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Peripheral nervous system (PNS) manifestations of Chediak-Higashi Disease (CHD)

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Abstract

Introduction—Chediak-Higashi disease (CHD) is a rare autosomal recessive disorder with hematologic, infectious, pigmentary, and neurologic manifestations. Classic CHD (C-CHD) presents in early childhood with severe infectious or hematologic complications unless treated with bone marrow transplantation (BMT). Atypical CHD (A-CHD) has less severe hematologic and infectious manifestations. Both C-CHD and A-CHD develop neurological problems.

Methods—Eighteen patients with CHD (9 A-CHD and 9 C-CHD) underwent electrodiagnostic studies as part of a natural history study (NCT00005917). Longitudinal studies were available for 10 patients.

Results—All A-CHD patients had either sensory neuropathy, sensorimotor neuropathy, and/or diffuse neurogenic findings. In C-CHD, 3 adults had sensorimotor neuropathies with diffuse neurogenic findings, and 1 adult had a sensory neuropathy. The 5 children with C-CHD had normal electrodiagnostic findings.

Discussion—CHD can result in sensory or sensorimotor neuropathies and/or a diffuse motor neuronopathy. It may take 2–3 decades for the neuropathic findings to develop, since children appear to be spared.

Keywords

Chediak-Higashi Disease; peripheral neuropathy; neurodegeneration; peripheral nervous system; genetic disorders

Introduction

Chediak-Higashi disease (CHD, OMIM#214500) is a rare autosomal recessive disorder due to a defect in the lysosome trafficking regulator protein (*LYST*) (1–3). The resultant lysosomal dysfunction has a detrimental effect on many end organs. The most lethal and early manifestations are recurrent severe infections and hemophagocytic lymphohistiocytosis (HLH), a lymphoproliferative disorder referred to as an “accelerated

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phase.” Variable degrees of oculocutaneous albinism and a bleeding tendency are also associated with the diagnosis. The presence of neutrophils with giant inclusion bodies is universally present and is pathognomonic for CHD. Neurologically, both CNS and PNS problems are prevalent, though cognitive decline, parkinsonism, and cerebellar ataxia are the most debilitating. In classic CHD (C-CHD), recurrent severe infections and transformation into an “accelerated phase,” often results in early demise, usually within the first decade. Bone marrow transplantation in patients with C-CHD has allowed survival into adulthood. Atypical CHD (A-CHD), observed in about 15% of patients, has a milder phenotype and is generally spared severe infections and the “accelerated phase”. A-CHD may go undetected until an incidental blood smear containing abnormal neutrophils is observed, or during evaluation of unexplained neurodegeneration in the second or third decade. The severity of disease, classic versus atypical CHD, may be determined by the type of allelic mutation in *LYST* (4). C-CHD gene defects are associated with either loss of function or protein-null alleles, while A-CHD patients may be heterozygous with at least 1 missense mutant allele that encodes for proteins with partial function (5).

Both C-CHD and A-CHD are prone to develop a similar spectrum of neurologic disorders. CNS manifestations of CHD include progressive cognitive decline, basal ganglia dysfunction with resultant parkinsonism, and cerebellar ataxia. PNS manifestations include peripheral neuropathy and amyotrophy. PNS manifestations of C-CHD were initially recognized in the late 1960s with the description of an 11 year-old girl with CHD and a lymphoreticular malignancy who developed progressive weakness and areflexia (6). Nerve biopsy showed massive cytoplasmic inclusions that were likely large lysosomes. Later autopsy studies on the same patient and 3 other children with C-CHD showed lysosomal and lipofuscin granules in dorsal spine ganglia, Schwann cells, astrocytes, nerve cells, and capillary endothelium. These peripheral nerves also showed widespread lymphohistiocytic infiltrations with axonal and myelin sheath degeneration (7), though it is not clear if these were a manifestation of the “accelerated phase”. Now that patients with C-CHD are frequently treated with BMT, which greatly diminishes the hematologic and infectious complications of the disease, they are surviving into adulthood (8). Interestingly, the peripheral and central neurological complications of CHD become more apparent as these patients enter their second and third decades (9). A-CHD patients are generally diagnosed later in life and survive into adulthood with a much reduced risk of “accelerated phase” or life threatening infections. As a result, A-CHD patients are not likely to undergo BMT. However, just like the C-CHD BMT patients, the A-CHD patients develop PNS and CNS neurological complications in later life (10, 11). In A-CHD, sural nerve biopsy showed loss of myelinated and unmyelinated fibers with no evidence of demyelination on teased fiber and electron microscope examination that were concluded to be an axonal neuropathy (11). Muscle biopsy in another A-CHD case showed neurogenic changes with fiber type grouping and atrophic fibers with acid phosphatase positive granules in the muscle fibers (12).

