Expression of genetic peripheral neuropathies in South African Children

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Abstract

Genetic peripheral neuropathies are described in European ancestries, with a population prevalence of 1:2500-1:10000. However, these diseases are under-reported and poorly understood in African populations. Definite, probable and suspected genetic peripheral neuropathy cases, were characterized from children based in an African setting. A hospital based retrospective cross-sectional study was conducted through a referral neuromuscular disease centre in South Africa. Diagnostic work-up consisted of clinical, neurophysiology, where available histology and genetics screens. Of 63 recruited children, 19 % had definite (genetic confirmed) and 81% probable (neurophysiology and or histology confirmed) hereditary causes for neuropathy. Of the 63 individuals, 12 (19 %) were of African, 26 (41 %) Mixed, 24 (38%) European, 1(2%) Asian ancestry. 52% were females. Twelve with genetic confirmation consisted of seven CMT1A (*PMP22 dup*), two *IGHMBP2*, one *MFN2*, one *SLC12A6* and one *SLC52A3.* Most children had axonal type of neuropathy (79.4 %): affecting African 11/12, Mixed 17/26, European 21/24 ancestries. Axonal neuropathy is the most common genetic neuropathy manifesting in children of African ancestry in South Africa. CMT1A was not identified in children of African ancestry.

Keywords : Genetic Peripheral Neuropathies, African, Children, CMT

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Introduction.

Globally, an estimated 2-7% of adults and children suffer from acquired and hereditary peripheral neuropathy (1). Genetic peripheral neuropathies are well described in European ancestries, with a population prevalence of 1:2500 -1:10000. In variance, these diseases are under-reported and poorly understood in African populations (2).

Charcot Tooth Marie (CMT), the commonest hereditary peripheral neuropathy, is estimated to affect 9.7–82.3/100,000 individuals in the European population (1). The true prevalence of CMT in children from low to middle income countries is not well defined with only a few reports from North and South Africa (3). CMT is a significant cause of morbidity and mortality and the many types of CMT are distinguished by age of onset, inheritance pattern, co-morbidities, severity and pathology for degree of axonal or demyelination or both (4). Common presenting symptoms in children and adults include weakness and muscle atrophy affecting the distal extremities, scoliosis; sensory dysfunction, visual or hearing impairment; respiratory compromise; impaired speech and dysphagia; and less frequently structural changes of the central nervous system with pyramidal signs and intellectual disability (4-6).

The dawn of next generation sequencing (NGS) has expanded and simplified the diagnostic yield of genes or molecules associated with CMT. In 2018, Magy *et al* proposed a gene-based classification of inherited neuropathies which includes a list of CMT-associated genes and correlation with the alphanumeric classification (7). An additional advantage of the Magy classification system is that a patient's findings can be described in terms of mode of inheritance, neuropathy type and gene. In European populations, autosomal dominant CMTIA is the most common genetic subtype, followed by X-linked CMT (CMTX) (8). In countries that have high consanguinity rates such as the Mediterranean basin and North Africa, autosomal recessive (AR) forms may account for 30 -50 % of all CMT types (2).

The few studies from Africa suggests that the predominant genes in patients with CMT are different from those identified in European populations (9-11). In a review by Yacolye *et al*, 11 genes (*LMNA, GDAP1, PMP22, MTMR2, MTMR13, Cx32/GJB1, PRX, MPZ, FGD4/FRABIN, SH3TC2*, and *GARS)* were associated with CMT in African ancestry patients, and in variance to European countries, there was a lower proportion of *PMP22*-associated variants (2).With several promising therapies for CMT on the horizon it is essential to maintain accurate databases of the children with hereditary neuropathies across all regions to inform the scientific community on the burden of confirmed cases and more pertinently to understand regionally expressed gene variants that should be prioritised for disease modifying therapies (12-14. The study's objectives were to describe the demographics, clinical phenotype, neurophysiological, histological and where available genetic variants, of children with highly suspected or confirmed CMT at the Red Cross War Memorial Children's Hospital (RCWMCH) neuromuscular disease service. By exploring whether the genetic variants, neurophysiological and phenotypical characteristics of children with Charcot Marie Tooth, from the Western Cape of South Africa, are different from those described elsewhere, will enable future directions for research and ideally targeted disease-modifying treatment options.

