Available online at www.sciencedirect.com

ScienceDirect

Neuromuscular Disorders 29 (2019) 961–967

www.elsevier.com/locate/nmd

GNE myopathy – A cross-sectional study on spatio-temporal gait characteristics

Gaurav Gomez[a], Meeka Khanna[a], Anupam Gupta[a,*], Atchayaram Nalini[b], K. Thennarasu[c], Saraswati Nashi[b], Kiran Polavarapu[b], Seena Vengalil[b]

[a] Department of Neurological Rehabilitation, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560029, India
[b] Department of Neurology, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560029, India
[c] Department of Biostatistics, National Institute of Mental Health and Neurosciences (NIMHANS), Hosur Road, Bangalore 560029, India

Received 21 June 2019; received in revised form 1 November 2019; accepted 4 November 2019

Abstract

GNE myopathy is a rare, predominantly distal myopathy, involving mainly the lower limbs and presenting with gait disturbances. In this cross-sectional study gait evaluation of 23 (14 men) genetically confirmed GNE myopathy patients was done using Instrumented walkway analysis (GAITRite®) along with video gait capture. We recorded the topographical pattern of muscles involvement in lower limbs and correlated Functional Ambulation Profile-FAP and Medical Research council-MRC grading of lower limb scores with duration of illness. Early foot flat, foot drop gait with wider out-toed stance and higher perturbations with increased pressure at heel and decreased arm swing were noted. Muscle topography showed predominant weakness in ankle dorsi-flexors, flexor hallucis longus, extensor hallucis longus, hip adductors and knee flexors with stark sparing of quadriceps and relative sparing of hip- abductors, extensors, flexors and ankle plantar-flexors. Gait parameters in women were significantly more affected than men ($p < 0.05$) for the same duration of illness. FAP score and MRC grading of lower limb scores correlated significantly with duration of illness ($p < 0.05$). We observed that ankle dorsiflexors were affected earliest with sparing of quadriceps muscles in these patients.
© 2019 Elsevier B.V. All rights reserved.

Keywords: GNE myopathy; Gait; GAITRite; Lower limb.

1. Introduction

GNE myopathy is a rare disease, which is also known by other names like Nonaka myopathy, distal myopathy with rimmed vacuoles-DMRV, hereditary inclusion body myopathy-HIBM, Inclusion body myopathy 2-IBM2 and quadriceps sparing myopathy. It has a prevalence of 1-21/1000,000 population. [1–5] It is an autosomal recessive disease caused by bi-allelic inheritance of variable mutations in the GNE gene on chromosome 9, encoding a bifunctional enzyme- uridine diphosphate-N-acetylglucosamine 2-epimerase /N-acetylmannosamine kinase required in sialic acid- 5-N-acetylneuraminic acid (Neu5Ac) synthesis, which in turn plays a role in glycoprotein and glycolipid stability. [6] GNE myopathy usually presents with foot drop in lower limbs, with progression from distal to proximal muscles with variable onset but occurs most commonly in the 3rd decade of life. It characteristically spares the quadriceps, even in late stages of illness. Usually posterior thigh muscles and anterior leg muscles are the more involved groups. [1,3]

The GAITRite is a relatively new equipment, which is considered reliable and is the current gold standard for temporal and spatial evaluation of gait. [7–9]. It has been used for gait analysis in patients with Facio Scapulo Humeral Dystrophy, Becker's Muscular Dystrophy, Limb Girdle Muscular Dystrophy, Amyotrophic Lateral Sclerosis, Multiple Sclerosis, Parkinson's disease and Myotonic dystrophy among other neurological disorders. It has also been used in otherwise health elderly individuals to observe the effect of assistive devices on gait. [7,9–17]

* Corresponding author.
E-mail address: anupam@nimhans.ac.in (A. Gupta).

https://doi.org/10.1016/j.nmd.2019.11.003
0960-8966/© 2019 Elsevier B.V. All rights reserved.

