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Clinical and Electrophysiological Spectrum of Inherited Neuropathies in Children: Experience in a Tertiary Neurology Hospital in a Country with Limited Resources

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Authors' contributions

This work was carried out in collaboration among all authors. Author BD designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Author MEH reported author NCS and managed the literature searches. Authors RNC and NS managed the analyses of the study. All authors read and approved the final manuscript.

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ABSTRACT

Background: Inherited neuropathy is a group of common neurologic disorders with heterogeneous clinical presentations. The study aimed to evaluate the clinical and electrophysiological profiles of children with inherited neuropathies and categorize them under various inherited neuropathies considering the clinical and electrophysiological parameters.
Study design: This was a hospital-based retrospective observational study.
Place and duration of study: The study was taken place in the department of Neurophysiology at a

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tertiary care hospital in Bangladesh. The duration of the study was three years, from January 2018 to December 2020.

Methodology: A total of 38 children with inherited neuropathies aged 0-17 years were included in the study. Considering the clinical, electrodiagnostic data, and other investigation reports obtained by review of medical records, we categorized the patient as having hereditary neuropathy affecting primarily the peripheral nervous system (PNS) and neuropathy as a part of other neurologic or multisystem disorders. Charcot-Marie-Tooth disease (CMT) was further divided depending on the electrophysiological findings.

Results: Among 38 enrolled children, 52.63% were male. Their mean age at the time of enrollment was 8.69 ±3.55 years. Family history of the same type of disease was found in 13.16% of cases and consanguinity was present in 15.79% of cases. Most of the children (78.95%) had neuropathy primarily involving the PNS. CMT1 (44.74%) was the most frequent phenotype among all inherited neuropathies, followed by CMT2 (18.42%). Frequently observed clinical findings of CMT include weakness (92.86%), small muscle wasting (78.57%), reduced or loss of deep tendon reflexes (96.42%), and foot deformities (57.14%). Only five patients received a definite genetic diagnosis.

Conclusions: The clinical spectrum of inherited neuropathies is diverse. Electrophysiological studies remain a powerful diagnostic tool in the evaluation of children with peripheral nerve disorders. Although CMT was the most frequent phenotype, neuropathy associated with other neurologic or multisystem disorders is not rare.

Keywords: Inherited neuropathy; children; nerve conduction study; peripheral nerves.

1. INTRODUCTION

The peripheral neuropathies (PN) are a heterogeneous group of disorders of the peripheral motor, sensory, and autonomic nerves. Broadly, it can be classified as acquired and inherited. Clinical features may overlap and distinction is often difficult. In children, PN differs from those present in adults because of the inclusion of a far greater number of inherited conditions. They are frequently underdiagnosed or misdiagnosed. This discrepancy is even more marked in infants with peripheral neuropathy [1]. A large prospective study observed that approximately half of the patients referred to peripheral neuropathy clinics have an unrecognized inherited cause [2]. Early recognition of peripheral neuropathies is important for accurate genetic diagnosis and counseling.

Inherited neuropathy is a group of common neurologic disorders with heterogeneous clinical presentations and genetic causes with an overall prevalence of 1:2500 [3]. The hereditary forms of peripheral neuropathies include Charcot-Marie-Tooth disease (CMT, also called hereditary motor sensory neuropathy, HMSN), the hereditary sensory and autonomic neuropathies (HSAN), the hereditary motor neuropathies (HMNs), and hereditary neuropathy with liability to pressure palsy (HNPP) [4]. These are non-syndromic disorders primarily or predominantly affecting the peripheral nervous system (PNS). However, many subtypes can be complicated by additional neurologic and non-neurologic features. There is also some overlap with neurometabolic (e.g., Refsum's disease, adrenoleukodystrophy, Krabbe's disease, Mitochondrial disorder), syndromic (e.g., Waardenburg–Shah's syndrome) and neurodegenerative disorders (e.g., motor neuron disease, spinocerebellar ataxia), where PNS involvement is a part of a more complex pathology [4].