In this paper, we present a summary of the electrodiagnostic findings of 18 patients with CHD, 9 with A-CHD and 9 with C-CHD. This represents the largest longitudinal study of PNS manifestations of CHD. Three detailed clinical cases highlight the spectrum of peripheral nerve manifestations observed in CHD. Prior clinical and molecular studies have been published for some of these patients (13–15).

Methods

Subjects

Patients were evaluated under clinical protocol 00-HG-0153 “Investigations into Chediak-Higashi Syndrome and Related Disorders” (NCT 00005917) approved by the National Human Genome Research Institute (NHGRI) Institutional Review Board. Written informed consent was obtained from all patients, including assent for children over the age of 7, when appropriate. The patients underwent multimodality assessment including clinical, genetic, functional, and electrodiagnostic evaluation. Many patients were evaluated serially, at yearly or more intervals.

Clinical Neurophysiology Studies

Nerve conduction studies were performed using standard methodology on a Nicolet Viking Select or EDX machine (Cardinal Health, Dublin, OH) and were compared to department-based normative values, included in the Supplementary Table S1, available online. In general, the median and sural sensory nerves and the fibular and median motor nerves were tested, though the specific selection of nerves depended on clinical status. Needle EMG was performed using a concentric needle and filter settings of 2k–10K with spontaneous and motor unit potential activity recorded according to standard methodology. When EMG was performed, it was generally limited to 2–3 muscles. Needle EMG was not well tolerated by several of the patients, thus information from this modality is limited. Active neurogenic changes in this study were marked by the presence of fibrillation potentials and positive sharp waves (fibs/psw) with or without the presence of chronic repetitive discharges (CRDs). Chronic neurogenic changes in this study was marked by the presence of long duration and/or high amplitude motor unit potentials with possible polyphasia. Generally, decreased recruitment was observed in the presence of neurogenic changes but was not specifically commented on in the tables.

Results

Of the 18 patients evaluated with electrodiagnostic studies, 9 had A-CHD, and 9 had C-CHD (Table 1). Eight C-CHD patients had received BMTs. One C-CHD (C9) was atypical in his clinical presentation, since he survived into his 30s without life-threatening infections or the accelerated phase; however his gene and protein studies were consistent with C-CHD, as he was homozygous for a nonsense mutation with no *LYST* protein produced. He never received a BMT but developed HLH at age 34 and succumbed to the disease. Based on the molecular and cell biologic findings and HLH presentation, he has been classified as C-CHD. Three representative patients, 2 with A-CHD and 1 with C-CHD, are described in further detail below.

Patient 1 (A4) was a 26 year-old Caucasian man who has A-CHD with parkinsonism and mild cognitive deficits. He was diagnosed with CHD at age 8 months. His clinical course was significant for frequent infections. At age 21, he began to develop progressive distal leg weakness and was noted to be areflexic. He subsequently has required bilateral ankle-foot orthoses for ambulation. In addition, his family reports decreased cognitive capacity. His