FAP (Functional Ambulation Profile) Score is an automated value generated by the GAITRite system, using various Spatio-temporal (ST) parameters from a total score of 100. The values for a normal adult fall between 95 and 100. FAP score is inversely proportional to the level of gait impairment and has been found to be a reliable marker of gait impairment in various related disorders. [18–21]

Very few studies have been done with GNE myopathy patients evaluating their functionality during the course of illness and no objective study is available in literature on the gait deterioration over time, which is the first symptom in most of these patients. [22] Studying the disease progression and its effect on ambulation would help in planning rehabilitation interventions, reducing health care cost and improving quality of life. The objective of this cross-sectional study was to identify and describe the topographical patterns of muscle weakness in ambulatory GNE myopathy patients who are at various phases of disease. We also attempted to identify variations in spatio-temporal gait parameters objectively, and correlate them with the muscle weakness pattern. Another objective was to observe if pattern of weakness has any gender bias.

2. Methods

This Cross-sectional study was conducted in the Gait analysis laboratory of the department of neurological rehabilitation in a tertiary research hospital between September 2017 and May 2018.

Institute's Ethics Committee approved the study and written informed consent was taken from all the participants. A total of 23 participants with genetically confirmed GNE myopathy were recruited with age ranging between 28 and 45 years. Participants who were medically stable and independent ambulators were included. Participants using walking aids or assistance for ambulation were excluded. We also excluded participants with medical co-morbidities that could cause errors in gait analysis.

2.1. GNE participants

Participants were recruited from the Neuro-muscular disorders clinic where diagnosis was made by a team of Neurologists. Individuals who demonstrated characteristic clinical features of GNE myopathy were further investigated. These patients showed normal to slightly elevated creatinine kinase-CK levels, electromyography and histopathological studies suggestive of GNE myopathy were investigated further using next generation sequencing and Sanger sequencing for confirmation of diagnosis. These genetically confirmed GNE myopathy patients were approached for written consent to participate in the study. Data regarding demographic details, history of complaints, family chart and clinical examination including detailed muscle charting by Manual Muscle testing (MMT) with grading as per MRC (Medical Research Council) was collected by one of the investigators.

2.2. GAITRite

It consists of a portable 16 feet long computerised mat embedded with a grid of over 18,000 pressure sensors. This allows for objective capture of temporal and spatial gait characteristics, values of which can be immediately visualised graphically and compared to normative data. The values obtained can be exported directly to Microsoft Excel for statistical analysis. The software has provisions to receive input from external video devices, providing scope for observational analysis with synced color-coded pictographical representation of pressure sensor triggering patterns by the subject's feet. Spatial and temporal parameters, line of progression, FAP score, base of support, phases of gait and out-toeing angle are objectively calculated by the software.

2.3. Experimental set-up

The participants were instructed to walk 4 times on the GAITRite walkway at a comfortable pace after feeding the data including the limb length into the software (version 4.8.7). The sensor data was sampled at 120 Hz and synced to the video recording of the walk. It was then reviewed immediately to sieve out errors and walks were repeated if needed, to obtain clean data for analysis.

2.4. Data capture

The Observational analysis was conducted using the synced video-sensor activation combo to determine the sequence of contact of various points of foot and their removal with colour coded pressure intensity displayed in real time at each point. Line of progression, duration of heel contact, toe contact and percentages were calculated automatically by the system.

2.5. Statistical analysis

One of the co-authors, from the department of Biostatistics analysed the exported data using SPSS 22.0 software. Data was found to be non-parametric using Shapiro Wilk test of normality. Correlations were evaluated using Spearman's Rho, considering a value of $p < 0.05$ to be significant. Comparison between men and women were made using Mann Whitney U test with value of $p < 0.05$ was considered significant.