The clinical spectrum of inherited neuropathies is diverse. Distinguishing inherited from acquired etiologies are often difficult, especially in the absence of recognized family history. Therefore, detailed clinical examination, nerve conduction studies (NCS), electromyography (EMG), laboratory test findings, and nerve biopsy can help in the identification of these inherited conditions. In recent years, the use of next-generation sequencing (NGS) has led to the identification of many previously unknown genes and genetic defects that cause neuropathy. However, diagnosis is often complex. The decision of which genetic test to order is often complicated, and the strategies to maximize the value of testing are evolving. Despite the wide range of genetic testing, treatment remains mainly supportive. In this study, we aimed to evaluate the clinical profile of patients with hereditary neuropathies. NCS was done in all cases and other laboratory tests were also performed when indicated. As genetic tests are

not often possible in our resource-limited setting, we tried to differentiate various inherited neuropathies considering the clinical and electrophysiological parameters. These may help further which genetic tests should be offered first.

2. MATERIALS AND METHODS

This hospital-based retrospective observational study was conducted in the Department of Neurophysiology at a tertiary neurology hospital in Bangladesh. Patients were referred to this department for electrodiagnostic (EDX) studies all over the country. We reviewed the medical records of 38 patients aged 0-17 years with hereditary neuropathies between January 2018 and December 2020. The hospital database was searched for to identify all children clinically having the features of hereditary neuropathies, and a separate NCS and EMG database was searched for all NCS and EMG which pointed towards inherited neuropathies. All this data was reviewed together to confirm the diagnosis of various inherited neuropathies. The inclusion was based on clinical and electrodiagnostic (EDX) criteria.

2.1 Clinical Clues for Inclusion

The clinical criteria for suspected hereditary neuropathies were children having a positive family history, early-onset disease, slowly progressive course, symmetrical, distal deficits, and no diagnostic clues for an acquired polyneuropathy or a genetic syndrome [4]. Clues and signs from a physical examination may include the following: (1) foot drop (2) high arches and hammertoes (3) inverted champagne bottle appearance of the legs (4) valgus or varus deformity with ankle-foot weakness; (5) recurrent painless foot ulcers; (6) palpable large nerves (7) refractory response to the treatment of acquired disease; and (8) major sensory loss without positive sensory symptoms [5]. Additional neurological and non-neurological findings were also noted when present. Children with a history of radiation or chemotherapy, known toxic exposure, or vitamin deficiency were excluded from the study. Patients having missing data were also excluded from the study.

2.2 Electrophysiological Criteria for Inclusion

Chronic, symmetrical involvement of peripheral nerves in electrophysiological studies in a clinically suspected patient was considered as having hereditary neuropathy. Suspected patients with HSAN were also included in the study even when the NCS findings were within the normal limit.

2.3 Procedure and Interpretation of Electrophysiological Studies

NCS of both upper limb (median and ulnar nerves) and both lower limbs (tibial, peroneal, and sural nerves) were done in all patients using the Neuropath S1 machine by Nihon Kohden. EMG was also done but not in all cases. In motor nerve conduction study (MNCS), distal latency (DL), amplitude and duration of compound muscle action potential (CMAP), conduction velocity (CV), conduction block (CB), and temporal dispersion (TD) were recorded. F wave was recorded in Median, Ulnar, and Tibial nerves where minimal latency was measured after supramaximal stimulation and identifying 10 F-waves in each motor nerve. In the sensory nerve conduction study, peak latency, sensory nerve action potential (SNAP) amplitude, and velocity were measured. EMG findings were interpreted as neurogenic(spontaneous fibrillation at rest, long-duration polyphasic MUAPs, decreased interference pattern), myogenic (low amplitude, polyphasic, short-duration MUAPs with early interference pattern) or normal according to standard criteria. When clinical findings were associated with chronic, symmetrical involvement of peripheral nerves in EDX studies, patients were considered as having hereditary neuropathy. Based on the electrophysiologic studies CMT was classified into demyelinating (CMT1), axonal (CMT2), and intermediate forms. The usual electrodiagnostic finding in demyelinated inherited neuropathies is widespread uniform slowing of conduction velocities and absence of CB and TD [5,6]. If EDX studies showed only a distal, symmetrical axonal pattern of motor nerve involvement in a clinically suspected patient, then it was categorized as HMN.

