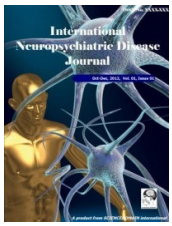

International Neuropsychiatric Disease Journal
3(1): 1-8, 2015; Article no. INDJ.2015.001
ISSN: 2321–7235

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Childhood Onset Familial Nemaline Rod Myopathy: A Report of Two Siblings

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Authors' contributions

This work was carried out in collaboration between both authors. Authors GS designed the study and wrote the protocol. Author GS preformed the statistical analysis, managed the literature search and wrote the first draft of the manuscript with assistance from author SS. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/INDJ/2015/12813
Editor(s):
(1) Thomas Müller, Department of Neurology Berlin Weißensee, St.Joseph-Krankenhaus Berlin-Weißensee, Germany.
Reviewers:
(1) Anonymous, University of the West Indies, Jamaica.
(2) Anonymous, Chang Gung Memorial Hospital, Kaohsiung, Taiwan.
(3) Ogunrin Olubunmi, Neurology Unit, Department of Medicine, University of Benin, Nigeria.
Peer review History: http://www.sciencedomain.org/review-history.php?iid=660&id=29&aid=5989

Short Research Article

Received 19th July 2014
Accepted 14th August 2014
Published 8th September 2014

ABSTRACT

Aims: Nemaline rod myopathy (NRM) is a rare form of congenital myopathy characterized by slowly progressive or non progressive muscle weakness and pathognomonic rod-like structures within the muscle fibers. Muscle weakness and hypotonia are apparent from the neonatal period. We report a rare presentation of NRM seen in two siblings with similar symptoms. Both had slender physique, delayed motor milestones including delayed walking, normal language and cognitive milestones, difficulty in fast movements and change of posture, difficulty in getting to standing from sitting posture and slowly progressive weakness and positive family history.
Study Design: Two siblings i.e. a brother and sister with provisional diagnosis of Nemaline Rod Myopathy were tested for all relevant diagnostic protocol with results analysed and discussed.
Place and Duration of Study: Department of Physiology, Pt. B.D. Sharma Post-Graduate Institute of medical Sciences, University of Health Sciences, Rohtak, Haryana, India.
Methodology: Investigations included CPK levels, motor-sensory conduction velocities, EMG studies, Muscle biopsy, MGT (Modified Gomori´s Trichrome) stain and histo-chemistry studies.
Results: CPK levels were raised (279U/l) with myopathic pattern of EMG with decreased motor unit potentials, recruitment with markedly decreased amplitude; mild decrease in motor conduction

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velocity in tibial-peroneal nerves in both with decreased ulnar nerve sensory conduction velocity in the girl and positive muscle biopsy; diagnosed as Nemaline Rod myopathy.
Conclusion: Nemaline myopathy should be suspected in children with generalized hypotonia and progressive muscle weakness along with delayed motor milestones. This report highlights the importance of EMG and conduction velocity studies along with histo-chemistry and ultra-structural examination in diagnosis of NRM in absence of availability of genetic studies.

Keywords: Myopathy; slow progressive; EMG; nerve conduction.

1. INTRODUCTION

Nemaline rod myopathy (NRM) is a rare form of congenital myopathy characterized by slowly progressive or nonprogressive muscle weakness and pathognomonic rod-like structures within the muscle fibers [1]. Disease severity is variable and unpredictable, with prognosis ranging from neonatal death to almost normal motor function. Recent advances in the identification of NRM disease genes demonstrate that NRM is a disease of the skeletal muscle sarcomere and, in particular, of the thin filaments [2]. In 1963, Shy et al. and Conen et al. published the first description of a novel myopathy characterized by the aggregation of rods (nemaline bodies) in the muscle fibres. This disorder was subsequently known as nemaline myopathy [3]. NRM was the 2nd of the specific myopathies to be defined. The incidence of this condition has been estimated to be varying from 1 in 50000 to 500000 [4]. Two separate studies from South and North India have reported incidence of NRM as 0.64% and 0.53% respectively amongst the congenital myopathies [5,1]. The term nemaline is derived from the Greek word 'nema' meaning thread [6]. Muscle weakness is usually most severe in the face, neck flexors and proximal limb muscles [7]. According to Wallgren-Pettersson, the weakness is mainly proximal and may extend distally in the latter periods. Muscle weakness may be diffuse, but it is often most pronounced in the face, neck and proximal limb muscles. Pharyngeal and respiratory muscles are frequently affected. Distal weakness appears late in the course of illness, but in some forms manifests at presentation [8].

