmic inclusions in muscle fibers, seen on staining the muscle biopsy specimen with Gomori Trichrome stain.[2,3] The condition manifests with a wide range of varied presentations ranging from early neonatal deaths to normal life span with almost normal muscle tone.[1,2,4] The condition is now being classified based on the genetic mutations and the severity of the clinical presentations.

CASE REPORT

A 13-month-old female child presented to OPD, with reliable parents, with complaints of productive cough and cold since, 20 days, and associated with difficulty in breathing and difficulty in feeding and fever since last 7 days. The patient was admitted for investigation and treatment, undergoing routine investigations like chest X-ray and complete blood count. On further probing, parents mentioned about their visit to a private hospital before 3 days for same complaints, and was treated with antibiotics and salbutamol nebulization for treating bronchopneumonia with a total leucocyte count of 25,000; but there was no improvement of symptoms. On examination, cough was productive in nature, but not relieved with medications. The patient experienced intermittent fever with 2-3 episodes per day, which was relieved with anti-pyretics. Nasal blockage was associated with whitish-green nasal discharge. A noteworthy examination point was aspiration of milk when fed with spoon and katori (small bowl); which was reported as patient not being able to suck during breastfeeding; so, the child was given expressed breast-milk with help of spoon. Past history of the patient, as

described by the parents, was significant for 3-4 visits/admissions to different hospitals (public and private sector), for complaints of decreased limb movements, at ages of 1.5 months, 4 months, and 10 months of age. One such admission was investigated with a high clinical suspicion (with slightly elevated Creatine Phosphokinase (CPK) and normal lactate) of Spinal Muscular Atrophy type 2 (SMA), and underwent SMA-PCR, but was negative.

Developmental history

Gross motor milestone: no neck holding present (normally achieved at age of 3 months). Fine motor milestone: immature pincer grasps present (normally achieved by age of 9 months). Language milestone: speaks bisyllables (normally achieved by age of 9 months). Social milestone: waves bye-bye (normally achieved by age of 9 months).

Family history

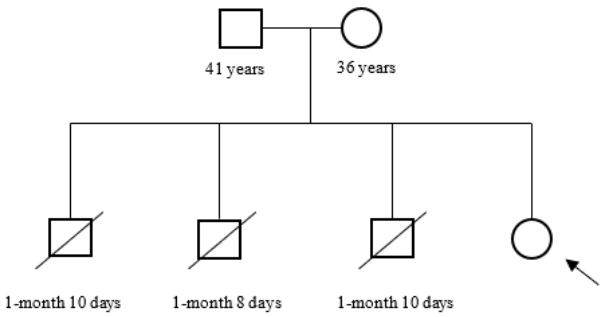

Figure 1: Two generation pedigree chart of the female child under study.

Clinical findings

Patient is tachypneic (60, normal <40), and tachycardic (150, normal 120-130) with subcostal in-drawings and bilateral crepitations on auscultation. CNS examination was significant for muscle power 0/5 in all limbs, loss of muscle tone (all major groups), and loss of deep tendon reflexes in all limbs.

Treatment

On admission, parenteral fluids, along-with antibiotics (ceftriaxone, levofloxacin, azithromycin) and nebulization (salbutamol and N-acetyl cysteine) and injectable paracetamol (acetaminophen) were given with appropriate dose and dosing, calculated based on child's weight. The patient was also put on L-tyrosine supplementation, as there have been some studies that suggest it's role in management of NM, but with little effectiveness. Patient was initially put on Continuous positive airway pressure (CPAP) mode of ventilation. Subsequently, after 3 days, patient had to be put on Synchronised intermittent mandatory ventilation (SIMV) mode. Due to prolonged duration of intubation, patient was tracheostomized to minimize complications. Patient had to be cardio-pulmonary resuscitated twice and put on inotropes, developed chicken-pox and treated with oral Acyclovir for 7 days, suffered episodes of Ventilator-associated pneumonia and bedsores due to prolonged bedrest and were managed accordingly, during the stay in hospital for almost over 19 months.

Investigations

Patient was subjected to chest X-rays when required, for pneumonia. On high clinical suspicion, the patient was tested for SMN gene mutation (for SMA), which was negative. On further investigation, ACTA1 gene mutation was positive, on whole genome, suggestive of nemaline myopathy. The variant detected was c541, p. Asp181ThrfsTer11 on exon, with heterozygosity.[4]

Belonging to a resource-limited geographical location (Bhavnagar, Gujarat, India), with lack of proper facilities, the test sample had to be sent to private laboratory at Bangalore, Karnataka, India. While suspecting some congenital myopathy, the treating team kept a whole list of all such myopathies as differentials; while subjecting the patient to whole genome testing. After the results, patient was indubitably diagnosed a case of NM, with aforementioned mutation.

Outcomes

From the available literature on this condition, and from family history of previous born siblings, we do not claim a very optimistic outcome in this patient. The condition itself has varied presentation, ranging from apparently normal lifestyle to death in early neonatal period, but on clinical assessment of this patient, it is not likely that this patient will attain a full or even satisfactory control over her muscle groups.