We classified CMT disorders into the following forms, according to the pattern of the damage/injury [5].

1. **Demyelinating:** CMT1, motor nerve conduction velocity of the nerves in the arm <38 m/s
2. **Intermediate:** motor nerve conduction velocity of the nerves in the arm 38 – 45 m/s
3. **Axonal:** CMT2, loss of CMAP amplitude and/or needle EMG denervation, a motor

nerve conduction velocity of the nerves in the arm >45 m/s.

The socio-demographic, clinical, and investigation profiles were entered in a predesigned questionnaire. Based on the clinical, electrodiagnostic data, and other investigation reports obtained by review of medical records, we categorized the patient as hereditary neuropathy affecting primarily PNS or neuropathy associated with other neurologic or multisystem disorders. Data were analyzed using SPSS version 20. Continuous data were presented as means and standard deviations whereas categorical data were presented as proportions. The study was approved by the ethical review committee of the hospital and informed written consent of the hospital authority was taken before starting the study.

3. RESULTS

We enrolled 38 patients (mean age 8.69±3.55 years; male 20, female 18). Most of the children were presented in late childhood and adolescence. The majority of them were from rural (39.47%) and semiurban (34.21%) areas and belonged to lower (34.21%) and middle (44.74%) socio-economic backgrounds. Consanguinity of marriage between parents was present in 15.79% of cases and 13.16% of cases other members of the family were affected (Table 1).

Table 1. Socio-demographic profile of the studied population

Variables	Number (%)
Age on presentation	
mean ± SD (years)	8.69 ±3.55
Range (years)	2-16
Age groups (years)	
1-5	9 (23.68)
6-10	16 (42.11)
11-17	13 (34.21)
Sex	
Male	20 (52.63)
Female	18 (47.37)
Habitat	
Rural	15 (39.47)
Semiurban	13(34.21)
Urban	10 (26.32)
Socio-economic condition	
Lower	13 (34.21)
Middle	17 (44.74)
Higher	8 (21.05)
Bold as Socio-economic condition	6 (15.79)
Consanguinity	5(13.16)

Table 2. Frequency distribution of hereditary neuropathies based on clinical and electrophysiological findings

Variables	Number (%)
Inherited neuropathies involving primarily PNS	**30 (78.95)**
CMT	28 (73.68)
Demyelinating (CMT1)	17 (44.74)
Axonal (CMT 2)	7 (18.42)
Intermediate	4 (13.16)
HMN	1 (2.63)
HSAN	1 (2.63)
Inherited neuropathies associated with other neurologic or multisystem disorders	**8 (21.05)**
Giant axonal neuropathy	1 (2.63)

Variables	Number (%)
Hereditary spastic paraplegia with neuropathy	1 (2.63)
Spinocerebellar ataxia with neuropathy	1 (2.63)
Metachromatic leukodystrophy	1 (2.63)
Friedreich`s ataxia	1 (2.63)
Mitochondrial disorder	1 (2.63)
Not specified	2 (5.26)

Based on the clinical and electrodiagnostic findings, we categorize the patients into two groups. Most of the children (78.95%) had neuropathies that primarily involved PNS. CMT1 (44.74%) was the most frequent inherited neuropathies followed by CMT2 (18.42%) and Intermediate form (13.16%). We found one child with HMN and one with HSAN. In this study, 21.05% of children were found to have peripheral neuropathy associated with other neurologic and non-neurologic findings (Table 2). Among them, two cases could not be specified further.