initial electrodiagnostic studies, at age 26, showed low sural sensory nerve action potential (SNAP) amplitude (3 μ V) and normal fibular compound muscle action potential (CMAP) amplitude (2.9 mV) (Figure 1). Two years later, the sural SNAP could not be recorded, the median SNAP remained normal (19 μ V), and the ulnar (11 μ V) and radial (8 μ V) SNAPs were low amplitude (details can be found in Supplementary table S2). Within 1 year, his right median CMAP abruptly decreased from 5.1 mV to 1.0 mV with clinical evidence of thenar atrophy. Three years later, the left median CMAP decreased from 9.6 mV to 2.3 mV. By comparison, the fibular CMAP recorded from the extensor digitorum brevis only gradually decreased from 2.9 mV to 1.3 mV over a 6 year period, and the ulnar CMAP remained stable. The motor and sensory conduction velocities were all normal, even in the low amplitude responses. For the motor nerve conduction studies (NCS), the fibular distal latencies became prolonged (5.3 ms to 7.4 ms) as the amplitude decreased, but other distal latencies and F-wave latencies were normal. Needle EMG studies, limited to leg muscles on the initial exam, showed active denervation with the presence 2+ fibrillation potentials/positive sharp waves (fib/psw) in the tibialis anterior and 4+ fib/psw in the medial gastrocnemius but not in the vastus lateralis. There were also mild chronic neurogenic changes with long duration motor unit potentials (MUPs) and polyphasia in tibialis anterior and medial gastrocnemius. MUPs were not evaluated in the vastus lateralis, and he did not tolerate further EMG testing. His younger brother (A5) showed similar findings though less severe.

Patient 2 (A8) was a 38 year-old man of South Asian descent with A-CHD who presented in his late 20s with parkinsonian features of rigidity and masked facies. He had mild cognitive deficits but was still working. On exam, he was noted to have spastic paraparesis and parkinsonism. He had a thin body habitus, but no isolated muscle atrophy or fasciculations were noted. On electrodiagnostic studies, he had normal CMAP (fibular 7.7 mV, median 12.9 mV) and SNAP (sural 13 μ V, median 55 μ V, ulnar 31 μ V, radial 33 μ V) amplitudes. The conduction velocities, distal latencies, and F-wave latencies were also normal. The needle EMG study showed mild active denervation in medial gastrocnemius and tibialis anterior with 1–2+ fibs/psw. Chronic neurogenic changes were noted on exam with the presence of high amplitude, long duration MUPs in the tibialis anterior, vastus lateralis, but less evident in the medial gastrocnemius, and first dorsal interosseous, and triceps. The biceps did not have large MUPs but was mildly fibrotic on insertion. Fasciculation potentials were also observed in the tibialis anterior and first dorsal interosseus. Studies performed 1 year later did not show any change. He has a 43 year-old sister with A-CHD (A7) who has parkinsonism and reported cognitive decline since age 30. She also presented with a spastic paraparesis and became wheel-chair restricted, although strength in her arms was generally preserved. Her electrodiagnostic studies showed low amplitude or nonrecordable CMAPs (fibular – NR, tibial 0.4 mV) and SNAPs (sural – NR) in the legs but normal potentials (median motor 7.1 mV, median sensory, 46 μ V, ulnar 22 μ V, radial 22 μ V) in the arm. The needle EMG showed active denervation with the presence of 2–4+ fibs/psw in the tibialis anterior, vastus lateralis, triceps brachii, and a year later also the biceps brachii. CRDs were observed the second year in the tibialis anterior and vastus lateralis. Chronic neurogenic changes with large MUPs and some polyphasia were observed in all muscles sampled. On the third year of evaluation, only the trapezius was sampled and showed large MUPs without

fibs/psw. A third sibling, a 33 year-old man (A10), with A-CHD also had difficulties with ambulation. However, he had a severe lumbar A-V fistula that likely caused a polyradiculopathy. The siblings were not the product of a consanguineous relationship, though both parents were from the same region in Pakistan. The 2 patients, A8 and A7, have consanguineous relationships with their first cousins. Their children are not known to have clinical manifestations of CHD.