Clinically, the nemaline myopathies present with proximal or generalized muscle weakness [9]. Clinical diagnostic studies include general neurologic exam, muscle strength assessment, serum CK test and, if affected, nerve conduction and concentric needle EMG, respiratory function tests and cardiological examination including ECG, 24-hour-Holter monitoring, and echocardiography [8]. According to Paganoni and Amato, evaluation of patients suspected of having a myopathy begins with a thorough history and clinical examination. This process leads to the elaboration of a clinical impression, based on symptoms, progression, family history, and examination findings. Further diagnostic tests are then ordered using a hypothesis-driven approach to add laboratory evidence in support of or against the clinical suspicion. Electrodiagnostic (EDX) studies, in this respect, are an extension of the physical examination and may help establish the diagnosis of myopathy [10]. Myopathies associated with muscle membrane irritability/myotonic discharges on EMG include congenital myopathies like Nemaline rod myopathy; the electromyography in these cases is myopathic [11].

Familial incidence of NRM has also been commented upon by Cartwright et al. [12] with two varieties: the infantile form which is autosomal recessive in inheritance; the less severe adult form being autosomal dominant. Jain et al. have also reported familial incidence of NRM [11].

With this background we report a case series of the adult type of NRM manifesting in two siblings (a man and his sister) with typical features and diagnostics with an unclear familial linkage of this disease to their grandfather.

2. CASE REPORT

The two patients were investigated according to the workup mentioned by Cartwright et al. [12] which included:

- Motor and sensory conduction velocities
- EMG studies
- Muscle biopsy with modifies Gomori's Trichrome staining (MGT)
- CPK (Creatine phospho-kinase)

Genetic diagnosis was not carried out in these patients as this modality was not available at our facility.

The first patient was a 21 year old male while the second patient was a 20 year old female (younger sister of above patient) (Illustration 1). There was a positive family history i.e. Both of his sisters (including the other patient) had similar complaints; the parents were normal, however, his grandfather suffered from an unexplained weakness with delayed motor milestones. Other features were likewise including a history of delayed walking.

3. RESULTS

The presenting features of both the patients were identical in most aspects (Table 1). However, the male patient had foot drop in the left foot; the female didn't have foot drop. Another diagnostic feature present only in the male patient was high arched palate.

Comparative CNS examination of the patients (Table 2) shows more or less similar CNS findings in the siblings. In the male patient, however, specific wasting of pectoralis supra and infraspinatus was seen along with generalized muscle wasting.

(Table 3) depicts comparison in clinical and investigative parameters in both patients. CPK levels were comparable. The sensory conduction velocity was normal in bi-lateral median and ulnar nerves; contrastingly it was decreased in the female. EMG showed an overall myopathic pattern in the female; in the male, Abductor digiti minimi showed normal pattern while biceps, tibialis anterior and deltoid showed a neuro-myopathic pattern while glutei, adductor longus and vastus medialis showed myopathic pattern. Muscle biopsy of both these patients diagnosed NRM.

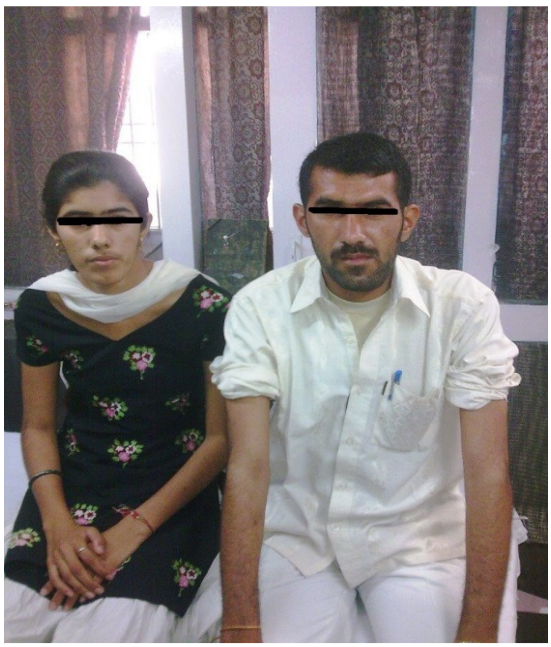
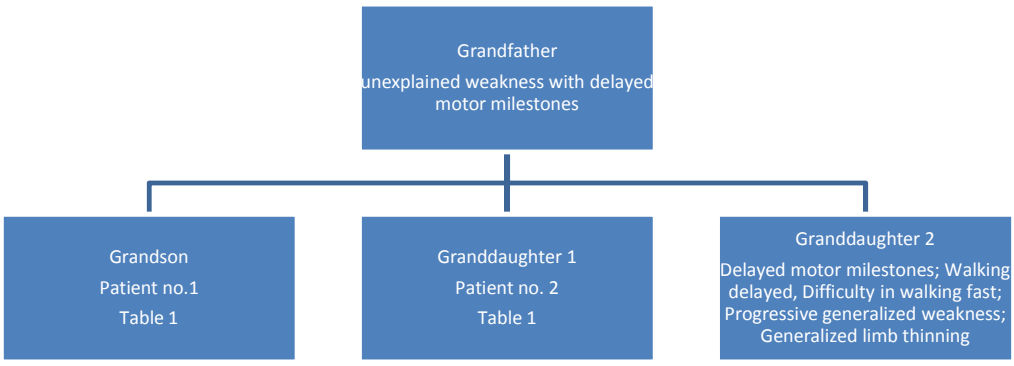


