Case series: Childhood Charcot-Marie-Tooth: Predominance of axonal subtype

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ABSTRACT

Case series reports on clinical features of pediatric hereditary neuropathy in Thailand is scarce. Subtype and clinical presentation in childhood-onset CMT differ from adult-onset. The aim of this study is to investigate the CMT phenotype in Thai children.

We retrospectively reviewed children diagnosed with CMT who followed up with Pediatric Neurology, Siriraj Hospital from January 1999 to June 2016. CMT subtypes determined by clinical presentation and neurophysiologic studies. Mutation analysis of PMP22 genes was performed in all demyelinating cases. The disease burden was assessed by CMT Neuropathy Score version 2 (CMTNSv2), CMT Examination Score (CMTES) and CMT Pediatric Scale (CMTPedS). 30 patients from 29 families with Hereditary Neuropathies, 25 diagnosed with CMT and 5 with HSAN. 8-year-old was the average age at first medical visit with disease-related problems. Twenty (67%) were male. Twenty-three were sporadic (77%). 16.7% was autosomal dominant and 6.7% was autosomal recessive. Clinical presentations in CMT children were walking difficulty and foot deformities. Nine (36%) CMT patients had demyelinating and sixteen (64%) had axonal. Forty percent had a history of delayed walking after 15-month-old. Foot deformities presented in all CMT patients, and twelve had foot surgery. 2 axonal CMT patients were wheelchair-dependence. Mean (SD) CMTNSv2, CMTES and CMTPedS were 15.44(9), 11.05(7) and 34(4) respectively. Our findings suggest Thai CMT children are predominantly axonal type. Patients with low socioeconomic status and mild symptoms may not seek healthcare. International collaboration in genetic testing is crucial in diagnosis and initiation of clinical trials in future.

1. Introduction

Charcot-Marie-Tooth disease (CMT) is the most common inherited neuromuscular disorder affecting at least 1:2500 to 1:1200 [1,2]. Approximately 25% (423/1652) of initial CMT patients registered in the international Inherited Neuropathies Consortium were 18 years of age or less [3]. The phenotype of CMT can be categorized into 2 main types, CMT1 (demyelinating) and CMT2 (axonal), by measuring the upper limb motor nerve conduction velocities (MNCV) on median or ulnar nerve. Demyelinating neuropathy is defined as MNCV < 38 m/s and axonal neuropathy as MNCV ≥ 38 m/s [1]. With the advent of more sophisticated DNA techniques since 1991, approximately 60–70% of patients can receive precise DNA diagnosis [3,5]. Various genes linked to CMT show diverse patterns of inheritance ranging from autosomal dominant (type 1 and 2), autosomal recessive (type 4) and x-linked [6]. Much is known regarding the adult-onset, demyelinating-type CMT. It is often less severe and can be confirmed by the presently available genetic testing. However, CMT of the axonal type is known to have more severe and earlier onset of clinical presentation. Concurrently, it is suspected to be the type which often present in childhood. On the other hand, genetic diagnosis is available for only a very small subset of axonal-type CMT, making genetic confirmation in children a challenge. Children also show greater incidence of axonal peripheral neuropathy compared with adults [7]. A study from the Netherlands find a causative gene in only 17% of axonal subtype patients aged 15–72 years [8]. Children also present with more autosomal recessive forms of disease compared with adults [9]. Early and accurate diagnosis using molecular genetics will not only allow for a more precise...
implementation of genetic counseling, it will also raise awareness and interest in the prevalence of axonal-type CMT. Thus leading to treatment development. At present, Thailand is limited in its capability for genetic diagnosis of CMT and only phenotype data are available.

2. Objective

The aim of this study is to assess the clinical manifestations and neurophysiologic findings of CMT disease in Thai children.

3. Methods

3.1. Study design and patient population

This is a descriptive retrospective case series study. Children and adolescents aged 0 to 23 years with the diagnosis of Hereditary Neuropathies evaluated by clinical and nerve conduction studies (NCS) at Siriraj Hospital between January 1999 and June 2016 were included in the study. Children were excluded from this study if NCS was undetermined. Siriraj Hospital is Thailand’s largest university-based national tertiary referral center. The protocol for this study is approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand.