Patient 3 (C3) is a 30 year-old woman with C-CHD, who had BMT at age 10. She had a history of learning difficulties, though she completed high school and received an AA degree. At age 8, she developed the “accelerated phase” and was treated successfully. At age 10, prior to BMT, she had an episode of quadriplegia with complete recovery. At age 25, she developed progressive bilateral foot drop. On neurological exam, she had bilateral leg weakness with greater weakness in distal leg muscles and normal upper extremity exam. She had diminished pinprick and vibration sensation in both distal legs. She was areflexic except for 1+ at the biceps. Her gait was wide-based and slow. On NCS, she had nonrecordable sural and low median (9 μ V), ulnar (8 μ V), and radial (5 μ V) SNAPs (Figure 2). The conduction velocities were slow (39 m/s) for only the median and ulnar sensory nerves. Her fibular and tibial CMAPs were nonrecordable, but they normal in the median (7.3 mV) and ulnar (6.9 mV) motor nerves. After 4 years, her median CMAP (2.4 mV) also became abnormal. Her median distal latency became prolonged (4.3 to 5.9 ms), and the conduction velocity also gradually slowed (50 to 38 m/s). This may have represented a local median nerve entrapment at the wrist, as there was no other electrophysiological evidence of a demyelinating disorder. The sensory SNAP amplitudes and conduction velocities did not change much during the follow-up periods. Initial needle EMG showed active neurogenic changes with 1–2+ fib/psw and CRDs in the medial gastrocnemius. Chronic neurogenic changes with large MUPs were noted in the vastus lateralis, medial gastrocnemius, and biceps brachii. Some connective tissue replacement was noted in the vastus lateralis. Four years later, needle EMG of only the biceps brachii and deltoid muscles showed active denervation with 1–2+ fibs/psw and chronic neurogenic changes with large MUPs.

A summary of the 3 patients shows either a pattern of progressive distal weakness with axonal sensorimotor neuropathy (Patient 1, A4), diffuse muscle weakness with a motor neuropathy or neuronopathy (Patient 2, A8, A7), or a possible combination of both length-dependent sensorimotor neuronopathy and more diffuse motor neuropathy/neuronopathy. Summary of the clinical and electrodiagnostic findings of all the A-CHD and C-CHD patients are presented in Tables 2 and 3 with specific details of the serial EDx findings (motor and sensory amplitudes and EMG findings) presented in Supplementary Tables S2 and S3.

For the A- CHD cohort, there were 7 men and 2 women with a mean age of 27.4 years (range 17–43) at the time of initial study. All patients received follow-up evaluations for 2–7 years (Table 2). The most common clinical finding was areflexia; 6 patients were completely areflexic, and 3 had absent ankle reflexes only. Five patients had progressive leg weakness, and 3 patients had leg weakness followed by arm weakness. Coexisting neurological entities included parkinsonism (4 patients), cerebellar ataxia (2 patients), and most had cognitive impairment. On initial evaluation with nerve conduction studies, 3 patients (A1, A3, A4) had

electrodiagnostic evidence of an axonal sensory polyneuropathy with low or absent sural SNAPs. During the follow-up period, 3 patients (A2, A5, A6) had decrease or loss of their sural SNAPs, and 2 patients (A2, A4) had decrease in fibular CMAPs. Needle EMG was performed on the 9 A-CHD patients and showed neurogenic abnormalities in 6 (A4–A9). The 3 patients with normal EMG had very limited sampling of muscles and were only examined once or twice early in follow-up. At the end of the follow-up period, only 1 patient (A1) had an isolated sensory neuropathy without additional abnormal electrodiagnostic findings, and she did not develop distal weakness. Four patients (A6, 8, 9), including the patient with an A-V fistula (A10), had normal NCS but evidence of chronic neurogenic changes by needle EMG. Three patients, with either abnormal motor and sensory NCS (A4, A7) or only low amplitude SNAPs (A5), had neurogenic changes on needle EMG. Two patients, 1 with low CMAP and SNAP amplitudes (A2) and the other with only low amplitude SNAPs (A3), had normal EMG findings, but the study was limited to 1 distal leg muscle sampled in an early visit. Both of these patients, a sibling pair, worsened clinically over the subsequent 7 years, particularly the older brother. For the NCS, the conduction velocities, distal latencies, and F-wave latencies, in general, were normal and did not suggest a demyelinating process. Overall, the findings in these 9 patients showed varying degrees of a combination of length-dependent polyneuropathy and a possible motor neuronopathy.