Patient is not able to gain sufficient muscle tone to support spontaneous breathing efforts, and thus requires permanent ventilatory support, till mortality. Additionally, owing to inherent risks and complications of such long-term ventilatory support, patient is prone to develop recurrent episodes of pneumonia (ventilator-associated pneumonia), poor speech, vocal palsy, tracheostomy site infection, bedsores from chronic bed-ridden state and others. No further diagnostic tests are required to support this condition or decide the management strategy of this patient, so avoiding any unnecessary financial and psychological drain to the parents.

DISCUSSION

Nemaline myopathy, is classified clinically into severe NM, typical NM, mild NM and distal NM.[3] The severe type of NM manifests in-utero, and is confirmed

clinically by presence of at-least one of the following; major muscle contractures, fractures, absent respiratory efforts or absent muscle movements and associated with ACTA1 gene mutation.[3] Severe form NM starts its manifestation antenatally as decreased quickening and decreased swallowing, leading to polyhydramnios.[5,6] The patient under study had multiple features suggestive of severe NM; like absent muscle movements, absent respiratory efforts, poor sucking reflex and early ventilator dependency. This condition affects the Actin (thin) filament in the muscle fibre, and as actin is present in not just skeletal muscles, but also smooth muscle fibres and cardiac muscle fibres; severity can also present itself as gastro-oesophageal reflux disease or achalasia cardia or chronic intestinal pseudo-obstruction and dilated cardiomyopathy.[5,7,8] NM can be diagnosed based on histopathological features of muscle biopsy. A characteristic finding is cytoplasmic inclusions known as Nemaline bodies/rods.[2,4,6] But, absence of these bodies cannot rule out the diagnosis of NM, variants of this condition can show core-like inclusions or cap-like inclusions or fibre-type disproportion.[2]

Genetic studies to check for specific mutations is a confirmatory diagnostic test for NM. Eleven gene mutations have been found to be associated with NM, of which NEB gene mutation is most common (encoding for Nebulin protein) and ACTA1 gene second most common mutation (encoding alpha actin) associated with NM.[3] This patient was positive for ACTA1 gene mutation on exon, which is inherited as autosomal dominant or recessive pattern.[4,9] We hypothesize it to be autosomal recessive mode of inheritance, as the parents (who both were not affected by this condition, and therefore both/one must have been a carrier of the mutated gene) had previous 3 male children who died at the age of 1 month and 8-10 days, and all had similar complaints of decreased limb movements and absent respiratory efforts.

First 2 children were put on ventilation for difficulty in breathing, and the third child succumbed to death at home for same reasons. A noteworthy hypothesis can be made from this case study, which will require further investigation and research to be proven; currently, there are no studies that talk about any gender predilection in NM, with respect to its incidence/prevalence or outcomes/prognosis; but the child under study has surprisingly out-grown her late siblings with significantly better prognosis and survival. We hypothesize, it is a possibility that severe NM (as in this case), might have better prognosis in affected females, as compared to affected males in same population. This needs to be thoroughly reviewed and researched further to establish its validity and authenticity, and might affect the treatment modalities.

The cardinal features of NM are weakness and hypotonia (and rarely, hypertonia), with maximum severity of disease seen in muscles of face and neck flexors.[2,5] This statement is supported in our case study, as observed by inability to uphold the neck on lifting the baby off the bed, from supine position even at age of 2 years (normally it is achieved by the age of 3 months). NM being a non-dystrophic myopathy, CPK levels are usually normal or slightly elevated (up to five times the normal upper limit), unlike other myopathies where CPK is a supportive finding.[2,5] This statement holds true in this patient, who had CPK value of 85 (normal upper limit is 20), along-with normal lactate values.

Recurrent respiratory infections; as evident in this patient by 3 separate hospital admissions for upper respiratory tract infection (URTI) and multiple episodes of pneumonia during the hospital stay; and respiratory insufficiency can lead to death in first weeks or months of life.[5,6,10] Patient had to be given multiple antibiotics with changing the drug regularly, to avoid risk of drug-resistance. She was given ceftriaxone, levofloxacin, azithromycin, amikacin, piperacillin-tazobactam, cefoperazone, ampicillin-sulbactam on different occasions during her stay in hospital, to combat pneumonia.

Currently, there are no treatment modalities available for curing NM, except for symptomatic management and/or ventilatory support and interventions as and when required.[2] Some studies support the role of L-tyrosine supplementation in management for NM, but isn't backed up in other studies.[3,11-13]

CONCLUSION

With such varied presentation of the condition ranging from apparently normal lifestyle with limited morbidities to early infant mortality; this patient has fortunately survived recurrent infections and severe hypotonia, and might possibly be weaned off the mechanical ventilatory support in near future. The patient made an exception from all her previous siblings, who succumbed to death in very early neonatal period; and have out-grown them with seemingly better prognosis. We expect her to lead a normal life, although associated with some minor morbidities, but managed with minimal support and/or interventions.

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