3.2. Procedures

Data extracted include patient history, family history of Hereditary Neuropathies, neurological examinations and results of nerve conduction studies (NCS). Patients are assigned the CMT subtypes and disease outcomes according to these data. Mutation analysis of PMP22 (duplication/deletion) and GJB1 is the only two available genetic testing service for CMT in Thailand. PMP22 copy number variation detection is done in all demyelinating cases. GJB1 gene analysis is not performed since there is no X-linked inheritance.

3.2.1. CMT disease outcome assessment measures

The disease severity was assessed by CMT Neuropathy Score version 2 (CMTNSv2) [10], CMT Examination Score (CMTES) and CMT Pediatric Scale (CMTPedS) [11]. CMTNSv2 was composed of nine assessments: symptoms (three items), signs (four items), and neurophysiology (two items). Each measurement was scored on a 0–4 point scale for a total possible score of 36. CMTNSv2 was the tool for assessing disease severity in patients aged 18 and older [10,12]. In very young infants where electrophysiology study was not possible, CMTES was used. The CMT examination score was calculated by the sum of the symptoms plus the signs in the CMTNSv2; it was therefore the CMTNSv2 without the electrophysiological testing. CMTPedS was the tool for assessing disease severity in children aged 3–20 years with CMT [13]. It consisted of 11-item scale measures of strength, dexterity, sensation, gait, balance, power and endurance. Scores ranged from 0 (not affected) to 44 (severely affected). However, because CMTPedS required special equipment not readily available to our Pediatric Neurology Service, only a subset of pediatric patients was assessed using this method in our study.

3.2.2. Clinical electrophysiology

Motor and sensory nerve conduction velocities (NCV) were performed by standard techniques. Temperature was maintained at 32 °C in the hands and feet for all patients. Surface electrodes were used in all studies. The amplitudes of the compound muscle action potential and sensory nerve action potential were recorded.

3.2.3. Statistical analysis

Data analysis was performed using PASW Statistics version 18.0 (SPSS, Inc., Chicago, IL, USA) Patient characteristics, clinical phenotypes, electrophysiology; NCV, genetic testing and CMT disease outcome measurements were summarized using descriptive statistics, presented as numbers and percentages or mean, SD and range.

4. Results

A total of 30 patients aged 3 to 23 years from 29 families with the diagnosis of Hereditary Neuropathies were identified. Demographic and familial characteristics of pediatric patients with Hereditary Neuropathies were analyzed and results were shown in Table 1. The age of patients evaluated at study time ranged from 3 to 23 years with a mean age of 16 years. Patients older than 18 years who had moved to the Adult Neurology service for follow up were also included. The age of first medical visit with disease-related problems ranged from 0 to 15 years with a mean age of 8 years. There were 7 patients with familial history of Hereditary Neuropathies (23%) 5 of which were autosomal dominant and 2 were autosomal recessive.

From 30 patients with Hereditary Neuropathies (Fig. 1), the most common diagnosis was Hereditary Sensory Motor Neuropathy (HSMN)/Charcot-Marie-Tooth (CMT). Other related diagnosis was Hereditary Sensory and Autonomic Neuropathy (HSAN).

4.1. Hereditary Sensory Motor Neuropathy (HSMN)/Charcot-Marie-Tooth (CMT)

Twenty five CMT patients were designated as demyelinating and axonal using clinical characteristic and electrophysiology (Table 2). Details on clinical characteristics of each CMT patients showed in Table 3. Nine patients (36%) were demyelinating subtype and 16 patients (64%) were axonal subtype. All patients had foot deformities, 80% were pes cavus, and the other 20% were pes planus. All patients had difficulties walking while 28% had dexterity problems. Two patients were diagnosed by sural nerve biopsy and classified as axonal subtype. None of the patients in the demyelinating subtype had dexterity problems compared to the 44% in the axonal group (p < .005). Patients in the demyelinating group also required less orthosis when compared with the axonal group (22% vs. 75%, p = .009). The mean CMTNS in axonal subtype was higher than demyelinating subtype (16.8 versus 12.7, respectively). Result of NCS is shown in Table 2. The MNCV for both Ulnar and Median are lower in Demyelinating group, however no statistical significant difference. The disease severity for children; CMTPedS (range 1–44) is measured by Professor Burns in only 5 patients. The scores were 31, 31, 33, 34 and 41.