Of the 9 C-CHD patients, there were 4 adults (mean 26.0 years, range 21–31 years) and 5 children (mean 4.8 years, range 4–5 years). Three adults (C2, C3, C6) were initially evaluated 18–22 years post-BMT. The 4th adult (C9) was not treated with BMT. Patient C3 had serial studies over 4 years, and patient C2 was seen twice during a 5 year period. The 3 older patients (C3, C6, C9) had hypo- or areflexia and bilateral leg weakness. The 21 (C2) year old patient only had areflexia on the initial exam, but at age 25 developed mild distal weakness and ataxia. On initial electrodiagnostic exam, the 2 oldest patients (C3, C9) had absent sural SNAPs with low upper extremity SNAPs. The lower extremity CMAPs were either not recordable (C3) or low amplitude (C9) but normal in the upper extremity. Follow-up studies for patient C3 were performed 5 years later and showed that the median CMAP had decreased by 70%, but the ulnar CMAP remained stable. Patient C6 had absent sural SNAPs with low upper extremity SNAPs but CMAPs. There were minor abnormalities in the conduction velocity, distal latency, and F-wave latencies which did not suggest a demyelinating disorder. All 3 patients had evidence of active and chronic neurogenic changes on needle EMG. The 21 year old (C2) patient only had nerve conduction studies performed; they were normal initially, but the sural SNAP became abnormal 5 years later. On clinical exam, the children had normal peripheral neurological exam, though they had mild cognitive deficits or speech delays. The 5 children had normal NCS, and 3 had normal needle EMG studies.

Discussion

This study presents the long-term PNS sequelae in a large cohort of patients with CHD from both classic and atypical forms. In many cases, CNS manifestations of CHD appear to precede clinical signs of peripheral neuropathy; however, both A-CHD and C-CHD patients develop PNS manifestations by their second or third decades. The longitudinal NCS demonstrate a very gradual decrease in SNAP amplitude while motor NCS may be

punctuated with relatively acute loss of amplitudes, such as in the case of the median motor nerve in the first patient described above (patient A4). The most common PNS finding is a length-dependent sensory or sensorimotor polyneuropathy. This generally occurs in the clinical setting of areflexia and progressive distal leg weakness. Both A-CHD and C-CHD patients may also develop diffuse chronic neurogenic abnormalities that likely reflect a motor neuronopathy. The diffuse neurogenic findings were more frequently observed in the older individuals who clinically showed signs of both UE and LE weakness. The 5 children with C-CHD did not show signs of neuropathy or neuronopathy in keeping with the observation that it takes several decades for the PNS findings to become clinically apparent. Also, the fact that only the adults who had BMT developed neuropathy and not the children with BMT, suggests that the neuropathy is related to a degenerative process and is not related to conditioning regimens with chemotherapeutic agents given prior to BMT in childhood.

It would be interesting to know whether an association exists between a specific type of CNS disorder and a particular pattern of PNS abnormalities. Of the 4 A-CHD patients with parkinsonism, 3 appeared to have diffuse chronic neurogenic findings, and only 1 had mild neurogenic findings in a distal muscle. Two A-CHD patients with cerebellar ataxia had sensorimotor neuropathies, but the data from the needle EMG was too limited to determine the extent of neurogenic abnormalities. The A-CHD patient with only a sensory neuropathy developed mild cerebellar symptoms after 6 years of follow-up and did not appear to have evidence of a motor neuronopathy. In the C-CHD patients, the 3 with chronic neurogenic abnormalities did not have evidence of parkinsonism, although 2 had evidence of incoordination. Overall, these observations are not sufficient enough to determine an association between specific CNS and PNS manifestations of CHD.

The particular genotype-phenotype correlation within the *LYST* gene may also play a role in determining certain predilections for specific types of neurologic impairment. A genotype-phenotype correlation exists in the 2 mouse models of CHD. The *beige* mouse closely mirrors C-CHD with pigment dilution, enlarged granules within multiple cell types, including leucocytes, and granulocyte dysfunction (16, 17), but it lacks neurologic manifestations. The second mouse model, *Lyst^{Ing3618}/Lyst^{Ing3618}*, created through ENU mutagenesis, is homozygous for a missense mutation (18). This model has a predominant neurologic phenotype with blunted pigment dilution, but lack of immunologic defects. This model more closely recapitulates the A-CHD phenotype. Unfortunately, in human CHD, a specific correlation between mutation types and neurological phenotype has not been made, except that A-CHD is more likely to be associated with missense mutations.