Materials and Methods:

This was a hospital based retrospective descriptive cross-sectional study conducted at the Red Cross War Memorial Children's Hospital (RCWMCH), a tertiary referral and teaching hospital located in Cape Town, South Africa. As part of standard practice, a database of diagnosis and demographics of all patients managed through the neurology service has been recorded since 2001 (n= 8850 by end 2023). From this database, patients with neuromuscular disorders (n=691) were identified and a subgroup with peripheral neuropathies were enrolled to this study. The neurological service at RCWMCH offers neurophysiological assessments, genetic counselling, limited genetic screening, and liaises with other multi-disciplinary departments for nerve biopsy and histology/ immunohistochemistry confirmation of peripheral neuropathy disorders. Peripheral neuropathy diagnosis was based on clinical phenotype, nerve conduction studies, family history and where available histology and the limited genetics screens (mainly *CMT1A)*. All patients (< 18 years old) who attend the clinic at RCWMCH with clinical signs suggestive of genetic peripheral neuropathy as the main or presenting co-morbidity were enrolled.

Children were defined with genetic peripheral neuropathy in-line with the following criteria:

Typical clinical appearance (5)*:*Distal muscle weakness and or atrophy, foot drop, pes cavus, high stepped gait, scoliosis, curled toes or fingers, tremor. Additional features included nerve pain (burning, shooting, stabbing, stinging), hearing loss, vocal cord paralysis, optic nerve atrophy, bulbar palsy, cold hands and feet, and woolly hair.

Muscle strength was manually evaluated using the standard medical research council scale MRC (15). Sensory involvement (in verbal children) was assessed in terms of the site and severity of pain, crude touch, vibration proprioception sense, hearing and visual impairment.

The Charcot–Marie–Tooth Neuropathy score-version 2 (CMTNS) was used to estimate disease severity and clinical disability) in children aged 3–18 years (16). Disability was classified according to CMTNS scores as mild (less than 10), moderate (11–20) or severe (>20).

The phenotypical type of CMT was assigned based on the presence of sensory and/ or motor symptoms of peripheral neuropathy and or a family history of a similar condition. Sensory and/or motor neuropathies were also diagnosed based on the presence of loss of joint position, vibration sense ,impairment of pain or temperature appreciation, weakness and atrophy as well as decreased deep tendon reflexes at the Achilles tendon and autonomic system impairment. Nerve conduction studies were reviewed to confirm and categorise neuropathy in most patients (axonal versus demyelinating versus mixed). Patients without a family history whose clinical history and electrophysiological findings were consistent with hereditary peripheral neuropathy were also included. In order to limit misclassification bias, further review of patients' clinical phenotype, family history, neurophysiological assessment, nerve biopsy histology/ immunohistochemistry confirmation of peripheral neuropathy and where available genetic results, was done by the RCWMCH team of paediatric neurologists until a consensus on the diagnosis was reached. Where possible attempts were made to reach the families telephonically to assess progress of clinical symptoms. The clinical phenotypes for CMT were assigned wherever possible under CMT1, CMT2,CMT3/4, CMT5 hereditary neuropathy with liability to pressure palsy HNPP and if possible, for subtype of CMT (CMT1A, CMT1B, etc) (17,18).

Neurophysiology: CMT1 (type 1, demyelinating motor and sensory neuropathy) characterized by loss of myelin and nerve conduction velocities (NCVs) below 38 m/s in patients with mature median motor nerve (19).

CMT2 (type 2, axonal degeneration motor and sensory neuropathy) primary effect axonal degeneration with patients showing normal or slightly reduced NCVs (> 38 m/s) and reduced amplitudes in patients with mature nerves.

CMT3 (demyelinating motor and sensory neuropathy with symptom onset in the first two years of life and extremely slow nerve conduction; median motor nerve conduction velocities of 12m/s or less) (19).