Mutation analysis of PMP22 gene was performed in all 9 demyelinating neuropathy cases. Only one patient demonstrated PMP22 duplication. GJB1 was not performed because there was no X-linked inheritance pattern in the family history.

4.2. Hereditary Sensory and Autonomic Neuropathy (HSAN)

There were 4 total families (5 patients) evaluated for HSAN at Siriraj Hospital, 2 patients were congenital insensitivity to pain and anhidrosis

Table 1

| Characteristics          | Values                  |
|--------------------------|-------------------------|
| Male; n (%)              | 20 (67%)                |
| Age; mean ± SD (range in years) | 16 ± 5 (3–23)            |
| Age at first visit; mean ± SD (range in years) | 8 ± 5 (0–15)             |
| CMTES (n = 21)           | 11.05 ± 7 (1–28)        |
| CMTNSv2 (n = 9)          | 15.44 ± 9 (1–29)        |
| CMTPedS (n = 5)          | 34 ± 4 (31, 33, 34, 34, 41) |

Data are mean ± SD and range; CMTES: CMT Examination Score, CMTNSv2: CMT Neuropathy Score version 2, CMTPedS: CMT Pediatric Score.
and 3 patients had ulceromutilating features and sensory neuropathy.

The first family were 2 patients with family history of consanguinity. The elder brother who was the second of four children had an uneventful prenatal history except for home-birth. His development was normal. He then came to Siriraj Hospital at the age of 1 year. By 1 ½ year of age he began having chronic corneal ulcers on both eyes. And, by 3 years old, had auto-amputation of his right 5th toe. His nerve conduction study was normal. He then had his sural nerve biopsy which showed unmyelinated fibers. The other children in this family appeared normal.

The second family was a patient with diagnosis of HSAN came to the hospital early in life due to multiple congenital abnormalities. Her mother had a history of frequent spontaneous abortion. Patient’s birth history was noted for birth from a cesarean section due to incomplete breech presentation, and birth asphyxia with an APGAR score of 3, 7, 7. She was a small for gestational age child (SGA). At birth she was noted to have right cupped ear with a subsequent normal hearing test. Her course during infancy was complicated by developed constipation for which Hirschprung disease was ruled out with a normal Barium enema at 1 month of age. At 4 months old, she also passed mucous bloody stool and at 7 months she presented with tearless crying and was diagnosed with infectious keratitis and exposure keratitis. By 1 year of age she had ulcerative lips and tongue and the tip of her tongue was torn. She also had intellectual disabilities and self-injuring behavior.

The last two families were patients presented with anhidrosis. The first one initially presented with heat stroke and long bones which were easily broken and as well as hyperlaxity of knee joints. The other had a history of anhidrosis since birth and was noticed to be easily irritable by heat. None had ulceromutilating features.