3. Results

3.1. Demographics and clinical features

Fourteen out of the total 23 participants, (61%) were men. The median age at evaluation was 33yrs (range 28–45 y), median age at onset of illness was 27yrs (range 16–42 y). The age of onset of illness varied within the cohort with 3 participants had onset between 15 and 20 years, 13 between 21 and 30 years, 5 between 31 and 40 years and 2 participants

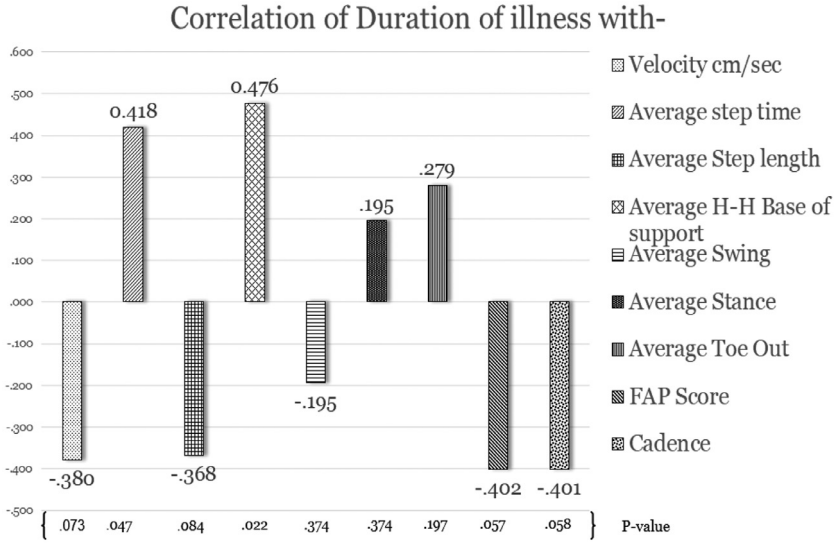

Fig. 1. GNE myopathy: Illness duration and it's correlation with gait parameters (with p values at the bottom of the figure in the bracket).

Table 1
Demographics and spatio-temporal gait characteristics of patients with GNE Myopathy.

	Mean	Median	Std. Deviation	Percentiles	
				25	75
Age	34.4	33	8.2	28	39
Duration of illness (yrs)	5.8	5	3.1	4	6.5
Age of onset (yrs)	28.7	27	7.9	24	32.5
Velocity (cm/sec)	74.7	79.5	23.1	56.3	94.5
Average step time (msec)	72	68	11	63	78
Average Step length (sec)	51.5	51.6	11.2	43.9	61.4
Average Base of support (cm)	14.5	13.9	5.8	9.3	18.1
Average Swing%	35.9	36.3	3.2	34.8	38.2
Average Stance%	64.1	63.7	3.2	61.9	65.3
Average Toe Out angle	18.4	17.5	8.6	12	22
FAP Score	81.3	88	16.8	72	95
Cadence	85.1	88	11.5	77.5	95.3

were over 40. The duration of illness varied between 3 and 18 years with a median of 5 years. 1 male patient with 18 years of illness duration was still ambulant at the time of recruitment in the study. Participants presented with foot-drop gait with difficulty in clearing objects early in the course of the disease, while those with more advanced progression complained of slowing of gait with a greater propensity to fall and inability to climb stairs or rise from the floor/ bed/ chair. They had an unstable gait with wider base, shorter steps, flail feet and significant out-toeing.

3.2. Temporal and spatial characteristics

The median and mean values of temporal and spatial gait parameters are represented in Table 1 and the correlation of different gait parameters with duration of illness are represented in Fig. 1.

3.3. Gender difference in the study

The mean age of presentation of illness varied for men and women. The mean age of presentation was 34.6yrs and 34.1yrs, age of onset of illness was 28.5yrs and 28.9yrs, and duration of illness was 6.1yrs and 5.2yrs for men and women respectively. Median comparison of gait parameters of men and women with Q25 and Q75 confidence intervals (error bars) are denoted in Fig. 2. There was statistically significant difference in gait parameters between the genders with women having slower speed ($p=0.007$), shorter steps ($p=0.002$), wider base of gait ($p=0.039$), and a more unstable FAP ($p=0.033$) gait with lower ankle dorsiflexors ($p=0.039$) and total MRC scores ($p=0.039$). Fig. 3.