Illustration 1. The siblings with long face, marfinoid features and wasting in upper and lower limbs



Genealogical tree

(Table 4) shows the electrophysiological parameters (Motor and sensory conduction velocity) of both the patients in both upper and lower limbs:

i. Conduction velocity of the axillary and ulnar nerves on both sides was decreased in the female patient, whereas it was normal in the male patient. The conduction velocity of peroneal nerve was decreased bi-laterally in both the subjects; CV in the tibial nerve was normal for the male subject on right side, however, it was decreased on left side and bi-laterally in the female patient. The Sensory CV (of the sural nerve) was decreased on the left side in the female.
ii. Amplitude of the axillary nerve was decreased on the left side in the female. The amplitude of the peroneal nerve was decreased bi-laterally in the female.
iii. Latency was normal in the male in both upper and lower limbs. The female had increased latency in the lower limbs.

Table 1. The presenting features of the patients are shown in the following table

Presenting features	Patient 1 (♂)	Patient 2 (♀)
Delayed motor milestones	Yes	Yes
Walking delayed	Yes, at 3 years	Yes, at 2 ½ years
Difficulty in walking fast, getting up from lying posture and buttoning/unbuttoning shirt	Yes	Yes
Progressive generalized weakness	Yes, since 4 years with left foot drop	Yes, since 3 years without foot drop
Gower's sign	Positive	Positive
Nasal twang	Yes	Yes
Long narrow face	Yes	Yes
High arched palate	Yes	No
Marfinoid features	Yes	Yes
Generalized limb thinning	Yes	Yes

Table 2. Depicting CNS examination findings of the patients

	Motor examination				Sensory examination	Reflexes	
	Bulk	Tone	Power	Co-ordination		DTR	Plantar
Male	Generalized thinning in all limbs, wasting of Pectoralis Supra and infraspinatus with lower limb muscles	Decreased in all limbs	Shoulder B/L- 4/5 Elbow B/L-4/5 Wrist B/L- 4/5 Handgrip -90%	Within normal limits	Normal for pain, touch, temperature, position and vibration	Preserved in B/L Biceps, supinator, triceps, knees, ankles	B/L-Flexor
Female	Generalized thinning in all limbs along with wasting more so in lower limbs	Decreased in all limbs	Shoulder B/L- 4/5 Elbow B/L-4/5 Wrist B/L- 4/5 Handgrip -90%	Within normal limits	Normal for pain, touch, temperature, position and vibration	Preserved in B/L Biceps, supinator, triceps, knees, ankles	B/L-Flexor

Table 3. Table depicting comparison in clinical and investigative parameters investigated for both patients

Parameter	Patient 1	Patient 2
Weakness	Proximo-distal progressive muscle weakness	Proximo-distal progressive muscle weakness
Facial Weakness	Absent	Absent
Tone	Hypotonia	Hypotonia
Deep Tendon Reflexes	Preserved	Preserved
CPK Levels U/L	290	270
Conduction Velocity (CV) m/s	Motor CV- i. B/L median and ulnar normal, Axillary nerve ↓ ii. B/L tibial and peroneal- ↓ with ↓ amplitude Sensory CV: B/L median and ulnar normal	Motor CV: i. B/L median normal and ulnar ↓, Axillary nerve ↓ ii. B/L tibial and peroneal ↓ with ↓ amplitude Sensory CV: B/L median normal and ulnar ↓
EMG	Abductor digiti minimi showed normal pattern while biceps, tibialis anterior and deltoid showed a neuro-myopathic pattern while glutei, adductor longus and vastus medialis showed myopathic pattern Myopathic features characterized by- ↓ recruitment, amplitude with short duration motor unit potentials	Myopathic pattern in B/L; Adductor longus, Gluteus maximus/medius, peroneal longus and Vastus medialis ↑ affected w.r.t. B/L biceps, deltoid, abductor digiti minimi Myopathic features characterized by - ↓ recruitment, amplitude short duration motor unit potentials
Muscle Biopsy	Fascicular architecture with central nuclei migration in significant number of muscle fibres MGT- red coloured granular rods in myofibres seen in light microscopy.Histochemistry- type 1 predominance	Distorted muscle fibres with ragged appearance at places. MGT stain-granular rods in myofibres Ultra-structural studies- rods arising from Z band

