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Kind and distribution of cutaneous sensation loss in hereditary transthyretin amyloidosis with polyneuropathy

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ABSTRACT

Objective: Report on the kind and distribution of somatotopic sensation loss and its utility in assessing severity of sensation loss in study of a large international cohort of patients with hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN).

Methods: Smart Somatotopic Quantitative Sensation Testing (S ST QSTing) using Computer Assisted Sensation Evaluator IVc (CASE IVc) was used to assess the somatotopic distribution of touch pressure (TP) and heat pain (HP) sensation loss twice of untreated hATTR-PN patients in the Ionis NEURO-TTR trial (www.clinicaltrials.gov, NCT01737398).

Results: Of the studied cohort of 169 patients, 163 (97%) had sensation loss, both TP and HP in 121/169 (75%), TP only in 39/169 (23%), and HP only in 3/169 (2%). Sensation loss typically affected both lower (152/169–90%) and upper limb (135/169–82%), and overall TP sensation loss was greater than HP loss, except for early-onset Val30Met patients in which HP exceeded TP loss.

Conclusion: Using S ST QSTing, a highly quantitated, standardized, referenced, and automated QSTing approach of the body's surface distribution of sensation loss we have shown that: 1) reliable and useful measurement of the body surface distribution of sensation loss is possible; 2) this measure is abnormal in most patients with hATTR-PN and is an indication of polyneuropathy severity; and 3) cutaneous sensation loss involves both large and small sensory fibers in this disease but slightly more small fibers in early onset Val30Met patients.

1. Introduction

Hereditary transthyretin amyloidosis with polyneuropathy (hATTR-PN) is a dominantly inherited disease caused by 1 of > 120 different point mutations in the transthyretin (TTR) gene. hATTR-PN causes a progressively severe sensorimotor-autonomic polyneuropathy. The disease, if untreated, causes death in 7.5 to 15 years [1]. The most commonly affected tissue is the peripheral nervous system, then heart and other organs [2]. Sensory nerve fiber degeneration is a prominent feature at biopsy or necropsy [3,4]. The somatotopic distribution and severity of sensation loss in this disease is still incompletely studied [5].

The usual clinical evaluation of somatotopic sensation loss is not ideal [6,7]. Standard quantitative and graded stimuli are not used, algorithms of testing are not standard, defined or validated, and reference values for somatotopic sites studied are not available. Even quantitative sensation testing at a standard site, e.g., of the foot or hand, provides only limited information because it is restricted to a single site which is not representative of the body surface distribution of sensation loss [6]. However, in the hands of expert neurologists, and despite these shortcomings, some previous studies have found that hATTR-PN is characterized by early distal limb sensation loss followed later by more widespread and severe loss of both small and large fiber sensation [8–11]. However, it is generally thought that clinical assessment of the body surface distribution of sensation loss would be insufficiently

Abbreviations: ANOVA, Analysis of variance; CASE IVc, Computer Assisted Sensation Evaluator IVc, manufactured by WR Medical Electronics, Maplewood, MN, USA; hATTR-PN, hereditary transthyretin amyloidosis with polyneuropathy; HP 0.5, heat pain threshold of 1–10 severity; HP5, heat pain stimulus response 5 of 1–10 severity; NIS, Neuropathy Impairment Score; PND, polyneuropathy disability; QST, quantitative sensory testing; S ST QSTing, Smart Somatotopic Quantitative Sensory Testing; TP, touch pressure sensation; TTR, transthyretin

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accurate and reproducible for the conduct of therapeutic trials. With the introduction of Computer Assisted Sensation Evaluator IVc (CASE IVc) and Smart Somatotopic QSTing programs, this assumption is no longer valid.

Computer-assisted (smart) somatotopic quantitative sensory testing (S ST QSTing) of the body's surface area, as used in this study, has been introduced to detect, characterize, and quantitate the kind, severity, and distribution of sensation loss over the body's surface area and to be able to do this reproducibly at different times and different medical centers. S ST QSTing, as performed with CASE IVc uses quantitated and graded touch pressure (TP) and heat stimuli, validated algorithm of testing and finding threshold and test scores, expressed as percentile values specific for modalities of sensation, and corrected for applicable variables of age, gender, anthropomorphic variables, and for somatotopic sites. Except for patient instruction, manual testing of the TP stimuli, and key entry of test responses, all aspects of testing, comparison to reference values, and reporting of results are automated [12]. It provides accurate assessment of sensation loss with low intra- and interobserver variability [13]. S ST QSTing evaluates both small (heat-pain (HP)) and large (TP) modalities of sensation loss.

In a retrospective review of patients with diabetes and hATTR-PN, we recognized that the somatotopic distribution of sensation loss was inadequately quantitated using usual QSTing at only a single anatomical site of the foot, which led to development of S ST QSTing [12,14]. This new approach was studied in the first 100 hATTR-PN patients entered into the Ionis NEURO-TTR trial. S ST QSTing measures provided a needed small sensory nerve measure in the composite measure, mNIS + 7_{Ionis} [15]. Although HP5 did not correlate with the Neuropathy Impairment Score (NIS) or its subscores, it did with small fiber symptoms of Neuropathy Symptom and Change Score (neuropathy symptoms score). Also, it was shown that trained technologists from multiple international centers could perform S ST QSTing proficiently. In addition, it was demonstrated that mNIS + 7 $_{Ionis}$, which included somatotopic measures of TP and HP, correlated significantly with neurologic signs, and disability and quality of life scores.