3.4. Observational gait analysis

On reviewing the synced pattern of activation of sensors to gait video, we noted the following changes, which become more prominent as the disease duration increases:

1. Participants with longer duration symptoms demonstrated a characteristic foot drop gait with initial contact occurring at the lateral forefoot border followed by rapid loading forces at the heel.
2. As the disease duration increased, the pressure distribution was more concentrated at the heel with poor push off at terminal stance. This was also reflected by an increased overlap between heel contact and toe contact time on the mat.
3. With further advancement of illness duration and severity, there was an increase in step width, angle of out-toeing, higher perturbations in stance phase, quicker swing phase, increased severity of Trendelenburg gait with a waddle and a decrease in arm swing.

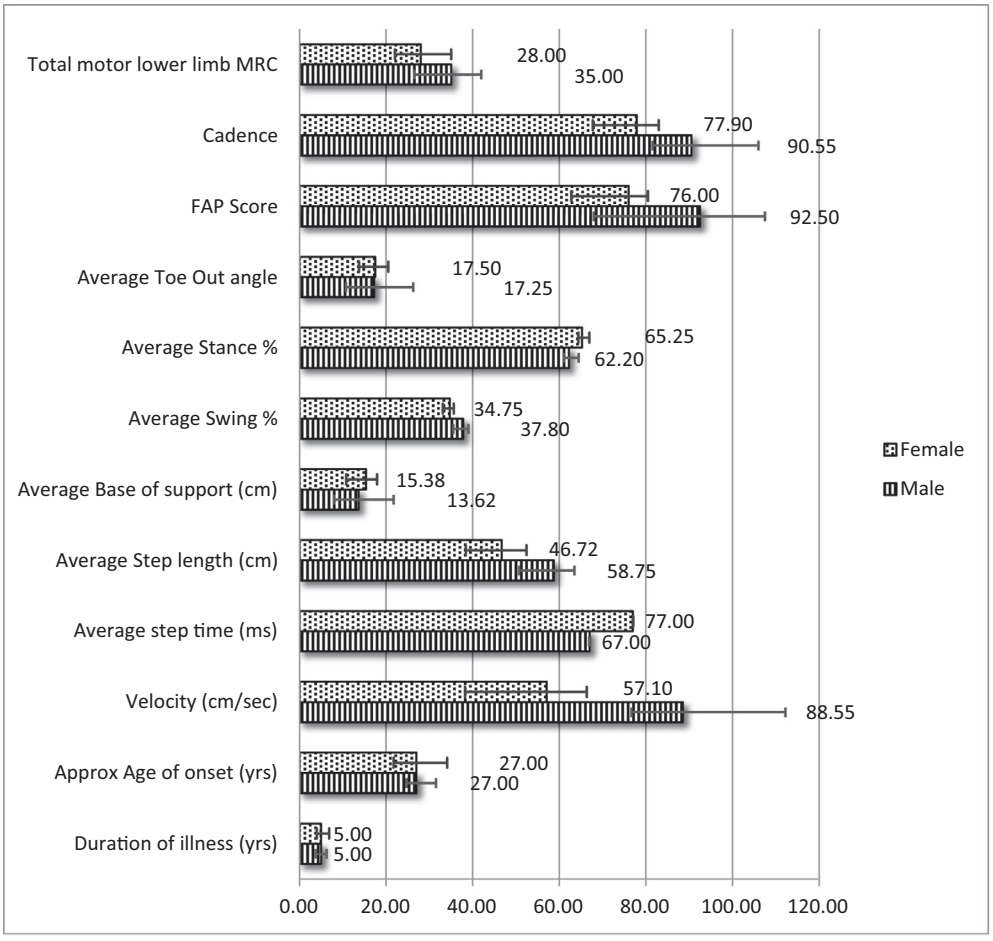

Fig. 2. Gender and spatio-temporal gait characteristics.

3.5. Muscle involvement pattern

The average MRC score of each muscle in our cohort is represented in Fig. 4.

