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THREE SIBLINGS WITH CHARCOT-MARIE-TOOTH DISEASE WITH NO OTHER FAMILY HISTORY

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ABSTRACT

Charcot-Marie-Tooth (CMT) disease is one of the most common inherited disorders of the peripheral nervous system. Patients diagnosed with CMT disease have axonal degeneration which results in muscle wasting, sensory loss and weakness. These patients have a very characteristic walking gait and shape of hands, along with other changes. Despite many common visible changes, no singular common genetic mutation for this disease or its cure has been identified. Therefore more case series for this disease needs to be identified so that future studies increase our knowledge about this disease. Here, we present a case series of 3 out of 4 siblings who have been diagnosed with CMT disease. Based on their age, these siblings show the different developmental stages of this disease. More of such case series need to be identified and reported so that we can identify the true genetic cause of this disease and develop a definitive cure for it.

INTRODUCTION

Charcot-Marie-Tooth (CMT) disease was first described in 1886 as a peripheral nerve disorder and since then it is now believed to be one of the most common inherited disorders of the peripheral nervous system[1]. The prevalence of CMT varies significantly across different countries, from 9.7/100000 in Serbia to 82.3/100000 in Norway[2]. No study has been published from Pakistan regarding the prevalence of CMT. The number of genetic mutations associated with this disease continues to grow beyond 1000, with over 80 genes involved[3]. However, the cause of a significant types of CMT remains unknown. Whatever the origin of the disorder might be, the final common pathway is that of axonal degeneration or demyelination involving mostly the largest and longest nerves[4]. Secondary axonal degeneration may lead to disability in demyelinating CMT and may be primary process in other.

The axonal degeneration in CMT disease tends to start in the extremities and then spreads to the proximal limbs which involve muscle wasting, sensory loss and weakness[5, 6]. In the feet it is observed that there are high arches, hammer toes, muscle wasting and weakness. Ultimately there is involvement of the leg and then the lower third of the thigh, producing the typical distal atrophy of the lower limbs. At this point the hands and forearms are also affected, while the same pattern evolves to include sensory loss and reduction of the deep tendon reflexes.

Disease onset is usually in the first two decades and then there is slow progression over decades. Usually the presentation includes pes cavus (or pes planus, often later progressing to cavus deformity); hammer toes; difficulty in running; twisting of the ankle and tripping; difficulty in walking; foot drop; steppage gait; wasting, weakness, and sensory loss of distal segments of lower and then upper limbs; difficulties in hand manipulation; and reduced or absent deep-tendon reflexes[7, 8].

Currently there is no treatment available for this disease. Further studies are required to understand this rare disease and possibly develop its treatment. The discovery of more cases is extremely crucial to understand this disease and better describe its clinical features. In this case series we describe a family in which 3 out of 4 siblings have been diagnosed with CMT disease and are potential candidates for further investigation.

CASE SERIES

A family presented to Aga Khan University Hospital in May 2018 in which 3 out of 4 siblings had difficulty walking in a straight line and holding objects. The

parents of these children were first cousins, however, nobody else in the family had a history of CMT or any other type of polyneuropathy. The symptoms of each patient are described below:

CASE 1:

The eldest sibling was a 13 years old male child and presented with difficulty in walking, foot numbness, and difficulty performing daily tasks, such as shirt buttoning. The first of these symptoms, difficulty in walking, started at the age of 4 years . His birth history was normal, and early motor milestones were achieved on time. On examination there was atrophy of thenar and hypothenar muscles, poor hand grip, high stepping gait, flat feet deformity and deep tendon reflexes were diminished, however, sensory examination was normal and senses of position and vibration were intact (figure 1A and B; Supplementary video 1). No other signs or symptoms were observed. EMG/NCV study was suggestive of sensory motor polyneuropathy.

CASE 2:

The next sibling was a 9 years old girl who presented with complaints of clumsiness in walking and running and difficulty in holding objects, which had started at the age of 4 years. Her birth history was normal, and developmental motor milestones were achieved on time. On examination there was high steeping gait, flat feet, and thin legs, wasting of muscles of hand, foot, and lower leg, with diminished deep tendon reflexes (figure 1C and D; Supplementary video 1). Sensory examination was normal. EMG/NCV study was suggestive of sensory motor polyneuropathy.

CASE 3:

The youngest sibling was a 6 years old boy who presented with difficulty in walking, which had started at the age of 5 years. His birth history was normal, and developmental motor milestones were achieved on time. On examination there was atrophy of foot and hand intrinsic muscles with flat feet, and thin legs, and diminished deep tendon reflexes (figure 1E and F; Supplementary video 1). Sensory examination was normal.

