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CASE REPORT

A Case of Spinal Muscular Atrophy Type 2 in a Child: A Genetic Condition Rarely Detected in Primary Care

Siti Mariam Abu Hussain[1], Nur Amirah Shibraumalisi[1], Hayatul Najaa Miptah[1], Anis Safura Ramli[1,2]

1 Department of Primary Care Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Selangor, Malaysia
2 Institute of Pathology, Laboratory and Forensic Medicine (I-PPerForM), Universiti Teknologi MARA (UiTM), Selangor, Malaysia

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Corresponding author:
Prof. Dr. Anis Safura Ramli,
Department of Primary Care Medicine,
Faculty of Medicine,
Universiti Teknologi MARA (UiTM),
Jalan Hospital, 47000 Sungai Buloh,
Selangor, Malaysia.
Email: anis014@uitm.edu.my

ABSTRACT

Spinal muscular atrophy (SMA) is a neurodegenerative disease affecting 4 out of 10,000 live births. It is an autosomal recessive genetic condition caused by mutations of the survival motor neuron gene 1 (SMN1), located at chromosome 5q. There are five types of SMA, from Type 0 to Type 4. Depending on the types, SMA can cause severe disability and death. This case report presents a case of a six-month old baby boy with gross motor developmental regression. There was a missed opportunity to detect this case in primary care. The baby was referred by a private paediatrician to a government hospital's outpatient paediatric clinic for losing his ability to roll over, lift his buttocks, and sit without support. Genetic testing confirmed the diagnosis of SMA Type 2. Receiving the diagnosis and caring for a child with SMA is a life-changing event for the parents and caregivers. The availability of gene therapy may change the prognosis and outcome of patients with SMA and should be offered if available. This case highlights the impact of the child's illness on the family and the importance of a multidisciplinary team approach in managing SMA. Primary care physicians play a key role in conducting thorough child health surveillance to ensure early identification and providing support to the child and the parents holistically as the disease progresses into adulthood. This includes providing long-term psychosocial support to improve their quality of life.

KEYWORDS: spinal muscular atrophy, type 2, gross motor developmental delay, genetic

INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive genetic condition affecting 4 out of 10,000 live births [1]. The prevalence of SMA in Malaysia is unknown. However, data from the Institute of Medical Research, Malaysia shows that 20–30 cases of SMA were detected per year from 2013 to 2017 [2].

The mutations occur at the survival motor neuron gene 1 (SMN_1) on chromosome 5q and are most commonly due to the deletion of exon 7 [1]. All individuals with SMA have mutations in both copies of their SMN_1. The mutations lead to the reduction of SMN proteins, which in turn, causes irreversible degeneration of the alpha-motor neurons in the anterior horn of the spinal cord and motor nuclei in the lower brainstem. These nerves control the muscles for breathing, swallowing, and moving limbs [3].

However, the survival motor neuron gene 2 (SMN_2) helps to produce some of the missing SMN proteins. Therefore, the severity of the disease is very much dependent on the SMN_2 gene copies. Infants with the most severe form of the disease, known as SMA Type 0, have only one copy of SMN_2 gene, infants with SMA Type 1 usually have two or three copies of SMN_2, Type 2 have three copies of SMN_2, Type 3 have three to four copies of SMN_2, and patients with Type 4 usually have four copies or more [3]. The neuronal apoptosis inhibitory protein (NAIP) gene is adjacent to SMN genes and has been identified to be associated with SMA. Some studies have suggested that a mutation in NAIP genes is a determinant factor for a more severe type of SMA [4].

Clinically, patients with SMA present with a progressive muscle weakness and atrophy. Depending on the types, SMA can cause severe disability and death. The onset of SMA Type 1 typically occurs among babies less than six months and they are severely disabled, cannot sit or stand, and usually die before the age of two years [5]. The onset of presentation for SMA Type 2 is between the ages of 6 to 18 months. Children with SMA Type 2 need help with walking and standing and have a shortened lifespan until the adolescent stage of life [5]. Children with SMA Type 3 are less disabled and may be able to stand on their own, sometimes without help, while SMA Type 4 begins in adulthood [5]. In this report we present a case of SMA Type 2 in a child, highlight the importance of early identification to ensure timely management, and discuss the complexity of managing SMA and the importance of a multidisciplinary approach involving primary care physicians.