CMT4 (autosomal recessive demyelinating / autosomal recessive axonal form, is usually more severe than other forms of CMT and symptoms may arise in early infancy with hypotonia or may manifest in later with toe walking (20).

Intermediate type (I-CMT) Individuals demonstrating signs of both demyelination and axonal degeneration, with NCVs between 25 and 45 m/s (17).

Histopathology: features suggestive of axonal and or demyelination on light microscopy, and where available electron microcopy (21 -23).

Final confirmation: where available, patients were further categorised as:

- Confirmed CMT: A patient with a definitive genetic test result.
- Probable case: A patient with clinical signs suggestive of CMT, with neurophysiological and histology findings compatible with peripheral neuropathy
- Suspected CMT: A patient with clinical signs suggestive of CMT but no other supporting data.

Convenience sampling methods were used to enrol historical cases listed in the neurology database and those currently accessing the NMD clinic.
Inclusion criteria: All patients with adequate information for definite, probable or suspected genetic peripheral neuropathy (n=63), were included**.**
Exclusion criteria: Patients with acquired peripheral neuropathy; metabolic, mitochondrial and neurodegenerative disorders (unless the peripheral neuropathy was the dominate clinical feature eg Riboflavin Transporter Deficiency (RTD)) and patients with inadequate medical information recorded.
Figure 1 summarises the patient recruitment flow diagram.
A standardized data collection tool was be used to collect the following information from the registry (see supplementary material).

i) Socio-demographic data (age, sex, ethnicity, area of residence) and clinical data (weight, height, head circumference, blood pressure)
ii) Clinical features specific to peripheral neuropathy
iii) Clinical markers that might assist categorisation e.g. optic atrophy, scoliosis, bulbar dysfunction, unusual hair (woolly) etc
iv) Laboratory results
v) Neurophysiology
vi) Histology results
vii) Genetic results (where available)

Primary study outcome was the proportion of Axonal vs Demyelinating neuropathy which as secondary variables was compared to patient ancestries and the specific genetic results.
The patients were de-identified from the data collection tool and then entered onto REDCap. To ensure confidentiality, unique numerical identifiers were used. The Statistical Package for Social sciences (SPSS) version 28 was used for quantitative analysis. Descriptive statistics including frequencies and means were generated and reported in tables and figures. Any associations were explored using the Chi-square or Fisher exact test. Results were considered significant when p-values were equal to or less than 0.05.
This study proposal was approved by the University of Cape Town Faculty of Health Science Human Research and Ethics Committee HREC REF 572/2022.The data analysis was in combinations of findings and not in a form that permitted individuals to be identified. Affected children were already attending the neurology service and had written consent attained from their parents and where possible assent from the children themselves for the study data collection. The study did not require additional interventions to the children and did not result in any additional cost to the hospital or the parents of the affected children.

Results

Of the 63 individuals compatible with hereditary peripheral neuropathy: 12 had a confirmed genetic cause, 50 probable and 1 suspected. Of those with a confirmed genetic cause, 12 (19%) were of African, 26 (41 %) Mixed, 24 (38 %) European, 1(2 %) Asian ancestry. 52% of the 63 children were females.