4. Discussion

More than 60% of the participants were men. Some earlier studies have reported women outnumbering men in their cohort. [4,23–25] Majority of our participants had onset of gait disturbance in the 3rd decade of life. Two participants had late onset of illness (in early 5th decade of life), which is not rare and has been reported earlier also. [14]

A key feature of GNE myopathy is late and negligible involvement of the quadriceps with gradual involvement of the proximal musculature in the lower limbs in the later stages of illness, which was observed in our study also. [1,26,27] A systematic review has reported that the disease process in the early stages affects predominantly; the gluteus minimus, biceps femoris, tibialis anterior and gastro-soleus. [28] Our study indicates that the hip adductors and ankle dorsiflexors are the most affected muscle groups early in the disease process, followed by knee flexors, hip flexors and hip abductors. Stabilization of the distal joints with the use of splints such as solid/leaf-spring Ankle Foot Orthoses (AFO) can improve efficiency, speed and stability of gait especially since the quadriceps sparing obviates the need to stabilize the knee. With this modification the main concern is pelvic stability which can be facilitated with walking aids in later stages of illness.

We observed that duration of illness correlated with increased delay in step time and wider base of support. Similarly there was decrease in walking speed, shorter step length, decrease in FAP score (i.e. increase in gait instability) and decrease in cadence with duration of illness, which was statistically significant ($p < 0.05$). Longer duration of illness correlated with quicker swing and longer stance and an increase in toe-out angle, although these findings were not observed to be statistically significant ($p > 0.05$). In our study, decrease in velocity correlated with increase step time, increase in step width, quicker swing and longer stance, decrease in FAP score and increase in cadence.

Women have been reported to have an earlier onset of disease. [5] Although men in our study were older at presentation, both men and women had a similar median age of onset of illness and duration of illness. The difference in gait parameters were statistically significant; Women walked slower, with a shorter step length, had a wider base of

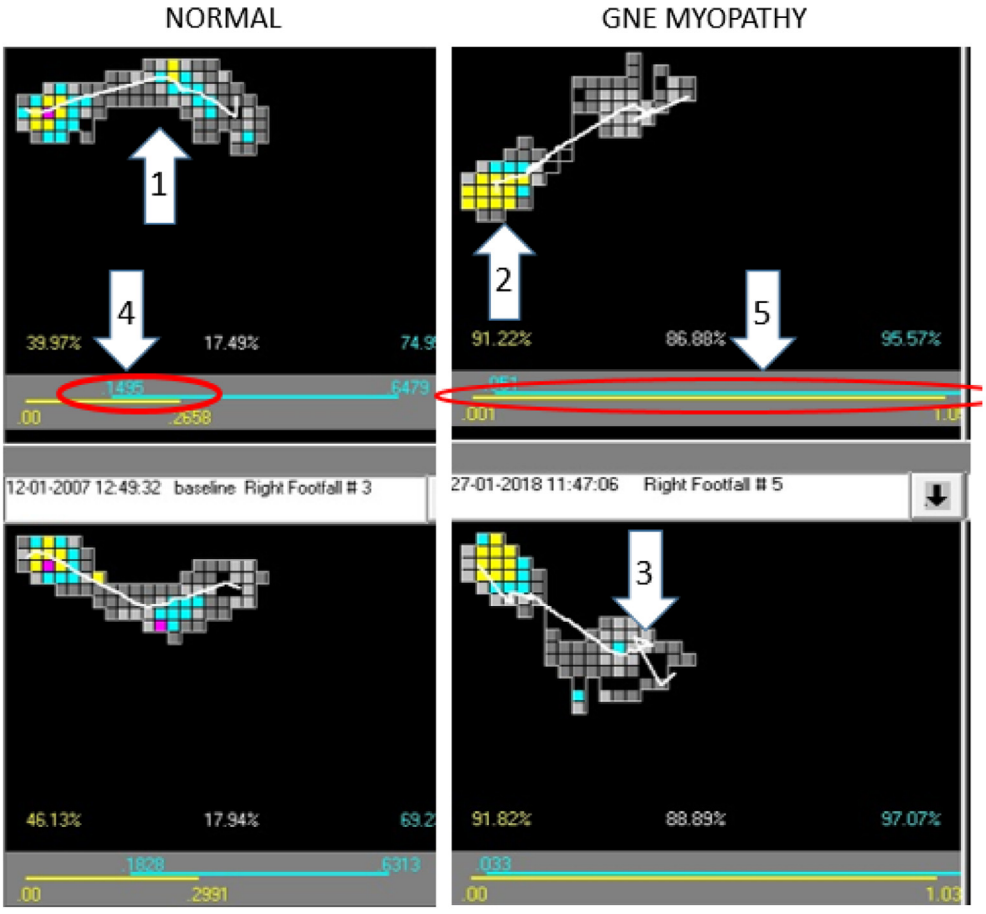

Fig. 3. Screenshot of Gait Pressure sensors display pattern of placement of foot.