The present study assesses the kind and body distribution of sensation loss in a large international cohort of hATTR-PN patients. We assess whether sensation loss is more severe in legs than in arms. Furthermore, we assess whether TP is more affected than HP sensation and whether it is different among genetic mutations, e.g., in early-onset Val30Met, late-onset Val30Met, and non-Val30Met hATTR PN patients. We also consider whether the S ST QSTing score provides sufficiently good characteristics and scores to be useful in monitoring severity of neuropathy and a treatment effect in therapeutic trials.

2. Materials & methods

The Ionis NEURO-TTR trial has been described in detail [16]. One of the primary outcome measures of the trial was mNIS + 7_{Ionis}, which includes S ST QSTing results as one of the +7 tests.

2.1. Description of mNIS + 7_{Ionis}

mNIS + 7_{Ionis} was described in previous publications [15,16]. The clinical and neurophysiological assessments were performed by neurologists, neurophysiologists, and technologists specially trained and certified for the trial. The components of mNIS + 7_{Ionis} are: NIS (values from 0 to 244), scored examination of muscle weakness, muscle stretch reflexes and sensation loss, five attributes of nerve conduction (± 18.6), heart rate deep breathing test (± 3.72), and S ST QSTing of TP and HP (0–80).

2.2. S ST QSTing

S ST QSTing evaluates small and large sensory nerve fiber dysfunction over the body's surface area using CASE IVc, made available to all study centers by WR Medical Electronics (Maplewood, MN, USA). Patients had to be alert and cognitive to testing and should not have taken mind-altering medical or recreational drugs or analgesics during the preceding 12 h before testing.

2.3. QSTing of TP

TP sensation was assessed using Dyck modification of Semmes-Weinstein nylon monofilaments providing nine magnitudes of force when bent to 5/6th of their extended length of −3,-2,-1, 0, 1, 2, 3, 4 & 5 ln gms. A forced choice algorithm of testing using a stimulus and a null stimulus given in pairs was used to estimate thresholds. Technologists used care to minimize impact with application of stimuli. The specific stimulus (null stimulus) to be given, the magnitude of monofilament to be used, the algorithm of testing and estimating thresholds, and comparison to stimulus reference values at defined somatotopic sites was managed by the software described in earlier publications [15,17]. Reference values specific for the ten possible somatotopic sites had been programmed into the CASE IVc system [19]. Detection thresholds for tested sites were expressed as a test step value, a percentile and point value (i.e., < 95th = 0; ≥95th– < 99th = 1; ≥99th = 2).

2.4. HP thresholds

For HP testing, the CASE IVc system employs a thermoelectric unit with a surface area of 3 × 3 cm. At defined somatotopic sites, it is used to assess heat as pain thresholds (HP 0.5), an intermediate level of pain severity (HP5 of 1–10 pain severity), and the stimulus response slope (HP5–0.5). In previous reports, we have described the increasing pyramidal- and trapezoid-shaped heat stimuli (steps 1–25) available to estimate the HP thresholds [18]. Thresholds are also expressed as percentiles and point scores. In S ST QSTing of HP, we use HP5 at ≥95th as low-grade abnormality and at ≥99th percentile as a more specific level of abnormality. In a recent paper, we provide healthy subject reference values for 10 unilateral somatotopic sites [19].

2.5. S ST QSTing algorithm

The S ST QSTing algorithm of testing was designed to assess the somatotopic distribution of TP and HP sensation loss assuming that the polyneuropathy impairments assessed are the same on both sides of the body, are length dependent within limbs, and can vary from only distal lower limb to more generalized somatotopic involvement. The approach used in S ST QSTing is shown in Fig. 1. The same 10 anatomic sites were used for TP and HP, as applicable. For the usual hATTR-PN patient, it was planned to perform the test in approximately two hours or less. To do this, several strategies were used in the design of the algorithm of testing; only one side of the body is evaluated (left side), assuming symmetry. Testing begins at site 2 (lateral leg) for lower limb and trunk sites and site 8 (volar forearm) for upper limb and face sites, assuming length-dependence of sensation loss. If at site 2 or 8 thresholds are < 95th, only sites 1 and 7 need to be tested, assuming length dependence. If thresholds at sites 2 or 8 are ≥95th, sequentially more proximal sites need to be tested until thresholds at these more proximal sites are < 95th. If thresholds at sites 2 or 8 are ≥99th, sites 1 or 7 need not be tested, a value ≥99th (a score of 2) being assigned. If thresholds at sites 2 or 8 are ≥95th - < 99th, sites 1 and 7 must be tested. Point scores are scored to give scores from 0 to 40 for one side and 0–80 for both sides of the body. In the Ionis NEURO-TTR oligonucleotide trial, S ST QST results were submitted to the Mayo Clinic Peripheral Nerve Laboratory for quality review.

2.6. Analysis plan

Data was analyzed using standard statistical techniques with a