CASE PRESENTATION

A five-month-old baby boy was brought by his mother for his routine follow-up and immunisation at a government primary healthcare clinic in Selangor in March 2019. During the check-up by a nurse, the baby's mother, a 27-year-old clerk, raised her concern regarding her child's developmental progress. She noticed that the baby had lost his ability to roll over and lift his buttocks, despite having a normal developmental milestone prior to this. However, her concern was not addressed, and she was informed that it can be normal for some children to have a slight delay in gross motor development. The baby was planned to be seen again in one month for further assessment by a medical officer at the government primary healthcare clinic. Nevertheless, before his next follow-up at the government primary healthcare clinic was due, his mother sought for a second opinion at a private paediatric clinic as she was worried about the baby's condition. The attending paediatrician did a thorough examination and referred the baby to an outpatient paediatric clinic at a government hospital for further assessment.

The baby was seen and thoroughly assessed at the hospital's outpatient paediatric clinic at the age of six months in April 2019. According to the mother, the baby had normal gross motor development progress and had achieved full head control by the age of five months. However, he was unable to sit without support, had lost his ability to roll over from prone to supine, and lift his buttocks since the last one month. Other developmental components of fine motor, speech, language, and social skills were appropriate to his age. He was able to grasp toys given to him and put them in his mouth. He vocalised with tuneful babbles and socially, he was friendly with strangers. He had no feeding and breathing difficulties. There was no history of head trauma, prolonged fever or neonatal jaundice. His antenatal history was uneventful and there was no record of reduced foetal movement reported during pregnancy. It was the first pregnancy for this mother. Detailed scan was not done in view of low-risk pregnancy and the parents were non-consanguineous. He was born full term, weighing 3.3 kg via emergency caesarean section for foetal distress. He was well and allowed to go home at day three of life. His routine newborn screening such as cord TSH, G6PD, and newborn examination were normal. There was no family history of congenital muscle disorder. His father was a 26-year-old policeman. They lived in a low-cost apartment in an urban area. The baby was looked after by a babysitter during office hours as both parents were working.

On examination, he was alert, had no dysmorphic feature, and appeared to be well. He was floppy and was not able to be put in a stand-up position. Gross motor assessment revealed that he was able to roll sideways but failed to roll from prone to supine completely. He was also unable to sit with or without support. When pulled to sit, his head control was good. However, his back was slightly curved. There was no noticeable frog-leg posture. These findings corresponded to the ability of a four-month-old baby. Neurological examination revealed that both lower limbs were hypotonic with a muscle power of 2/5 proximally and distally. Both of his upper limbs were hypotonic with a muscle power of 4/5 proximally and distally. The tendon reflexes in the upper limbs, knee jerk reflexes, and ankle jerk reflexes were absent. There was no apparent muscle or tongue fasciculation to suggest lower motor neuron lesion. Primitive reflexes

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were not demonstrated. Hearing distraction test was normal, and the child was able to follow the toys showed to him. Examination of all other systems were unremarkable.

Baseline blood investigations including full blood count, renal profile, electrolytes, liver profile, thyroid function test, lactate, and glucose analysis were normal. Creatine kinase (CK) value was normal with a reading of 127 units/L. Special investigations to exclude Inborn Error Metabolism (IEM) study, brain MRI, and EEG were ordered to rule out metabolic disorders and seizure disorders. The provisional diagnosis at this point of time was SMA, thus genetic screening for SMA was sent. Referrals to physiotherapy, occupational therapy, ophthalmology, and otolaryngology were made for early intervention while waiting for the results to come back.