In this study, most of the patients with CMT presented with weakness (92.86%) and wasting of small muscles of the limbs (78.57%) with reduce or loss of deep tendon reflexes (DTRs) (96.42%). Foot deformities were observed in 57.14% of cases and only 7.14% of cases had a hearing impairment. Only 6 (15.79%) patients had sensory complaints. One patient with HSAN presented with pain insensitivity, anhydrosis, and skin Ulcer. EDX showed a demyelinating, axonal, or mixed pattern in CMT cases whereas NCS was within the normal range in a patient with HSAN-IV (Table 3).

Table 3. Clinical and investigation findings of inherited neuropathies involving primarily PNS

Variables	Clinical features	Investigation findings
CMT	Weakness and wasting of limbs Reduced or loss of DTRs Foot deformities Developmental delay Ataxia Sensory disturbances High steppage gait Hearing impairment Scoliosis	NCS and EMG – CMT1 – Demyelinating CMT 2 – Axonal Intermediate – Mixed pattern
HMN	Weakness of limbs Wasting of small muscles of feet and hands Reduced DTRs	CPK – 145 U/L NCS and EMG- Motor axonal polyneuropathy
HSAN-IV	Developmental delay, pain insensitivity, anhidrosis, skin ulcer	NCS and EMG- Normal

Table 4. Clinical and investigation findings of inherited neuropathies having other neurologic or non-neurologic features

Name of the disease	Clinical features	Investigation findings
Giant axonal neuropathy	Distal limb weakness and muscle wasting Ataxia Kinky hair	MRI of the brain- Cerebellar atrophy NCS- Axonal pattern sensorimotor polyneuropathy
Hereditary spastic paraplegia with neuropathy	Weakness of lower limbs Reduce ankle reflexes, Plantar response-Extensor, Clonus-present	MRI of dorsal spine- Normal NCS- Axonal type of sensorimotor polyneuropathy
Spinocerebellar ataxia with neuropathy	Ataxia, dysarthria, reduced DTR with upgoing plantar response	MRI of the brain- Atrophy of brainstem and cerebellum NCS – Sensory axonal neuropathy
Metachromatic leukodystrophy	Developmental delay, ataxia,	MRI of the brain –

Name of the disease	Clinical features	Investigation findings
	reduced tendon reflexes, nystagmus, Planter response - Extensor	Leukodystrophy NCS – Sensorimotor polyneuropathy of demyelinating pattern
Friedreich`s ataxia	Ataxia, decreased deep tendon reflexes with an upgoing plantar response, absent position, and vibration sense.	MRI of the brain – Cerebellar atrophy NCS – Sensory neuropathy of axonal type
Mitochondrial disorder	Microcephaly, developmental delay, dystonia, seizure, hypotonia, reduced ankle reflex.	MRI of the brain – Cortical atrophy, non-specific leukopathic change CSF- Increased lactate NCS- Sensorimotor axonal neuropathy
Not specified	Microcephaly, developmental delay, seizure, ataxia, hyporeflexia,	MRI of brain- normal NCS – Sensorimotor axonal neuropathy

Table 5. Hereditary neuropathies confirmed by genetic analysis

Diagnosis	No. of cases	Genes identified
CMT1A	2	PMP22 duplication
CMT4F	1	PRX (-)
HSAN	1	NTRKI
Intermediate CMT	1	PLEKHG5(-)

Among the studied children, only 8 (21.05%) patients had neuropathy not primarily affecting the PNS. They were diagnosed based on clinical and other investigation profiles. However, a definite diagnosis was not possible in 2 cases (Table 4).

Among the studied population, only 5 of the 38 children (13.16%) received a specific genetic diagnosis. Two children revealed duplication at 17p11.2 containing the PMP22 gene and were diagnosed as CMT1A (Table 5).