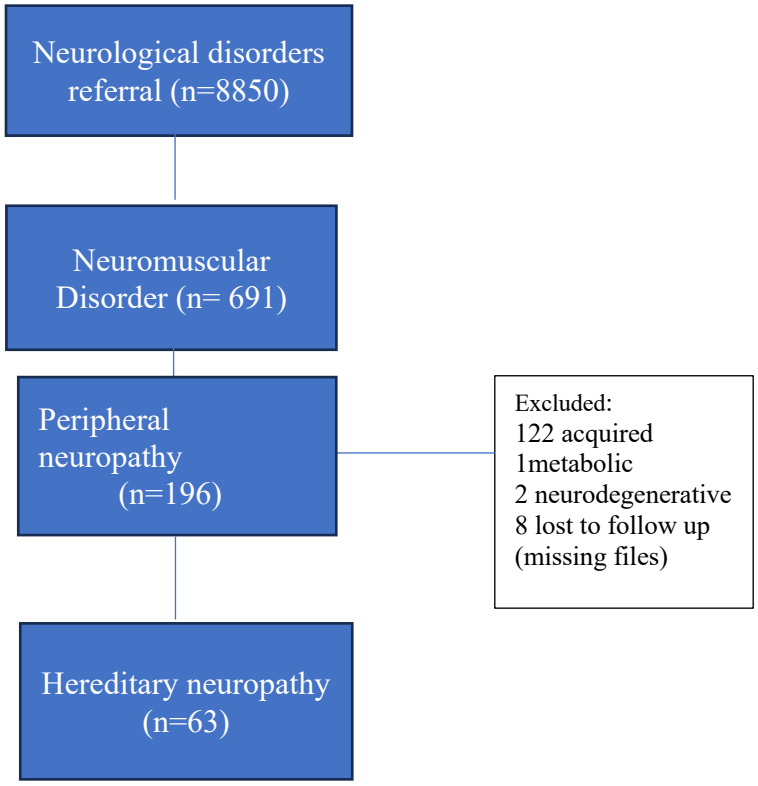

Figure 1: Flow chart of patients enrolled

Table 1: Demographics characteristics of 63 children

	Axonal (n=50, 79%)	Demyelinating (n=13, 21%)	P value
Age onset symptoms (months)	39.1(SD 36.3)	40.8 (SD 30)	0.4
Age at diagnosis (months)	(N=35) 79.9 (SD 51.1)	(N=9) 127.1 (SD 138.04)	0.05
Sex Male Female	 23 (76.6) 26 (81.3)	 7 (23.3) 6 (18.8)	 0.75

Ancestry			
African	11 (91.7)	1 (8.3)	-
Asian	1 (100)	0	
European	21 (87.5)	3 (13.5)	
Mixed	17 (65.4)	9 (34.6)	
Family history			
Yes	18 (75)	6 (25)	0.53
No	32 (82.1)	7 (17.8)	

Neurophysiological abnormalities were : 50 with axonal and 13 with demyelinating patterns.

Most children had axonal type of neuropathy (79%): affecting African 11/12, Mixed 17/26, European 21/24 ancestries.

Age of disease onset varied, ranging from birth early childhood to adolescence (0–132 months, mean 40.0, SD+/− 36.8) and did not differ among the children when compared by type of neuropathy. A clinical diagnosis of hereditary neuropathy was made earlier in children with axonal neuropathy compared to those demyelinating types, p value 0.05.

Table 2: Common presenting features in hereditary neuropathy for 63 children

	Axonal (N=50)	**Demyelinating (N=13)**	**P value**
Sensory			
Numbness	**4**	**0**	**0.57**
Pain			
Foot	**12**	**1**	**0.14**
Hand	**4**	**0**	**0.57**
Pins & needles	**4**	**0**	**0.57**
Pin prick abnormal	**18**	**5**	**1**
Vibration abnormal	**18**	**6**	**0.75**
Hearing impairment	**6**	**2**	**0.49**
Visual impairment	**6**	**1**	**1**

Motor			
Hand weakness	**13**	**3**	**1.0**
Hand tremor	**9**	**3**	**0.68**
Leg weakness distal	**44**	**12**	**0.4**
Tripping/falls	**20**	**8**	**0.27**
Unsteady ankles	**23**	**7**	**1.0**
Feet abnormalities	**34**	**9**	**1.0**
Hammertoes/clubfeet	**6**	**2**	**0.64**
Pes cavus	**17**	**7**	**0.34**
Arthrogryposis	**2**	**0**	**1.0**
Scoliosis	**11**	**5**	**0.28**
Tight Achilles' tendon	**31**	**8**	**1.0**
Ophthalmoplegia	**2**	**1**	**-**
Bulbar dysfunction	**5**	**0**	**-**
Respiratory distress at birth	**8**	**1**	**1.0**
Feeding difficulty at birth	**8**	**1**	**1.0**
Autonomic dysfunction			
Sweating excessively	**1**	**1**	**=**
Cutaneous lesion			
Woolly hair	**2**	**0**	**-**
Atrophic skin changes	**2**	**0**	
Nerve enlargement	**0**	**4**	
Intellectual disability	**10**	**3**	**0.68**
CMT score	**12**	**18**	**0.01**