At the age of seven months old, he came for his second follow-up. His condition remained the same. His gross motor development corresponded with that of a four-month-old baby. His IEM study, brain MRI, and EEG showed normal findings. His genetic analysis came back and confirmed the diagnosis of SMA. A homozygous deletion of exons 7 and 8 of the SMN_1 gene, with SMN_1/SMN_2 copy number: 0/3 were detected. The presence of ≥3 copies of SMN_2 can be correlated with a milder phenotype of SMA [3]. Therefore, the diagnosis of an intermediate form of SMA Type 2 was made based on the child's age at the onset of presentation. Further investigations such as electromyography and muscle biopsy were not done since the diagnosis of SMA was confirmed. Both parents were informed of the serious diagnosis, complications, and prognosis of the disease. They were overwhelmed by the diagnosis as they thought the condition could be a result of some assault to the brain during delivery, even though there was no history to suggest this.

The impact of the child's illness on the family was assessed. A multidisciplinary management team involving a paediatrician, paediatric cardiologist, primary care physician, physiotherapist, and occupational therapist were arranged. Physiotherapy and occupational therapy were initiated to help him achieve maximum motor function. His cardiac function was assessed by a paediatric cardiologist as SMA could be associated with structural cardiac pathology. The child was also given a long-term follow-up at the paediatric clinic. Both parents were referred to the genetic clinic for genetic testing and counselling. They have a high chance of getting another child with a similar condition in future pregnancies. The child's debilitating illness, frequent hospital visits, and the prospect of getting another child with the same condition caused physical, emotional, and financial constraints on this young family. His mother had to quit her job to take care of him. Therefore, long-term psychosocial support to improve their quality of life and pre-pregnancy counselling were provided by the primary care physician.

DISCUSSION

This child was diagnosed with SMA Type 2 at the age of six months old. SMA Type 2 consists of 20% of the cases and it is less severe as compared to Type 1 [6]. Children with SMA Type 2 will be able to eventually sit without support albeit some delay. However, they will never be able to stand independently or walk [6]. The weakness is predominantly at the proximal muscle, and it affects the legs more than the arms. Complications due to muscular weakness may also lead to dysphagia, progressive scoliosis, restrictive lung disease, and respiratory insufficiency [6]. As a result of immobilisation, children with SMA Type 2 will be prone to develop joint contractures, ankylosis of the mandible, and bronchopneumonia [7,8]. Their life expectancy varies from 10 to 40 years old [9].

SMA is rarely detected in primary care and the diagnosis is often delayed due to the primary care physicians' inexperience in identifying the condition [10]. Early identification and referral are important to ensure timely management is initiated. It begins with screening of symptoms and surveillance of early childhood development by healthcare providers during routine child health visits. During the assessment, the pathology of muscle weakness should be identified. The origin could either be acquired centrally from the brain or peripherally (neuromuscular). Central causes usually present with global developmental delay, while peripheral causes typically present with gross motor developmental delay or regression [10]. History of

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prenatal, perinatal, or neonatal insults is suggestive of central causes, while having a family history of neuromuscular diseases may suggest peripheral causes. A thorough physical examination to assess neurological functions and developmental milestones is vital to detect neuromuscular disorders. In this case, a peripheral cause was suspected as he was floppy and exhibited areflexia, and there was no history of head trauma. Failure to reach normal developmental milestones should prompt healthcare providers to refer the child for further evaluation. In this case, the child should have been promptly referred to a Family Medicine Specialist for further assessment when the mother raised her concern during his routine immunisation follow-up at the primary healthcare clinic. Thorough assessment must be done at the primary care level and immediate referral should be made for confirmation of diagnosis and further management. Initial investigations that can be done in primary care include CK and thyroid function. A raised CK might indicate peripheral neuromuscular problems such as dystrophinopathies, but a normal CK does not rule out neuromuscular problems [10] as demonstrated in this case.