4. DISCUSSION

Peripheral neuropathy refers to a disorder of the PNS affecting axons, myelin, and/or Schwann cells. Peripheral neuropathy becomes increasingly prevalent with advancing age [7]. Although peripheral neuropathy is less common in children, a wide range of disorders are associated with this disease like hereditary, metabolic, inflammatory, and acquired causes. Guillain-Barre syndrome is the most common acquired neuropathy in children [8]. The prevalence of inherited peripheral neuropathy in children is near about 0.2% [9]. and 30 to 70% of all cases of pediatric peripheral nerve disease are due to hereditary neuropathies [10,11]. CMT is the most common inherited disease of the human peripheral nerve [12].

In this study, we reviewed 38 children aged 0-17 years with inherited neuropathies. Their mean age during enrolment of the study was 8.69 ±3.55 years, among them 52.63% were male and 47.37% were female. The literature stated that most hereditary neuropathies present during the first two decades of life [6]. The majority of the inherited neuropathies are transmitted as autosomal dominant (AD) traits, although X-linked and autosomal recessive (AR) forms also exist. Apparent sporadic patients are common and due to de novo mutations [13]. In Northern Europe and the United States, AD inheritance is exponentially more common than AR. However, in populations where consanguinity is more frequent, such as in Mediterranean and Middle Eastern regions, AR inheritance is much more common [14]. Our study found the same type of disease among other family members of the patient in 13.16% of cases, whereas consanguinity was present in 15.79% of cases. However, the pattern of inheritance is difficult to assess as phenotypic variation is high in hereditary neuropathies.

In this study, most of the children (78.95%) had neuropathy primarily involving the PNS. CMT

was found in 73.68% of all cases in which CMT1 was the most frequent phenotype. Two patients of HMN and HSAN were also categorized. Friedman et al in a study observed that among 1652 cases of hereditary neuropathies CMT1 (55%) was the most common followed by CMT2 (14%), CMTX (7%), HMN (3%), and HSAN (3%) [15]. Among 38 children, 8 (21.05%) had features of other neurological and/or non-neurological findings along with peripheral neuropathy. They were reviewed further considering clinical, imaging, and other laboratory parameters. A specific diagnosis was not possible in 2 cases. The pathophysiology of peripheral neuropathy in neurometabolic and neurodegenerative disorders is even more complex and remains unknown in many disorders [16-21].

There is a wide range of heterogeneity in the presentations of many of the hereditary neuropathies even in a single family. Patients may become symptomatic in early infancy or at an advanced age [1]. In early-onset disease, motor developmental milestones can be delayed [8]. In this study, only 23.68% of cases presented within 5 years of age, and most of them had a motor delay and hypotonia. Despite phenotypic variability, the typical clinical course of many patients with CMT includes normal early developmental milestones followed by gradual weakness and sensory loss during the first two decades of life. DTRs are typically hypoactive or absent very early in the disease course. Foot deformities (most often pes cavus) can be an early sign and may be the only manifestation in mildly affected patients [4]. Sensory complaints are unusual in the pediatric age group and clinical sensory testing under the age of 6 to 7 years is often difficult and unreliable [8]. The literature reviewed that the disorder may also be associated with neuropathic pain, skeletal deformities, deafness, cognitive deficits, tremor, impaired speech, and dysphagia [3]. In this study, most of the CMT patients presented to us with weakness and wasting of limb muscles. Reduce or loss of DTRs was found in almost all the cases. Pes cavus deformities were found in half of the cases. Only 6 patients complained of neuropathic pain and hearing impairment found in only 2 cases.

