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ARTICLE

Ulnar sensory-motor amplitude ratio: a new tool to differentiate ganglionopathy from polyneuropathy

Razão de amplitude sensitivo-motora ulnar: novo parâmetro para diferenciar ganglionopatia de polineuropatia

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ABSTRACT

The objective of this study was to evaluate if the ratio of ulnar sensory nerve action potential (SNAP) over compound muscle action potential (CMAP) amplitudes (USMAR) would help in the distinction between ganglionopathy (GNP) and polyneuropathy (PNP). **Methods:** We reviewed the nerve conductions studies and electromyography (EMG) of 18 GNP patients, 33 diabetic PNP patients and 56 controls. GNP was defined by simultaneous nerve conduction studies (NCS) and magnetic resonance imaging (MRI) abnormalities. PNP was defined by usual clinical and NCS criteria. We used ANOVA with post-hoc Tukey test and ROC curve analysis to compare ulnar SNAP and CMAP, as well as USMAR in the groups. **Results:** Ulnar CMAP amplitudes were similar between GNP x PNP x Controls (p=0.253), but ulnar SNAP amplitudes (1.6±3.2 x 11.9±9.1 x 45.7±24.7) and USMAR values (0.3±0.3 x 1.5±0.9 x 4.6±2.2) were significantly different. A USMAR threshold of 0.71 was able to differentiate GNP and PNP (94.4% sensitivity and 90.9% specificity). **Conclusions:** USMAR is a practical and reliable tool for the differentiation between GNP and PNP.

Key words: clinical neurophysiology, ganglionopathy, polyneuropathy, sensory neuronopathy, ulnar nerve.

RESUMO

O objetivo deste estudo foi avaliar se a razão entre as amplitudes dos potenciais de ação sensitivo (SNAP) e motor (CMAP) do nervo ulnar (USMAR) auxiliaria na distinção entre ganglionopatia (GNP) e polineuropatia (PNP). **Métodos:** Revisamos os estudos de neurocondução e eletromiografia de 18 pacientes com GNP, 33 com PNP diabética e 56 controles. GNP foi definida pela presença simultânea de anormalidades na neurocondução e na ressonância magnética cervical. PNP foi definida por critérios clínicos e neurofisiológicos usuais. Usamos o teste ANOVA com Tukey post-hoc e análise da curva ROC para comparar o SNAP e CMAP ulnares, assim como o USMAR entre os grupos. **Resultados:** As amplitudes dos CMAPs ulnares foram similares entre GNP x PNP x Controles (p=0,253), mas as amplitudes dos SNAPs ulnares (1,6±3,2 x 11,9±9,1 x 45,7±24,7) e os valores de USMAR (0,3±0,3 x 1,5±0,9 x 4,6±2,2) foram significativamente diferentes. Um corte de 0,71 para a USMAR foi capaz de diferenciar GNP de PNP (sensibilidade de 94,4% e especificidade de 90,9%). **Conclusões:** A USMAR é um parâmetro útil e confiável para o diagnóstico diferencial entre GNP e PNP.

Palavras-Chave: neurofisiologia clínica, ganglionopatia, polineuropatia, neuronopatia sensitiva, nervo ulnar.

Ganglionopathies (GNP), also known as sensory neuronopathies, are a group of conditions characterized by primary and selective damage to the dorsal root ganglia (DRG) of the spinal cord and sensory nuclei of the brainstem[1,2]. The etiologies are diverse and include immune-mediated diseases, vitamin deficiencies, drug toxicity, paraneoplastic syndromes and genetic causes, but many patients are yet defined as idiopathic[1,2]. The clinical presentation is characterized by diffuse, often asymmetric, sensory deficits and marked ataxia due to loss of proprioception[1,2].

In neurological practice, it is important to differentiate GNP from polyneuropathies (PNP) because the etiologies, therapeutic strategies and prognosis are often diverse[3]. Clinically, GNP can be distinguished from PNP due to a purely sensory dysfunction and the absence of length-dependent gradient of involvement. Often it is not possible to define a clear pattern of symmetry or predominant distal involvement (either by clinical or electrophysiological criteria), making it difficult to distinguish a GNP from a sensory PNP.