SMA is a complex condition that requires long-term multidisciplinary team management. Caring for a child with a debilitating condition such as SMA is a life-changing experience as it places huge physical, emotional, and financial burdens on the parents, families, and caregivers, which may lead to stress, anxiety, and depression [11]. The child and his family need long-term physical and psychosocial support to improve their quality of life. A co-management between the paediatrician and the primary care physician in providing long-term follow-up would be the most appropriate in this case. Follow-up by the primary care physician plays a vital role in supporting the child and the parents holistically as the disease progresses into adulthood. These include ensuring their psychosocial well-being and facilitating them in their needs as a primary care setting is more accessible as compared to a hospital setting. Parents should be offered social support from the welfare department and support groups such as Persatuan Spinal Muscular Atrophy Malaysia. The welfare department would be able to help the parents in registering the child as a disabled person or "Orang Kurang Upaya (OKU)" for the child's benefit.

With regard to the mother's future pregnancy, genetic testing for both parents is required to determine their carrier status. If one of them is a carrier, their chance of having a child with SMA is 1 in 4 [12]. Prenatal testing can be offered to couples with the carrier status, allowing them to make an informed decision on the continuation of pregnancy. If the parents decide to continue with the pregnancy, early utero referral to a tertiary centre for gene therapy is an option. This treatment involves administration of gene therapy via the umbilical cord, which is targeted at the SMN_1 gene. With this treatment, the affected foetus may have a better outcome, prognosis, and chance of recovery [13]. Another option is via preimplantation genetic diagnosis, whereby an embryo is tested for genomic abnormalities prior to implantation in the uterus [12]. However, this service is not widely available in Malaysia.

Recent advances in the treatment of SMA include development pharmacotherapies such as nusinersen (Spinraza®) and risdiplam (Evrysdi ®) [14]. These medications enhance the function of the SMN_2 gene to produce a more stable protein that is essential for body muscles' function in patients with SMA. However, they do not provide permanent benefits and are a lifelong requirement. Spinraza® is administered via intravenous injection, while Evrysdi® is consumed orally on a daily basis. The treatment costs approximately USD125,000 per dose and four doses are required per year for Spinraza®, while it costs approximately USD340,000 per year for Evrysdi ® [14]. In May 2019, another novel treatment for SMA, onasemnogene abeparvovec (Zolgensma®), was approved in America [15]. Zolgensma® is the first gene therapy indicated for SMA patients who are less than two years old, through a single intravenous injection. This therapy permanently corrects the mutations via adenovirus as a vector delivering the missing copy of the SMN_1 gene [15]. This medication costs USD2.125 million [15]. Unfortunately, these novel pharmacotherapies are not widely available in Malaysia.

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CONCLUSION

SMA is an autosomal recessive genetic condition that is rarely detected in primary care. Early identification and diagnosis are pivotal to ensure timely management. This case highlights the complexity of managing SMA and the importance of a multidisciplinary approach. Primary care physicians play a central role in early identification, prompt referral, and provision of long-term psychosocial support to the child and parents in overcoming the challenges of living with a debilitating disability. Parents need to be adequately informed on the genetic inheritance of SMA and its implications on future pregnancies. Early identification of SMA in utero can be done via prenatal testing, and gene therapy can be offered to improve foetal outcomes.

How does this paper make a difference to clinical practice?

- SMA is an autosomal recessive genetic condition that is rarely detected in primary care.
- Primary care physicians need to conduct thorough child health surveillance and developmental assessment during routine child health visits to ensure early identification and referral for confirmation of diagnosis and management.
- SMA requires long-term multidisciplinary team management.
- Primary care physicians play a vital role in supporting the child and the parents holistically as the disease progresses into adulthood.
- This includes providing long-term psychosocial support to improve their quality of life.

Conflict of Interest

Authors declare none.

Ethical Approval

Not applicable. Permission from the parents have been obtained to publish this case report.

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We would like to thank the parents for their permission to publish this case report. Unfortunately, the baby has died in 2022 at the age of 3 years old, due to aspiration pneumonia.

Authors' contribution

All authors were involved in drafting the manuscript and in revising it critically for important intellectual content. All authors approved the final version of this article.

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