Beige mouse and human CHD cells are shown to have defective lysosomal exocytosis and membrane repair (19) which may result in gradual accumulation of toxic substances within the cell. This results in oxidative injury to the cell and neuronal cell death. Additionally, the aberrant accumulation of lysosomes interferes with the extensive membrane trafficking essential to neuronal viability and axonal transport mechanisms (20, 21). Early reports of biopsies that showed profuse lymphohistiocytic infiltrates led to the impression that there was an inflammatory response(7). These cases are likely limited to patients in the midst of

the “accelerated phase” rather than the adult patients with either post-transplant C-CHD or A-CHD.

In C-CHD, BMT allows for the correction of hematologic abnormalities related to lysosomal transport. It does not inhibit the ongoing injury of neuroglial cells within the PNS and CNS. Likewise, A-CHD is not spared the long-term sequelae of neurologic injury. Except for 1 case report in which prednisolone was used to treat peripheral neuropathy (22), there are no effective treatments for the neurological complications of CHD. Overall, the PNS manifestations of the CHD are less debilitating than those in the CNS but may provide a convenient method of monitoring future treatments.

CHD is a rare disorder that is important to consider in patients who present with PNS involvement such as distal motor and sensory impairment/or foot drop. This is especially true if systemic disease features such as oculocutaneous albinism, pigment dilution, excess bleeding immune deficiency, and/or neurological problems, including early onset parkinsonism or cerebellar ataxia, are present. Diagnostic work-up would include examination of the peripheral blood smear for neutrophils with giant inclusions and genetic testing of the *LYST* gene. For classic CHD, BMT is a serious consideration to prevent the HLH, or the “accelerated phase”, although one should understand that BMT does not appear to prevent future CHD-related neurological deficits. Currently, there is no effective targeted treatment to mitigate the ongoing nervous system involvement of CHD. There is a symptomatic response to L-Dopa for those patients with parkinsonism. Comprehensive rehabilitation and orthotics may provide substantial benefit for those with significant peripheral nervous system impairment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

A-CHD	Atypical Chediak-Higashi Disease
C-CHD	Classic Chediak-Higashi Disease
CHD	Chediak-Higashi Disease
BMT	Bone marrow transplant
NCS	Nerve conduction studies
MNCS	motor NCS
SNCS	sensory NCS

EMG	Electromyography
A-V fistula	Arterio-venous fistula
LYST	Lysosome trafficking regulator protein
CNS	Central nervous system
PNS	Peripheral nervous system
UE	Upper extremity
LE	Lower extremity
HLH	hemophagocytic lymphohistiocytosis
Fibs/psw	Fibrillation potentials and positive sharp waves
CRD	chronic repetitive discharges
SNAP	sensory nerve action potential
CMAP	compound muscle action potential
MUP	motor unit potential

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A. Motor nerves

B. Sensory nerves

Figure 1.

Serial nerve conduction studies for A-CHD subject (A4).

Six year follow-up of an A-CHD patient (A4). A. Serial amplitudes (mV) from MNCS of the fibular, tibial, median, and ulnar motor nerves. B. Serial amplitude (μV) from SNCS of the sural, median, ulnar, and radial sensory nerves.

A. Motor nerves

B. Sensory nerves

Figure 2.

Serial nerve conduction studies for C-CHD subject (C3).

Four year follow-up of a C-CHD patient (C3). Serial amplitudes (mV) from MNCS of the fibular, tibial, median, and ulnar motor nerves. B. Serial amplitude (μV) from SNCS of the sural, median, ulnar, and radial sensory nerves.