Table 4. Depicting motor and sensory conduction velocity of upper and lower nerves

	Axillary (motor)						**Median (motor)**					
	Right			**Left**			**Right**			**Left**		
	CV	**L**	**A**	**CV**	**L**	**A**	**CV**	**L**	**A**	**CV**	**L**	**A**
M	56	2.8	12	58	2.92	11	52.1	4.2	7.9	52	4.37	7.8
F	48	3.1	6.4	49.6	3.02	6.7	51	4.37	7.3	50	4.2	7.2
	Ulnar (motor)						**Peroneal (motor)**					
	Right			**Left**			**Right**			**Left**		
	CV	**L**	**A**	**CV**	**L**	**A**	**CV**	**L**	**A**	**CV**	**L**	**A**
M	52.4	4.2	9.6	52	4.5	9.4	39	10.4	5.3	36.3	9.9	3.5
F	46	5.1	8.8	45	5.0	8.4	36	8.86	1.9	37.9	8.43	2
	Tibial (motor)						**Sural (sensory)**					
	Right			**Left**			**Right**			**Left**		
	CV	**L**	**A**	**CV**	**L**	**A**	**CV**	**L**	**A**	**CV**	**L**	**A**
M	41	9.5	18.6	37	10.7	2.5	60	1.88	33.6	57	1.92	47.5
F	36.1	9.6	7.5	32	10.6	8.2	54.5	2.29	96.7	48.3	2.17	99.1

INDEX: 1. M: Male Subject; F: Female Subject. CV: conduction velocity (m/s); L: Latency (milli secs); A: Amplitude (milli volts)

4. DISCUSSION

Wallgren-Pettersson and Laing have described the diagnostic features for classifying NRM based on the report of the 70th ENRMC International Workshop on Nemaline myopathy. The diagnostic features for Mild childhood or juvenile onset NRM are a childhood or juvenile onset of symptoms with no facial weakness or foot drop [13].

These diseases are generally nonprogressive or slowly evolving, phenomenologically involving the structural proteins of the muscle and thus, leading to floppiness. These patients have weakness, hypotonia, elongated facies, and skeletal deformities and, at times, may be associated with cardiomyopathy in view of the close structural resemblance of cardiac muscle to striated skeletal muscle. The disease manifests at different ages, depending on the penetrance of the genetic mutations. Clinically, neonatal, childhood and adult forms are distinguished on the basis of the age of onset and the clinical features. The neonatal form is the most severe, while childhood and adult forms have slower progression disease [5].

Ryan et al. reported pathologic findings in 124 Australian and North American cases of primary NRM. Rods were present in all skeletal muscles and diagnosis was possible at all ages. Most biopsies contained nemaline bodies in more than 50% of fibers, although rods were seen only on electron microscopy in 10 patients. He further classified NRM as congenital, childhood, and adult forms, on the basis of age of onset and clinical features [14].

Muscle biopsies were processed for H and E staining by Jain et al. [11]. The most common congenital myopathy was central core disease (24%) followed by nemaline rod myopathy and multi-mini core disease (20% each).

Several clinical types of NEM are recognized based on the age of disease onset and severity of muscle weakness, ranging from a severe neonatal often lethal subtype to milder non-progressive or slowly progressive forms that present in infancy, childhood or adulthood. Muscle weakness may be diffuse, but it is often most pronounced in the face, neck and proximal limb muscles. Pharyngeal and respiratory muscles are frequently affected Distal weakness appears late in the course of illness, but in some forms manifests at presentation [15].