Common presenting features:

Walking difficulties were the most common initial symptoms. Clinical severity of symptoms according to CMTNS grading varied: 22/59 mild (0-9 score), 22/59 moderate (10-20 score) and 15/59 severe (> 20 score) categories with most patients presenting with a moderate to severe phenotype. Children with demyelinating neuropathy had worse symptom severity scores at presentation, P value 0.009

Clinical sensory involvement was reported in 25/63 (39%) patients and tended to be more frequent with the axonal neuropathy type. Eight patients presented a sensorineural hearing defect whilst nine were visually impaired.

Intellectual disability (where peripheral neuropathy was the dominate clinical feature) was reported in 16 children: 13/50 (26 %) in the axonal type versus 3/13 (23%) the demyelinating type of neuropathy.

Histological features: Sural nerve biopsy results were available for 22 children of which axonal degeneration was identified in 14/22, 4/22 had demyelinating features supported by onion bulb formations, two demonstrated giant axonal neuropathy whilst two demonstrated non-specific results.Two of the children with genetic confirmed causes for neuropathy had axonal degeneration reported on nerve histology results : one CMT1A and one MFN2.

Table 3: Clinical phenotype by ancestry for 63 children

	African (n=12)	**Asian (n=1)**	**European (24)**	**Mixed (26)**	
ALS (Juvenile)	**0**	**0**	**1**	**0**	
Anderman syndrome	**0**	**0**	**1**	**0**	*DNA confirmed 1*
CMTA1	**0**	**0**	**3**	**4**	*(DNA confirmed 7)*
CMT1				**1**	
CMT2	**7**	**1**	**11**	**11**	*DNA confirmed 1*
CMT3	**1**	**0**	**0**	**3**	
CMT4	**0**	**0**	**0**	**1**	
CMT5	**0**	**0**	**3**	**3**	
CMTX	**0**	**0**	**1**	**1**	
Congenital axonal Neuropathy	**0**	**0**	**0**	**1**	
dHMSN	**2**	**0**	**0**	**1**	
GAN	**2**	**0**	**0**	**0**	
RTD3	**0**	**0**	**1**	**0**	*DNA confirmed 1*
SMARD1	**0**	**0**	**2**	**1 (juvenile)**	*DNA confirmed 2/3*

ALS- Amyotrophic lateral sclerosis(juvenile onset with peripheral neuropathy dominant features), dHMSN- Distal hereditary motor sensory neuropathy, GAN- Giant axonal neuropathy, RTD3- Riboflavin transporter deficiency type 3, SMARD1- Spinal muscular atrophy with respiratory distress type 1