Electrophysiological examination is a fundamental step in the diagnostic process of peripheral neuropathy. It allows for the classification of CMT into demyelinating (CMT1) and axonal (CMT2) forms. The standard cut-off for demyelinating motor nerve conduction velocity (MNCV) is 38 m/s in the upper extremities. Axonal forms (CMT2) exhibit MNCVs greater than 45 m/s but should have a decrease in compound muscle action potential (CMAP) amplitudes. Conduction velocities are performed in the upper limbs because CMAP amplitudes are often unobtainable in the legs due to either conduction failure or secondary axonal degeneration [5]. CMT1 can be classified further based on CV [13]. Considering the electrophysiological findings, this study revealed demyelinating (CMT1), axonal (CMT2) and intermediate forms of CMT in 44.74%, 18.42%, and 13.16% of cases respectively. In a German cohort, the proportion of CMT1 to CMT2 was 2:1 [22]. Some patients and families cannot be designated as a demyelinating or axonal pattern and are classified as intermediate CMT as in our study. In a study, it has mentioned that the majority of patients having EDX findings in the intermediate range have a mutation in *CMTX1* [23]. Nerve biopsy was not done in any patient in this study.

In the study, we found a boy of 2 years 6 months old who presented with developmental delay, hypotonia, skin ulcer, anhydrosis, and insensitivity to pain. NCS parameters were within normal limit and later he was diagnosed as HSAN IV confirmed by the genetic study. The literature stated that in HSAN, a loss of the sensation of pain may be the main clinical symptom, with subsequent or consequent injuries and painless fractures, and type IV is associated with anhydrosis and mental retardation [24]. Another 13-year-old boy was diagnosed as HMN as he had distal limb weakness, wasting, and distal motor axonal neuropathy on NCS.

CMT, HMN, and HSAN are genetically highly heterogeneous with close to 100 different genes involved [4]. We usually offer genetic tests to all suspected patients but all cannot afford it. Moreover, we have to send the sample to the neighboring countries and it costs nearly 400 US Dollars. We offered genetic tests based on the clinical and EDX findings. Two of our suspected CMT1 cases were offered for quantitative analysis of PMP22 copies and HSAN gene panel was done in one patient. In this study, a definite genetic diagnosis was possible only in five children. Two children had duplication of the PMP22 gene; mutation in PRX, PLEKHG5, and NTRKI gene were noted in patients having CMT4F, Intermediate CMT, and HSAN respectively. However, providing an accurate

diagnosis in hereditary neuropathies is important for patients and families, although no causal therapy is currently available for any subtype [4]. The correct diagnosis puts an end to the stressful search for the cannot helps to prevent known complications and provide appropriate genetic counseling. EDX provides a clue which genetic test should be done first. Now the most efficient diagnostic algorithms for the molecular diagnosis of CMT are based on clinical and electrophysiological data [25]. The application of molecular genetic tests to some specific inherited peripheral nerve disorders has provided complementary information to EDX studies. Quantitative analysis of PMP22 copies is the obvious first-tier analysis in patients with a diagnosis of CMT1. For those with CMT2 and HMN, Sanger sequencing of MPZ, GJB1, and MFN2 should be considered as the next step. When HSAN is suspected, HSAN gene panel should be done. If all these tests are negative, then whole exome or genome sequencing should be done [4].

5. CONCLUSIONS

The diagnosis of hereditary neuropathy in a child who resides in a resource-poor setting is based on history and clinical findings. EDX studies remain a powerful diagnostic tool in the evaluation of children having peripheral nerve disorders. Most of the children reviewed in this study were presented in late childhood and adolescence. CMT was the most frequent inherited neuropathy where CMT1 was found more common than CMT2. The genetic diagnosis was possible in few cases. Considering the clinical and electrophysiological parameters we may point towards a specific genetic test and that will be more appropriate in a country with limited resources.

6. LIMITATIONS

The study has few limitations. It was a single-center study and sampled size was small. The inclusion of a larger number of patients and more genetic tests would have given a clearer picture and reflect the actual scenario.

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This research project was not funded by any group or any institution.

CONSENT

Written informed consent was taken from the parents or guardians before inclusion in the study.

ETHICAL APPROVAL

Ethical clearance from the ethical review committee (ERC) of the hospital was taken before starting the study.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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