In this study, the male patient presented with high arched palate; his sibling did not show this feature; both our subjects being categorized as Childhood form of NRM; contrary to North et al. who have reported this being a feature of congenital form of NRM [16]. Deepti et al. have discussed the clinical and diagnostic features of four patients of NRM. Of these four patients, two patients were categorized as Congenital Class NRM, one as Childhood NRM and the last as Adult type NRM. The patient diagnosed with Childhood NRM in the Deepti series was a 26 year old female who presented with slowly progressive Proximo-distal muscle weakness of both extremities since 2 years, no hypotonia of limbs or of neck muscles; no ocular, facial or bulbar weakness and no contractures or cardiac s/s. Serum was non-reactive for HIV type 1 and2. The biopsy of quadriceps revealed normal polygonal fibers with peripherally placed nuclei and sub-sarcolemmal aggregation of eosinophilic material. Modified Gomori.strichrome (MGT) stain and toluidine blue-stained resin sections revealed sub-sarcolemmal linear rods forming palisading clusters in a variable proportion of fibers (Nemaline Rods); however, both of our subjects were of the Childhood NRM type [5]. The features of both these patients were quite similar to those described by Deepti and co-workers; i.e. slowly progressive Proximo-distal muscle weakness of extremities, no neck hypotonia (though limb hypotonia was present), no ocular, facial or bulbar weakness and no contractures or cardiac complaints.

Clinical data of patients who were diagnosed with congenital myopathy between 2001 and 2006 was retrieved by Jain et al. [11]. Muscle biopsies were processed for HandE staining, enzyme histochemistry and immunohistochemistry. During the 6 year period, 1.12% of the muscle biopsies were diagnosed as congenital myopathies (25/2215). The most common congenital myopathy was central core disease (24%) followed by nemaline rod myopathy and multi-mini core disease (20% each). The case diagnosed as Childhood NRM was a 30 year old female, who presented with frequent chest infections and generalized muscle weakness; CPK levels were 272 IU/L; the EMG was myopathic pattern; the clinical diagnosis being myasthenia gravis with NRM as the histo-pathological diagnosis. Our two patients were younger; CPK levels were comparable (Table 3) in both cases; however the female patient had myopathic pattern on EMG, while the male sibling had normal, myopathic and neuro-

myopathic patterns in different muscles tested [Table 3].

EMG examination of the female patient in our study was myopathic in all muscles; in contrast abductor digiti minimi showed normal pattern while biceps, tibialis anterior and deltoid showed a neuro-myopathic pattern in the male patient with rest of the muscles had myopathic pattern. These findings were contrary to the findings of Youssef et al. wherein adults with NRM were showing neurogenic pattern with long duration, high amplitude, decreased recruitment and long polyphasic potentials [17]. They have reported that in adults with NRM, these features are primarily seen in distal muscles such as the tibialis anterior. In our study, the EMG of the male patient showed that the proximal muscles of the lower limb were more affected than the distal lower limb muscles with decreased recruitment, decreased amplitude and short duration motor unit potentials. In the female patient, lower limb muscles were similarly more affected; both proximal and distal muscles being equally affected i.e. early recruitment in adductor digiti minimi, deltoid and biceps; decreased recruitment in all three glutei, tibialis anterior and vastuslateralis with short duration motor unit potentials with decreased amplitudes.

Olive et al. have conducted a clinical study on a family from Spain of whom 4 had NRM, that included general neurologic exam, muscle strength assessment according to the Medical Research Council (MRC) grading scale, serum CK test, and, if affected, nerve conduction testing and concentric needle EMG. Respiratory function tests and cardiological examination including ECG, 24-hour-Holter monitoring, and echocardiography were performed in two affected individuals. The unaffected 7 members of this family were also included as a control group. The disease had started in childhood by affecting proximal and distal muscles and causing slowness of movements [15].

5. CONCLUSION

Nemaline myopathy should be suspected in children with generalized hypotonia, progressive muscle weakness with delayed motor milestones. Decrease in conduction velocity signifies peripheral neuropathy probably due to axonal degeneration affecting the myelinated/unmyelinated fibres. This report highlights the importance of EMG, CV, muscle-biopsy, CPK levels and ultra-structural examination in diagnosis of Nemaline rod myopathy in absence of the availability of genetic studies. According to Yiannikas et al., there is a reduction in density of myelinated fibers and electron microscope features of axonal degeneration affecting myelinated and unmyelinated fibers in NRM [18]. This may explain the decrease in conduction velocity seen in both the siblings in the instant study.

CONSENT

These patients were sent for Electrodiagnostic tests to confirm diagnosis of Nemaline Rod Myopathy from the Department of Medicine of our Institute. As they came on their own accord for these tests, no formal written consent was required.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=660&id=29&aid=5989