support, quicker swing and longer 'stance phase' percentage. Although women, due to their shorter stature are expected to have slightly lower gait velocity, the difference was more pronounced in our cohort. [29] FAP score is independent of gender and should fall between 95 and 100. Our study showed a significantly lower score in women suggesting they had objectively greater gait impairment. This could imply that women have a more drastic drop in gait efficiency over time i.e. a more rapid disease progression. There was no other study found in patients with GNE myopathy in literature comparing the disease process on gender basis.

Most participants in the study had foot-drop, which correlated with the least MRC score for ankle dorsiflexors at presentation and a steep slope of decline with increase in duration of disease. Ankle dorsiflexors' weakness is compounded with plantar flexor weakness later in the disease, which results in instability at the ankle (flail foot) causing increase in perturbations during stance. As the plantar flexor weakness increases, the ability of the limb to distribute weight via active plantar flexion, to the mid and forefoot diminishes resulting in a poor or negligible push off at mid and terminal stance phases. With such a flail ankle, all the weight of the body is mainly concentrated at the heel which is picked up by the pressure sensors. Studies in other Myopathies such as Facio-scapulo-humeral Dystrophy (FSHD) revealed inverse relation between ankle dorsiflexor strength and heel pressure percentage. [30]

5. Conclusion

In the present study we observed that ankle dorsiflexors and hip adductors are the earliest muscles involved in GNE myopathy participants with gradual involvement of other muscle groups as the illness advances. There was significant correlation between the duration of illness and average step time & average heel-to-heel base support. Greater gait difficulty in women as compare to men with similar illness duration was observed. Progression from foot drop to flail

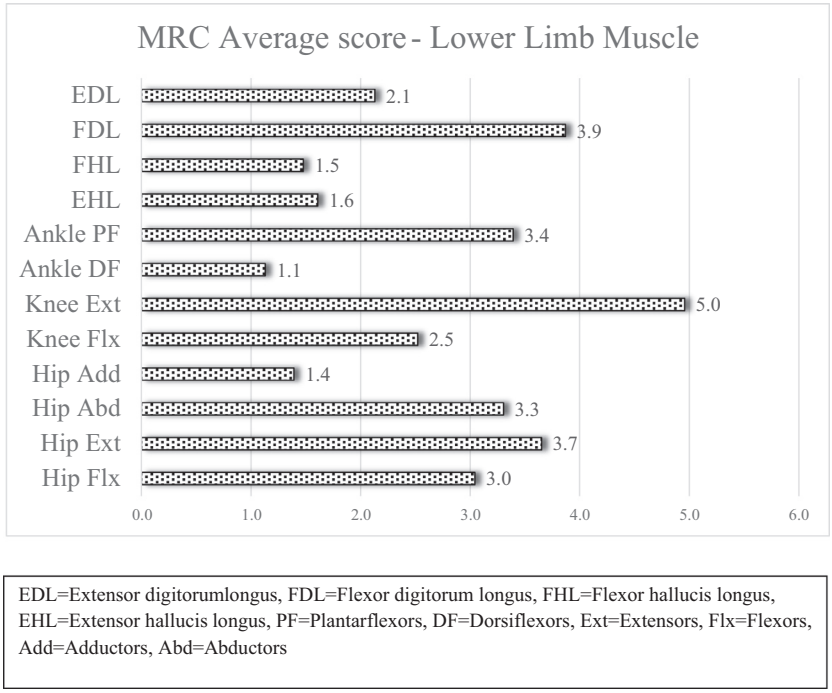

Fig. 4. MRC Muscle power grading of the lower limb muscles at the time of gait assessment.
X axis: MRC grade of muscle power, *Y* axis: muscle/s involvement in the lower limb.

foot, Trendelenberg and waddling gait as the illness advances was noted. FAP scores correlated well with worsening gait parameters proving its utility as an objective measure of gait impairment.