The parents were informed that there is no treatment available that can cure the CMT disease, however, it has been shown that the physical and occupational therapy improves the quality of life of these patients. The parents were also counselled about the importance of foot care of their children and if required, the possibility of getting corrective surgery. Parents were also informed that since this is a genetic disorder, if they have another child the possibility of having CMT is much higher in that child than average. Therefore, they should be very careful before making the decision of having another child.

DISCUSSION:

Although CMT disease does not reduce the life expectancy of patients, it is an extremely debilitating disease. The symptoms of this disease, specially foot drop and a high-stepped gait can cause frequent tripping or falls and reduce the quality of life of patients. Since the definitive genetic cause of this disease is yet to be discovered, the treatment options remain very limited. Large scale drug trails with ascorbic acid have not shown promising results[9]. Drug trails in mutant animal model have shown effective results but these results were not replicated in human trails.

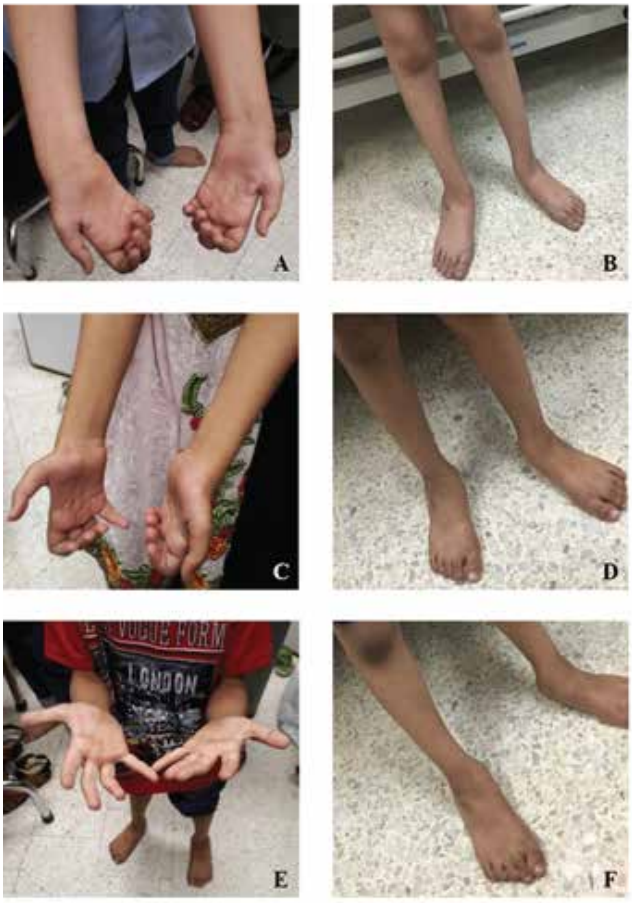
It is a strange fact that the common deficit found in all CMT disease patients is axonal degeneration involving mostly the largest and longest nerves[10], yet the number of genetic mutations associated with CMT is over 1000[2]. Therefore, it is fair to say that the true common genetic cause remains unidentified. Until this genetic cause is identified the complete pathology of CMT cannot be understood and a definitive treatment cannot be developed.

Here we have reported a case series of 3 siblings (from a family with 4 children) who have been diagnosed of CMT disease. The mere fact that the only treatment which could be advised to them was physical and occupational therapy shows how restricted our knowledge about this disease and its treatment is. More case series of this disease needs to be reported so that more avenues of research can be identified.

CONCLUSION:

Charcot-Marie-Tooth is a debilitating disease that causes difficulty in difficulty in walking, foot drop, muscle wasting and weakness, along with sensory loss of distal segments of limbs and reduced or absent deep-tendon reflexes. No treatment except for physical and occupation therapy can be prescribed for CMT patients. Here, we have reported a case series of 3 siblings diagnosed with CMT disease. Identification of this and other such case series helps us to better understand this disease and develop treatments for it by opening new venues for research.

Figure 1: Pictures of hands and legs of all three patients showing classic signs suggestive of Charcot-Marie-Tooth Disease. A, B) Pictures of hands and legs of Patient 1 shows advance stages of muscle contracture and wasting. C, D) Pictures of hands and legs of Patient 2 also show advance stages muscle contracture and wasting. E, F) Pictures of hands and legs of Patient 3 (the youngest of the 3 affected siblings) show beginning of signs of muscle contracture and wasting.



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