Table 1

Demographics

	Number	Age at Initial Evaluation Mean (range)	Gender
Atypical CHD	9	27.4 (17–43)	7M,2F
Classic CHD	9	14.2 (4–31)	4M,5F
CHD-Total	18	21.8 (4–43)	11M,7F

Table 2

Atypical Chediak-Higashi Disease – Electrodiagnostic Findings

	Gender, Age (1 st visit)	Neuro sx onset (age)	Years f/u	Neuro Findings	Sensory SNAP	Motor CMAP	Needle EMG
A1	F, 24	26	4	Areflexic, recent mild imbalance	Low sural *	Normal	NI distal leg
A2 ^a	M, 22	21	7	Areflexic, distal weakness & sensory loss, ataxia	Low sural *	Low fibular *	NI distal leg #
A3 ^a	M, 17	21	7	Mild distal weakness, mild rigidity & tremor, cognitive decline	Low sural *	Normal	NI distal leg #
A4 ^b	M, 26	21	6	Areflexic, arm/leg weakness, parkinsonism, cognitive decline	Low radial & ulnar, sural NR	Low fibular & median *	AN/CN in proximal & distal LE
A5 ^b	M, 23	23	6	Areflexic, mild distal weakness	Low radial, ulnar, sural	Normal	AN/CN in distal LE
A6	M, 21	20	5	Areflexic, distal leg weakness, parkinsonism, cognitive decline	Normal	Normal	Mild CN in distal LE
A7 ^c	F, 43	30	3	Hyperreflexic except absent ankle DTR, Arm/leg weakness, parkinsonism, cognitive decline	Sural NR, median nl	Fibular NR, Low tibial, median nl	Distal AN & diffuse CN In UE & LE
A8 ^c	M, 38	28	2	Hyperreflexic except absent ankle DTR, parkinsonism, cognitive decline	Normal	Normal	Distal AN & diffuse CN In UE & LE
A9 ^c	M, 33	23	3	Progressive leg weakness, Lumbar AV fistula	Normal	Normal	AN, CN in LE only

^a Siblings-family 1,^b Siblings-family 2,^c Siblings-family 3

* Decreased from normal values in the course of follow-up studies.

Only one muscle sampled during an early visit

Abbreviations: AN – active neurogenic changes, CN-chronic neurogenic changes, LE – lower extremity, UE - upper extremity, DTR – deep tendon reflexes, AV – arteriovenous, NR – no response, sx – symptoms, CMAP – compound motor action potential, SNAP-sensory nerve action potential.

Table 3

Classic Chediak-Higashi Disease – Electrodiagnostic Findings

	Gender, Age	BMT age	Neuro sx onset age	Neuro Findings	Sensory SNAP	Motor CMAP	Needle EMG
C1	M, 5	10 & 18 mo	-	Normal neuro exam, mild cognitive deficit	Normal	Normal	nd
C2 ^a	F, 21	3 yo	25	Areflexic, (trace incoordination & (distal LE weakness age 25)	Low sural [*]	Normal	nd
C3 ^b	F, 30	10 yo, accelerated phase age 7	25	Distal LE weakness & sensory loss, ataxia, cognitive loss	Low median, ulnar, radial, & sural NR	Borderline low median & ulnar, fibular & tibial NR	AN & CN in UE & LE by age 33
C4	M, 5	8 mo	-	Normal neuro exam w/mild speech delay	Normal	Normal	nd
C5	F, 5	20, 24, & 25 mo	-	Normal neuro exam, Mild cognitive deficit	Normal	Normal	NI
C6	M, 22	6 mo	21	Areflexic, Decreased distal LE strength and sensation	Low ulnar, radial, & sural NR	Normal	AN & CN in distal LE, CN in proximal LE
C7	F, 5	20 mo	-	Normal neuro exam, mild cognitive deficit	Normal	Normal	NI
C8	F, 4	6 mo	-	Normal neuro exam, mild cognitive deficit	Normal	Normal	NI
C9	M, 31	-	27	Areflexic, distal weakness, ataxia, cognitive decline	Low median, & sural NR	Low fibular	AN/CN in distal LE

^a Patient C2 - Evaluated twice in 5 year span.^b Patient C3 – Evaluated serially over 4 years^{*} Decreased from normal at first study

Abbreviations: AN – active neurogenic changes, CN-chronic neurogenic changes, LE – lower extremity, UE- upper extremity, NI – normal, nd – not done, NR – no response, CMAP – compound motor action potential, SNAP-sensory nerve action potential.