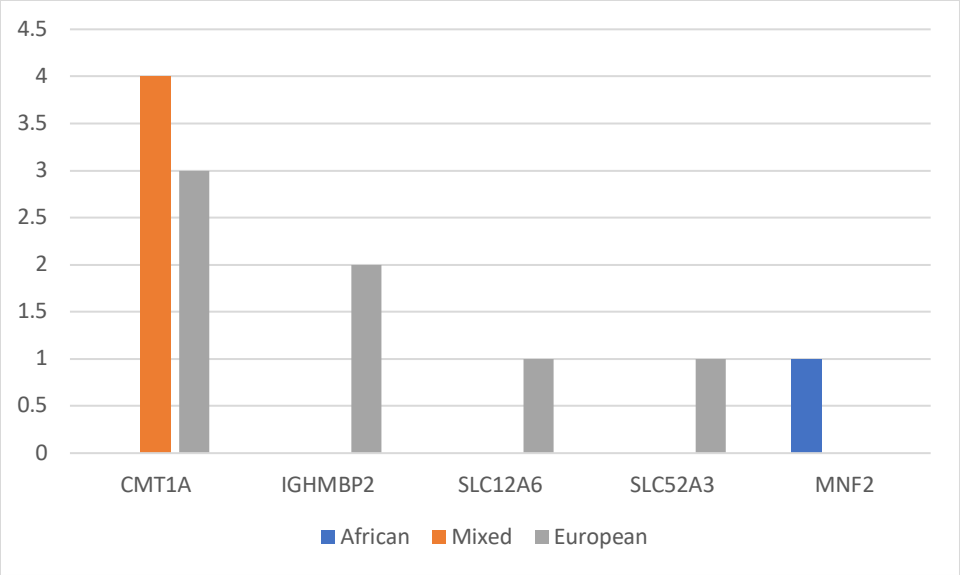

Figure 2: Genetic confirmed causes for peripheral neuropathy for 12 children by ethnicity.

Twelve children were genetically confirmed : seven *CMT1A*, two *IGHMBP2*, one *MFN2*, one *SLC12A6* and one *SLC52A3*, see figure 1. Fifty-one had a probable cause for neuropathy. None of children with CMTIA were of African ancestry.

Table 4. Gene variants for 12 children with peripheral neuropathy

Case	Official symbol	Genomic Reference	Transcript Reference	Gene variants	Assembly	Chromosome	Location
A,B, C, D, E, F, G	PMP22	NG_007949.1	NM_000304.3	-	GRCh38.p14 (GCF_000001405.40)	17	NC_000017.11 (15229779..15265326, complement)
H	IGHMBP2	L361P	NM_0021180.2		GRCh38.p14 (GCF_000001405.40)	11	NC_000011.10 (68903891..68940601)
I	IGHMBP2		NM_0021180.2	-	GRCh38.p14 (GCF_000001405.40)	11	NC_000011.10 (68903891..68940601)
J	SLC12A6	LRG_270	NM_133647.1	c.3031C>t(p.R1011X; p.Arg1011Ter)	GRCh37	15	
K	SLC52A3	LRG_1394	NM_033409.3		(GRCh37/hg19	20	
L	MFN2	LRG_255	NM_014874.3	p.Arg104Trp(c.310C>T)	GRCh38.p14 (GCF_000001405.40)	1	NC_000001.11 (11980444..12013508)

Discussion

This retrospective study of children with clinically suspected CMT from South Africa, found a predominance of axonal type of neuropathy across all ethnicity groups. This outcome differs from European settings where demyelinating neuropathies are the more prevalent types (1). Similar to our findings, studies from North Africa reported a lower proportion of PMP22 among participants of African ancestry (2). Studies conducted in North Africa identified only 4 families with PMP22 associated CMT (9, 10). This may be due to the limited studies on CMT in Africa or, alternatively, the genetic architecture of CMT among people of African and non-African ancestries is significantly different. Presently the sole genetic test offered by the National Health Laboratory Service (NHLS) in SA is screening for PMP22 deletion/duplication, which resulted in the genetic confirmation of seven children of non-African ancestry only with CMT1A. MFN2 mutation as a cause for axonal neuropathy was genetically confirmed in a child of African ancestry at an overseas collaborative research centre. This was provided as a favour to our centre. The remaining children in the study with similar phenotypes, especially axonal peripheral neuropathy could not access genetic testing so they and their families lacked genetic and definitive diagnostic closure. Mahuyu et al reported on 2 adults of African ancestry with MFN2 mutation also from South Africa (3).
Two children of European ancestry had SLC12A6 and SLC52A3 respectively, genetically confirmed at overseas centres after the parents funded the studies. The child with SLC52A3 gene mutation was previously reported by Elks et al in two siblings from South Africa (24).