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Nerve conduction studies (NCS) are able to evaluate separately peripheral motor and sensory fibers. This helps to determine the relative proportion of sensory over motor impairment in peripheral nervous system diseases, and might prove useful to separate GNP from PNP[4]. In this setting, we hypothesized that the ratio of the ulnar sensory nerve action potential (SNAP) amplitude divided by its compound muscle action potential (CMAP) amplitude would be a good parameter to assist in this differentiation. We have then proceeded with this investigation by reviewing and comparing NCS in a sample of patients with GNP, length-dependent PNP and healthy controls.

METHODS

Subjects

We reviewed the electrodiagnostic studies of 107 subjects: 18 patients with GNP, 33 patients with PNP, and 56 normal controls. All subjects were evaluated by clinical neurophysiologists from the Department of Neurology of the University of Campinas (UNICAMP) between 1998 and 2011. The study was approved by our institution Ethics Committee, and a written informed consent was obtained from all participants.

Inclusion criteria

GNP

The diagnosis of GNP was set when we could demonstrate simultaneous damage both to central and peripheral extensions of DRG[5,6]. This was established by a combination of electrophysiological and spinal cord magnetic resonance imaging (MRI) criteria: (1) NCS showed widespread reduction of SNAP amplitudes (in a sural nerve and at least one other sensory nerve of the upper limbs) combined with normal sensory conduction velocities, motor NCS and electromyography (EMG); (2) cervical spinal cord MRI showed hyperintense T2 lesions in the dorsal funiculi. Each GNP patient presented sensory ataxia and preserved motor strength.

PNP

The diagnosis of PNP was defined by NCS and clinical presentation. The NCS required at least one abnormality (potential amplitude, conduction velocity or distal latency) on at least two of the following nerves: median motor, peroneal motor, median sensory and sural. The clinical presentation required at least one abnormality along muscle strength, tendon reflexes, distal sensation or autonomic dysfunction judged to be due to diabetic polyneuropathy[7,8]. All patients in this group had diabetes mellitus, but no other possible etiologies for PNP. These were excluded through anamnesis and extensive laboratory work-up[8].

Control group

This group included only asymptomatic subjects with normal neurological examination, NCS and EMG[8].

Exclusion criteria

Patients with clinical or electrodiagnostic evidence of brachial plexopathy, C8-T1 radiculopathy or ulnar mononeuropathy were not included in our study[9].

Electrophysiology

NCS and EMG were performed using Nihon Kohden devices model MEB-9200J or Neuropack 2. All subjects had skin temperature maintained above 30ºC.

Ulnar sensory conduction studies were performed antidromically, with ring surface electrodes recording from the right fifth finger and stimulation at the right wrist at a distance of 100–140 mm from the active recording electrode. Stimulations were repeated 3–10 times to assure supramaximal stimulation, and the highest possible SNAP amplitude was registered.

Ulnar motor conduction studies were performed by recording with surface electrodes on the abductor digiti minimi muscle of the right hand and stimulating at the wrist, 40–70 mm away from the active recording surface electrode. Stimulations were repeated 3–10 times to assure supramaximal stimulation, and the highest CMAP amplitude was recorded. Responses obtained by more proximal stimulations were not considered in the study.

Additional NCS and EMG were performed to assess motor impairment or length-dependent gradient of involvement according to inclusion and exclusion criteria described above. Those additional studies are not reported here.

Ulnar sensory-motor amplitude ratio (USMAR) was calculated by dividing the ulnar SNAP amplitude (uV) by the distal ulnar CMAP amplitude (mV) for each subject.

Statistical analysis

Demographic and NCS data of patients and controls are detailed with descriptive statistics. We compared the ages and the gender distribution in the three groups using ANOVA and Pearson's chi-square tests, respectively. Ulnar SNAPs, ulnar CMAPs and USMAR values were compared in the GNP, PNP and control groups using ANOVA, with post-hoc Tukey test for the USMAR values. We used a ROC curve to assess the usefulness of USMAR in the differentiation between GNP and PNP. Level of significance was set at α=0.05 for all comparisons. Statistical analyses were performed with SYSTAT v9.0 (San Jose, CA) and SPSS v17 (Chicago, IL) softwares.