5.1. Limitations and further scope of the study

The results of the study should be inferred cautiously in the light of small sample size. Further studies can incorporate elements of dynamic testing of gait Eg: Use of hurdles, open vs closed eye gait comparison and dual task gait assessment. Use of outcome scales for disability and evaluation of energy expenditure such as PCI (Physiological cost index), may be of use to further quantify degree of affection and disability. Follow up analysis may be of importance to analyze disease progression pattern and the effect of rehabilitation with and without the use of orthoses such as AFOs and walking aids on gait of these participants.

Acknowledgement

The following colleagues assisted in the research by providing diagnosis including genetic confirmation of diagnosis of GNE myopathy: Veeramani Preethish-Kumar, Deepa Sekar, Muddasu Suhasini Keerthipriya, Chevula Pradeep-Chandra-Reddy.

References

[1] Pogoryelova O, González Coraspe JA, Nikolenko N, Lochmüller H, Roos A. GNE myopathy: from clinics and genetics to pathology and research strategies. Orphanet J Rare Dis 2018;13. [Internet] May 2 [cited 2018 May 27] Available fromhttps://www.ncbi.nlm.nih.gov/pmc/articles/PMC5930817/.

[2] Huizing M, Carrillo-Carrasco N, Malicdan MC, Noguchi S, Gahl WA, Mitrani-Rosenbaum S, et al. GNE myopathy: new name and new mutation nomenclature. Neuromuscul Disord NMD 2014;24(5):387–9.

[3] Nishino I, Carrillo-Carrasco N, Argov Z. GNE myopathy: current update and future therapy. J Neurol Neurosurg Psychiatry 2015;86(4):385–92.

[4] Bhattacharya S, Khadilkar SV, Nalini A, Ganapathy A, Mannan AU, Majumder PP, et al. Mutation spectrum of GNE myopathy in the indian sub-continent. J Neuromuscul Dis 2018;5(1):85–92.

[5] Pogoryelova O, Cammish P, Mansbach H, Argov Z, Nishino I, Skrinar A, et al. Phenotypic stratification and genotype-phenotype correlation in a heterogeneous, international cohort of GNE myopathy participants: first report from the GNE myopathy disease monitoring program, registry portion. Neuromuscul Disord NMD 2018;28(2):158–68.

[6] Argov Z, Mitrani-Rosenbaum S. The hereditary inclusion body myopathy enigma and its future therapy. Neurother J Am Soc Exp Neurother 2008;5(4):633–7.

[7] Lopez-Meyer P, Fulk GD, Sazonov ES. Automatic detection of temporal gait parameters in poststroke individuals. IEEE Trans Inf Technol Biomed 2011;15(4):594–601.

[8] Vallabhajosula S, Humphrey SK, Cook AJ, Freund JE. Concurrent validity of the zeno walkway for measuring spatiotemporal gait parameters in older adults. J Geriatr Phys Ther 2017;1 Dec.

[9] Parmar V, Kumar AS, Harper WM, Menz HB, Latt MD, Tiedemann A, Mun San Kwan M, Lord SR. Reliability of the GAITRite walkway system for the quantification of temporo-spatial parameters of gait in young and older people. Gait Posture 2004;20(1):20–5 Gait Posture. 2006;23(4):523.

[10] Berthelsen MP, Husu E, Christensen SB, Prahm KP, Vissing J, Jensen BR. Anti-gravity training improves walking capacity and postural balance in participants with muscular dystrophy. Neuromuscul Disord 2014;24(6):492–8.

[11] Aprile I, Padua L, Iosa M, Gilardi A, Bordieri C, Frusciante R, et al. Balance and walking in facioscapulohumeral muscular dystrophy: multiperspective assessment. Eur J Phys Rehabil Med 2012;48(3):10.