5. Discussion

Our case-series study indicates that, contrary to reports from previous studies, there is a larger proportion of Thai children with CMT is of the axonal type (64%). In previously published data, Cornett et al. [14] studied 520 children and adolescents aged 3 to 20 years with CMT. They found that the prevalence of CMT subtype was CMT1A 48.5%, CMT2A 6.0%, CMT1B 2.9%, CMT4C 2.5%, and CMTX1 1.9%. Comparing to the previous genetic study in adult CMT patients by Sporta et al. [15], the prevalence of CMT subtype was CMT1A 48.5%, CMT2A 6.0%, CMT1B 2.9%, CMT4C 2.5%, and CMTX1 1.9%. Comparing to the previous genetic study in adult CMT patients by Sporta et al. [15], the prevalence of CMT subtype was CMT1A 48.5%, CMT2A 6.0%, CMT1B 2.9%, CMT4C 2.5%, and CMTX1 1.9%. Comparing to the previous genetic study in adult CMT patients by Sporta et al. [15], the prevalence of CMT subtype was CMT1A 48.5%, CMT2A 6.0%, CMT1B 2.9%, CMT4C 2.5%, and CMTX1 1.9%. Comparing to the previous genetic study in adult CMT patients by Sporta et al. [15], the prevalence of CMT subtype was CMT1A 48.5%, CMT2A 6.0%, CMT1B 2.9%, CMT4C 2.5%, and CMTX1 1.9%.
| Patient no | Gender | Age at diagnosis | Clinical features | Family history | Inherited pattern | NCS pattern | Genetics study |
|------------|--------|------------------|-------------------|----------------|------------------|------------|----------------|
| 1          | M      | 13               | Walked before 15 months, pes cavus, difficulty with walking and balance, sensation loss, burning sensation, scoliosis | No             | Demyelinating    | Negative for PMP22 mutation |
| 2          | M      | 13               | Walked before 15 months, pes cavus, difficulty with walking and balance | Yes AD         | Demyelinating    | Negative for PMP22 mutation |
| 3          | F      | 11               | Walk after 15 months, pes cavus, difficulty with walking and balance, burning sensation | No             | Demyelinating    | Negative for PMP22 mutation |
| 4          | M      | 15               | Walk after 15 months, foot deformities (toe out and foot drop), difficulty with walking and balance, sensation loss, total hearing loss | No             | Demyelinating    | Negative for PMP22 mutation |
| 5          | M      | 4                | Walk after 15 months, pes cavus, difficulty with walking, scoliosis | No             | Demyelinating    | Negative for PMP22 mutation |
| 6          | M      | 9                | Walked before 15 months, pes cavus, difficulty with walking | No             | Demyelinating    | Negative for PMP22 mutation |
| 7          | M      | 15               | Walked before 15 months, pes cavus, difficulty with walking | No             | Demyelinating    | PMP22 duplication |
| 8          | M      | 13               | Walked before 15 months, pes cavus, difficulty with walking | No             | Demyelinating    | Negative for PMP22 mutation |
| 9          | M      | 1                | Walk after 15 months, pes cavus, sensation loss | No             | Demyelinating    | Negative for PMP22 mutation |
| 10         | F      | 1                | Walk after 15 months, clubfoot since birth, pes cavus, difficulty with walking and balance, difficulty with buttons and utensils, scoliosis | No             | Axonal           | Not performed |
| 11         | M      | 7                | Walk after 15 months, pes cavus, difficulty with walking and balance, difficulty with buttons, scoliosis, sensation loss, partial hearing loss | No             | Axonal           | Negative for PMP22 mutation |
| 12         | F      | 6                | Walked before 15 months, pes planus, difficulty with walking and balance, difficulty with buttons, sensation loss | No             | Axonal           | Negative for PMP22 mutation |
| 13         | F      | 4                | Walked before 15 months, unidentified foot deformity, difficulty with walking and balance, difficulty with buttons and utensils, sensation loss, optic nerve atrophy | No             | Axonal           | Negative for PMP22 mutation |
| 14         | M      | 2                | Walk after 15 months, pes planus, difficulty with walking and balance, difficulty with buttons and utensils, burning sensation, sensation loss | Yes AD        | Axonal           | Not performed |
| 15         | F      | 5                | Walk after 15 months, pes cavus, difficulty with walking and balance, difficulty with buttons and utensils, sensation loss | No             | Axonal           | Negative for PMP22 mutation |
| 16         | F      | 8                | Walk after 15 months, pes cavus, difficulty with walking and balance, difficulty with buttons, sensation loss | No             | Axonal           | Not performed |
| 17         | M      | 4                | Walked before 15 months, pes cavus, difficulty with walking and balance, difficulty with utensils | No             | Axonal           | Negative for PMP22 mutation |
| 18         | M      | 13               | Walked after 15 months, pes cavus, difficulty with walking, scoliosis | Yes AD        | Axonal           | Negative for PMP22 mutation |
| 19         | M      | 9                | Walked before 15 months, pes planus, difficulty with walking, skin ulcers | Yes AD        | Axonal           | Not performed |
| 20         | F      | 5                | Walked before 15 months, pes cavus, difficulty with walking | No             | Axonal           | Not performed |
| 21         | F      | 12               | Walked before 15 months, pes cavus, difficulty with walking, sensation loss, skin ulcers | No             | Axonal           | Negative for PMP22 mutation |
| 22         | M      | 13               | Walked before 15 months, pes cavus, difficulty with walking, sensation loss | No             | Axonal           | Negative for PMP22 mutation |
| 23         | M      | 13               | Walked before 15 months, pes cavus, difficulty with walking, sensation loss | Yes AD        | Axonal           | Negative for PMP22 mutation |
| 24         | M      | 14               | Walked before 15 months, pes cavus, difficulty with walking | No             | Axonal           | Not performed |
| 25         | F      | 13               | Walked before 15 months, pes cavus, difficulty with walking, sensation loss, scoliosis | No             | Axonal           | Not performed |
degenerative peripheral neuropathies which occurs in this age group. This is consistent with our findings. Bienfait et al. [8] conduct a genetic analysis (gene panel for CMT2) of clinically diagnosed axonal CMT patients from 18 families. The specific genes are able to be identified in only 17% of the families.