RESULTS

Group characteristics

The groups were similar in respect to gender distribution and mean age (p=0.108 and 0.06, respectively) (Table). In the PNP group, 32 out of 33 patients had reduced or absent ankle jerk, 28 had impaired vibration sensation at the hallucis and 2 had gait instability.

Table. Demographic and neurophysiological data of the subjects included in the study.

	GNP (n=18)	PNP (n=33)	Controls (n=56)	p-value*
Age (mean±SD, years)	53.0±2.7	56.9±7.0	52.0±11.4	0.06
Gender (M:F)	10:8	21:12	23:33	0.11
Ulnar SNAP amplitude (mean±SD, μV)	1.6±3.2	11.9±9.1	45.7± 24.7	<0.001
Ulnar CMAP amplitude (mean±SD, mV)	12.0±6.2	9.0±2.6	9.3±1.6	0.33
USMAR (mean±SD)	0.3±0.3	1.5±0.9	4.6±2.2	<0.001

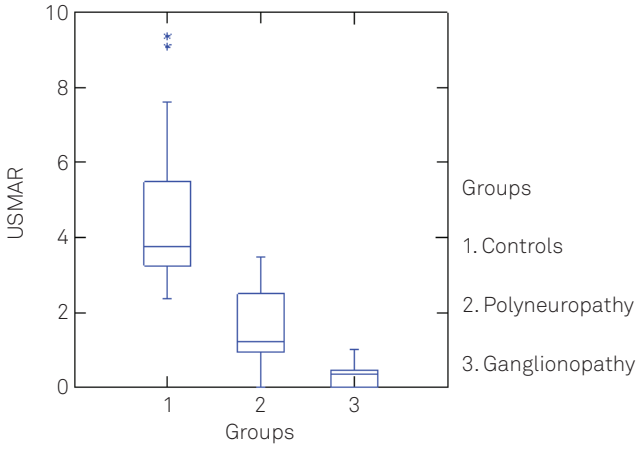
*ANOVA p-values; GNP: ganglionopathies; PNP: polyneuropathies; SD: standard deviation; M: male; F: female; SNAP: sensory nerve action potential; CMAP: compound muscle action potential; USMAR: ulnar sensory-motor amplitude ratio.

SNAP, CMAP and USMAR distribution

No significant difference was observed regarding the CMAP amplitudes of the ulnar nerve (p=0.253). We found significant differences between ulnar SNAP amplitudes and USMAR values among each of the three groups (p<0.001 and p<0.001, respectively) (Table). As expected, the lowest mean USMAR was observed in the GNP group, and the highest in the control group (Fig 1).

ROC curve

The area under the ROC curve was 0.929, showing that USMAR was able to differentiate both groups (Fig 2). A cutoff of 0.71 for USMAR presented the best profile to discriminate between GNP and PNP (94.4% sensitivity and 90.9% specificity).



USMAR: ulnar sensory-motor amplitude ratio.

Fig 1. Box and Whiskers Plot showing the distribution of ulnar sensory-motor amplitude ratio values in the three groups.

DISCUSSION

GNP are a distinctive group of peripheral nervous system diseases and may be the first manifestation of systemic disorders, such as cancer and Sjögren's syndrome[10,11]. In clinical practice, GNP must be differentiated from sensory PNP, but this is not always a simple task. The hallmarks of GNP — disproportionate sensory involvement and multifocal distribution of deficits — are often difficult to determine either by clinical or electrophysiological criteria. Sometimes, additional investigation such as spinal cord MRI, skin biopsy with epidermal nerve fiber density evaluation or even dorsal root ganglia biopsy is needed to reach the correct diagnosis[6,12-14]. Although valuable, some of these tests are expensive, invasive and time-consuming. Therefore, other diagnostic tools are needed to differentiate GNP and PNP.

Camdessanché et al. investigated whether SNAP amplitudes of the median, ulnar, radial, sural and superficial peroneal nerves would individually enable the distinction between GNP and PNP[3]. They found that nerves in the upper limbs are significantly more compromised in GNP, but using different thresholds to separate GNP and PNP sensitivity and specificity values ranged between 70 and 85%[3]. This motivated us to investigate other parameters derived from NCS that might work better.