[12] Doglio L, Pavan E, Pernigotti I, Petralia P, Frigo C, Minetti C. Early signs of gait deviation in Duchenne muscular dystrophy. Eur J Phys Rehabil Med 2011;47(4):8.
[13] Pistacchi M. Gait analysis and clinical correlations in early Parkinsons disease. Funct Neurol 2017;32(1):28.
[14] Radovanović S, Milićev M, Perić S, Basta I, Kostić V, Stević Z. Gait in amyotrophic lateral sclerosis: is gait pattern differently affected in spinal and bulbar onset of the disease during dual task walking? Amyotroph Lateral Scler Front Degener 2014;15(7–8):488–93.
[15] Galli M, Cimolin V, Crugnola V, Priano L, Menegoni F, Trotti C, et al. Gait pattern in myotonic dystrophy (Steinert disease): a kinematic, kinetic and emg evaluation using 3D gait analysis. J Neurol Sci 2012;314(1–2):83–7.
[16] Sosnoff JJ, Weikert M, Dlugonski D, Smith DC, Motl RW. Quantifying gait impairment in multiple sclerosis using GAITRite^{TM} technology. Gait Posture 2011;34(1):145–7.
[17] Davis PC, Bach TM, Pereira DM. The effect of stance control orthoses on gait characteristics and energy expenditure in knee-ankle-foot orthosis users. Prosthet Orthot Int 2010;34(2):206–15.
[18] Givon U, Zeilig G, Achiron A. Gait analysis in multiple sclerosis: characterization of temporal–spatial parameters using GAITRite functional ambulation system. Gait Posture 2009;29(1):138–42.
[19] Sosnoff JJ, Weikert M, Dlugonski D, Smith DC, Motl RW. Quantifying gait impairment in multiple sclerosis using GAITRite^{TM} technology. Gait Posture 2011;34(1):145–7.
[20] Nelson AJ, Zwick D, Brody S, Doran C, Pulver L, Rooz G, et al. The validity of the gaitrite and the functional ambulation performance scoring system in the analysis of parkinson gait. NeuroRehabilitation 2002;17(3):255–62.
[21] Gouelle A. Use of functional ambulation performance score as measurement of gait ability: review. J Rehabil Res Dev 2014;51(5):665–74.
[22] Nalini A, Gayathri N, Nishino I, Hayashi YK. GNE myopathy in India. Neurol India 2013;61(4):371–4.
[23] Sim JE, Park H-J, Shin HY, Nam T-S, Kim SM, Choi Y-C. Clinical characteristics and molecular genetic analysis of korean participants with GNE myopathy. Yonsei Med J 2013;54(3):578–82.
[24] Sunohara N, Nonaka I, Kamei N, Satoyoshi E. Distal myopathy with rimmed vacuole formation. A follow-up study. Brain J Neurol. 1989;112(Pt 1):65–83.
[25] Alrohaif H, Pogoryelova O, Al-Ajmi A, Aljeryan LA, Alrashidi NH, Alefasi SA, et al. GNE myopathy in the bedouin population of Kuwait: genetics, prevalence, and clinical description. Muscle Nerve 2018;58(5):700–7.
[26] myopathy AZ. a personal trip from bedside observation to therapeutic trials. Acta Myol 2014;33(2):107–10.
[27] Argov Z, Bronstein F, Esposito A, Feinsod-Meiri Y, Florence JM, Fowler E, et al. Characterization of strength and function in ambulatory adults with GNE myopathy. J Clin Neuromuscular Dis 2017;19(1):19–26.
[28] Tasca G, Ricci E, Monforte M, Laschena F, Ottaviani P, Rodolico C, et al. Muscle imaging findings in GNE myopathy. J Neurol 2012;259(7):1358–65.
[29] Whittle M. Gait analysis: an introduction. Oxford; Boston: Butterworth-Heinemann; 1991. p p. 230.
[30] Aprile I, Padua L, Iosa M, Gilardi A, Bordieri C, Frusciante R, et al. Balance and walking in facioscapulohumeral muscular dystrophy: multiperspective assessment. Eur J Phys Rehabil Med 2012;48(3):393–402.