The mean (SD) of CMTNSv2 in our study is 15.44 (9) for all CMT patients; 12.7 (6.4) for demyelinating subtype and 16.8 (10.3) for axonal subtype. Our result is similar to previous studies by Fridman et al. [3] who review 906 childhood and adult CMT cases. They find the mean CMTNS score for CMT1A is 13.7 (6.5), CMT1X is 13 (6.8), CMT2A is 14.3 (8.7), and CMT1B is 13.7 (7.7). Szy et al. [16] look at 72 adult patients with CMT1A and show a mean score for CMTNS of 13.2 (6.15).

Due to our lack of resources and equipment, the disease severity is measured by Professor Burns using CMTPedS (range 1–44) in only 5 patients. The mean score (SD) of 34 (4) is higher than previous study by Cornett et al. [14]. They review 474 children and adolescents with CMT and the mean (SD) CMTPedS total score for the entire sample was 21.5 (8.9). This indicates that Thai children with CMT have more severe symptoms. However we need to enroll more patients to measure CMTPedS and also perform the genetic testing to see clearer correlation between genotype, phenotype and disease severity score.

Currently, HSAN can be categorized into 5 main subtypes based on clinical characteristics, mode of inheritance, electrophysiological features, metabolic defects, and specific genetic markers [17]. It is known that HSAN IV is a rare autosomal disorder with estimated incidence 1 in 25,000 [18,19]. Our 5 patients with diagnosis of HSAN can be subtyped into HSAN IV by clinical presentation. The much higher incidence of HSAN among CMT children at our institution can be attributable to 2 main factors. Firstly, greater consanguinity among Southeast Asian population when compared to Westerners [20] may already contribute to this observed phenomenon by making such autosomal recessive disorder more prevalent. In addition, when looking at the higher severity at presentation compared to other population, it is possible that patients with mild disease do not seek medical attention. As a result, only severe cases come to our attention, HSAN being among the severest.

The study has several limitations in our study. The specific treatment for CMT is not yet available in Thailand, so our patients are treated with supportive care, and physical therapy. Since we performed in a single center with small population, the result of the study couldn’t represent the whole CMT population in Thailand, thus we presented with this case series study. However, with interesting result of axonal predominate, the future study with multiple centers in Thailand would yield more information and analytical results. Also our study showed small number of patients with family history, this could be explained due to the low medical literacy in our population and less severity of disease might deceived as normal healthy family members.

6. Conclusion

Clinical presentations and molecular genetic of Hereditary Neuropathies are diverse. For most patients especially in developing countries, diagnostic studies are limited to clinical assessment. Clinical presentations including onset of symptoms, presence of scoliosis, sensory and autonomic involvement, respiratory compromise, upper limb involvement, visual or hearing impairment, pyramidal signs and mental retardation can be used to identify specific subtypes. These clues may assist in targeted genetic testing and aid in the diagnosis of children where DNA testing is not possible. An international collaboration in genetic testing is crucial to the identification of phenotype-genotype correlation for a better understanding of the disease and future clinical therapeutic trials.

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Ethical approval

This protocol for this study was approved by the Siriraj Institutional Review Board (SIRB).

Contributors

OS and SL conceptualized, designed, and coordinated the study. TP and CL provide genetic work up data. AT reviewed patient charts, collected data, participated in statistical analysis, wrote the first all subsequent drafts of the manuscript, and approved the final manuscript as submitted. TP participated in data entering. OS supervised data collection, participated in statistical analysis, critically revised the manuscript, and approved the final manuscript as submitted. CL, TP and SL critically revised the manuscript and approved the final manuscript as submitted.

Declaration of Competing Interest

All authors declare no conflicts of interest.

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