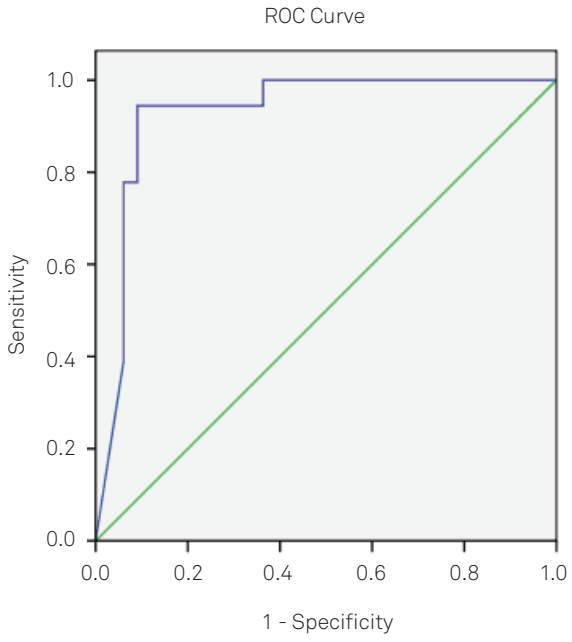


Fig 2. ROC curve for the determination of threshold differentiating ganglionopathy from polyneuropathy.

Severe involvement of distal sensory nerves of the legs (sural and superficial peroneal) is a frequent finding both in GNP and PNP, sometimes with unobtainable sural SNAPs on more severe cases[3]. This limits the usefulness of indices that rely upon SNAP amplitudes of these nerves to differentiate GNP and PNP, such as the sural/radial amplitude ratio (SRAR)[15,16]. In our study, we have thus chosen to investigate an upper limb nerve. Although the median nerve could have been used for the same purpose, the ulnar nerve was preferred due to a lower rate of entrapment mononeuropathies[17-19]. Radial nerve was not chosen either, because motor NCS of this nerve are not routinely performed. To assess the proportion of sensory over motor involvement, not covered by the previous indices, a comparison of SNAP and CMAP amplitudes of the same nerve through a ratio was an intuitive choice. Furthermore, such ratios compare different nerves in the same patient, which possibly reduces variability due to aging, as discussed by Rutkove et al.[15].

Numerical indices based on electrodiagnostic studies have already been proposed for similar situations. Cocito et al. elaborated the Terminal Latency Index (TLI) and found that low values (<0.26 for the median nerve and <0.33 for the ulnar nerve) suggested anti-MAG neuropathy instead of classical chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)[20]. Regarding common PNP, Rutkove et al. assessed the expected length-dependent gradient of involvement with their SRAR, for which values lower than 0.40 were considered as a good parameter for the diagnosis of mild axonal PNP[15]. In a further study, the threshold value to separate healthy controls and patients with neuropathy was 0.36[16].

As expected, our results showed lower USMAR values for the GNP patients when compared to those of diabetic PNP patients. Statistical analysis revealed that a USMAR value equal to or lower than 0.71 was able to differentiate GNP from diabetic PNP with a good combination of sensitivity and specificity (94.4 and 90.9%, respectively), confirmed by ROC curve analysis. These values indeed proved better than isolated SNAP values of upper limb nerves to discriminate GNP and PNP[3].

We have chosen diabetes mellitus as the single etiology for the PNP group because this is the most frequent and the best studied model of length-dependent PNP[21,22]. By choosing a unique etiology, the PNP group was made more homogeneous, which helped in the comparison with GNP. In addition, there is no description of GNP related to diabetes. Despite this, we acknowledge that further prospective studies with other etiologies for PNP are needed for a wider validation of USMAR. Another limitation, related to the study design, is due to the asymmetry often found in GNP, so that our research could be improved with bilateral calculation of the USMAR. We also emphasize that a complete ulnar electrodiagnostic evaluation should be performed before the USMAR calculation in order to exclude focal mononeuropathies, since these might obviously influence the result.

We conclude that the USMAR is a useful and reliable tool for the differential diagnosis between GNP and PNP. It can be easily calculated in any standard electrodiagnostic evaluation, with no additional cost or significant time spending.

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