In resource limited settings the cost of genetic screening for the most common genes causing CMT and other genetic peripheral neuropathies is expensive and inaccessible outside research facilities. Practitioners in these settings inevitably rely on clinical, neurophysiological or histological assessments, where available, as the standard of care for the diagnosis of children presenting with possible genetic peripheral neuropathies. This leaves the large majority of children with probable genetic causes for peripheral neuropathy with an unclear definitive aetiology. Evidently there is need for more genetic analysis on this population as we can assume there are unique variants yet to be identified as pathogenic since most screens are interpreted from European ancestry populations. Expanded access to genetic peripheral neuropathy screening in this setting will inform the scientific community on the burden of confirmed cases and set a basis for future gene therapies.

Nerve biopsy results were available for twenty-two children in this cohort. Ultrastructural features on nerve biopsy in some types of CMT and assist delineation of probable genotype e.g PMP22 duplication/deletion, CMT4B, CMT2A2 (MFN2) (21). The histopathological evaluation of peripheral nerve biopsies for genetic peripheral neuropathy, when appropriately performed by a reliable laboratory, still remains a valuable investigative modality even though it is an invasive procedure. In some cases, the clinical and electrophysiological data alone may fail to specify the subtype if the pathogenic genes are not identified (21). In paediatric age group, significant peripheral nerve maturation changes occur between birth and 5 years in the fibre density, myelination, fibre size and thickness which has a bearing on the interpretation (22). Mature adult histological pattern is achieved in the pre-school years (22). This needs to be considered in interpreting both light and electron microscopy peripheral nerve biopsy findings in children. Peripheral nerve biopsy findings may not only provide diagnostic data, but also prognostic and

management information for the individual and other family members. Few centres in resource limited countries are able to provide a comprehensive molecular genetic work up and still rely on clinical, neurophysiology and histology for a diagnosis.

We observed the prevalence of moderate or severe phenotypes of 37% and 25% respectively among thirty seven of the 63 participants with complete data. The mean CMTNV2 scores of 18 at presentation in the demyelinating type neuropathy was similar to what has been observed by Murphy and colleagues in a multi-centre natural history study of sixty-three patients (16). These data demonstrate the presence of moderate-to-severe disease burden and the potential impact on quality of life without targeted treatment intervention.

Limitations**:** This was a retrospective study and some case files had missing information such as anthropometry. Some children had relocated and were lost to follow up, hence reducing the sample size of children with genetic neuropathies presenting to RCWMCH. The group consultations with the paediatric neurologists based in the NMD service aimed to ensure consensus on the patient categorisation and this was further reinforced by the telephonic consultations with the overage patients no longer attending the service.
The strength of the study is the large number of children from an African setting, with probable genetic cause for peripheral neuropathy who have documented clinical phenotype, neurophysiology, nerve biopsy histology/immunohistochemistry and where available genetic results. In resource limited settings the cost of genetic screening for the most common genes causing CMT is expensive and inaccessible outside research facilities. This study will provide evidence to be recommended for the current and future targeted disease-modifying treatment options for children in an African setting and assist in the development of focus areas for further study in this population.

Conclusion: Axonal peripheral neuropathy is the most common genetic neuropathy manifesting in individuals of African ancestry in South Africa. CMT1A was not identified in children of African ancestry. Expanded CMT screening in this setting will inform the scientific community on the burden of confirmed cases and more pertinently set a basis for future gene therapies.

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Conflict of interest.

None declared.

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Supplementary:

Data Collection tool

1. Study ID number …….

A Demographic history

2. Date Today / / / Date of Birth / /
3. Age in Months……..
4. Gender: 0 Male 1 Female
5. Race: 1 African 2. Asian 3. Caucasian 4. Mixed

B. Clinical history

6. Presenting symptoms list: ……..……
7. Foot pain ☐ Leg cramps ☐ Unsteady gait ☐ Daily trips /and falls ☐ Hand pain ☐ hand weakness ☐ Hand tremor ☐ Sensory Symptoms ☐
8. . Select system/systems predominantly involved
    a. Sensory symptoms: Pain, tingling, or numbness, often in the hands and feet,
    b. Motor symptoms: Muscle weakness and loss of mass (muscle atrophy), often in the feet and lower legs, respiratory distress, feeding difficulty
    c. Autonomic symptoms: Impaired sweating, or low blood pressure after standing up from sitting or lying down.
    d. Physical deformities: High foot arches, hammer-shaped toes, or a curved spine (scoliosis).
    e. Cranial involvement: Ophthalmoplegia, drooling, vocal cord palsy
9. .Other systems involved, list ……

C. **Examination Findings**

10. BP 0 Normal 1 Low 2 High 3 Not done
11. Weight/age Z score 0. Normal 1. Abnormal low 2. Abnormal high 3. Not done
12. Height for age Z score 0. Normal 1. Abnormal low 2. Abnormal high 3. Not done

13. BMI 0. Normal 1. Abnormal low 2. Abnormal high, 3. Not done
14. HC SD 0. Normal 1. Abnormal low 2. Abnormal high, 3. Not done

15. . Dysmorphic 0 No 1 Yes
16. If yes List ……
17. Skin lesions 0 No 1 Yes
18. .If yes List ……
19. Cranial nerves 0 Normal 1 Abnormal , 2 Not done
20. If abnormal list…….. ……

.**Sensation**

21. Pain 0 Normal, 1 abnormal, 2 Not done ,
22. Light touch 0 Normal, 1 abnormal, 2 Not done
23. Joint position 0 Normal, 1 abnormal, 2 Not done
24. Vibration Pain 0 Normal, 1 abnormal, 2 Not done

25. If abnormal list ……. ……

26. Posture 0 Normal, 1 abnormal, 2 Not done ,

27. If abnormal list ……. ……

28. Tone 0 Normal, 1 abnormal, 2 Not assessed ,

29. If abnormal list ……. ……

30. Power 0 Normal, 1 abnormal, 2 not assessed ,
31. If Abnormal
32. Hand grip 0 Normal 1 abnormal
33. Foot Plantar flexion 0 Normal 1 abnormal
34. Foot Dorsiflexin 0 Normal 1 abnormal

35. If abnormal list ……. ……

36. DTR 0 Normal, 1 abnormal, 2 Not assessed,

37. If abnormal list ……. ……

38. Gait 0 Normal, 1 abnormal, 2 Not assessed

39. If abnormal
40. Gait foot drop, 0 No 1 Yes
41. Difficulty heel walking, 0 No 1 Yes
42. Difficulty toe walking, 0 No 1 Yes

43. If abnormal list ……. ……

44. Cerebellar function 0 Normal, 1 abnormal, 2 Not assesed ,

45. If abnormal list ……. ……

46. MSS
47. Scoliosis 0 Normal ,1 abnormal ,2 Not assessed
48. Foot posture abnormalities (high arch) 0 Normal ,1 abnormal ,2 Not assessed
49. Contracture 0 No,1 Yes

50. If yes list area involved…….

51. Other systems 0 Normal ,1 abnormal ,2 Not assessed
52. If abnormal list……..

D Neurological evaluations.

53. NCS:
54. Sensory Nerve Action Potential 0 normal 1 abnormal 2 Not done

55. Motor nerve studies 0. Normal 1. Demyelination 2. Axonal 3. Intermediate 4 Other

56. Histology :0 Normal 1 abnormal 3. Not done
57. If abnormal list……

58. Neuroimaging: 0. Normal 1. Abnormal

59. If Neuroimaging abnormal list……

60. Genetic test child : 0. Normal 1. Abnormal 2. Not done

61. If genetic testing done ,list result…….

62. Genetic test Mother : 0 Normal 1. Abnormal 2. Not Done
63. If genetic testing done list result …….

64. Genetic test Father : 0. Normal 1. Abnormal 2. Not done

65. If genetic testing done, list result…….

66. Genetic test Sibling: 0 Normal 1. Abnormal 2. Not Done
67. If genetic testing done list result …….

E. Supportive care

68. Physiotherapy
69. Occupational therapy
70. Speech therapy
71. Dietician
72. Respiratory support
73. Orthopedics