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Review Article

Development of measures of polyneuropathy impairment in hATTR amyloidosis: From NIS to mNIS + 7

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ABSTRACT

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is a rare, life-threatening disease, caused by point mutations in the transthyretin gene. It is a heterogeneous, multisystem disease with rapidly progressing polyneuropathy (including sensory, motor, and autonomic impairments) and cardiac dysfunction. Measures used to assess polyneuropathy in other diseases have been tested as endpoints in hATTR amyloidosis clinical trials (i.e. Neuropathy Impairment Score [NIS], NIS-lower limb, and NIS + 7), yet the unique nature of the polyneuropathy in this disease has necessitated modifications to these scales. In particular, the heterogeneous impairment and the aggressive disease course have been key drivers in developing scales that better capture the disease burden and progression of polyneuropathy in hATTR amyloidosis.

The modified NIS + 7 (mNIS + 7) scale was specifically designed to assess polyneuropathy impairment in patients with hATTR amyloidosis, and has been the primary endpoint in two recent, phase III studies in this disease. The mNIS + 7 uses highly standardized, quantitative, and referenced assessments to quantify decreased muscle weakness, muscle stretch reflexes, sensory loss, and autonomic impairment. Physicians using this scale in clinical trials should be specifically trained and monitored to minimize variability. This article discusses the different scales that have been/are being used to assess polyneuropathy in patients with hATTR amyloidosis, their correlation with other disease assessments, and reflects on how and why scales have evolved to the latest iteration of mNIS + 7.

1. Introduction

Hereditary transthyretin-mediated amyloidosis (hATTR amyloidosis) is an inherited, rapidly progressive, life-threatening disease [1–3]. It is caused by mutations in the transthyretin (TTR) gene that result in misfolded TTR proteins which aggregate as amyloid deposits in multiple tissues, leading to a multisystem disease with a broad clinical presentation [1,4,5]. Symptoms include sensory, motor, autonomic, and cardiac dysfunction that can lead to significant morbidity and disability, and mortality; the median survival is 4.7 years following diagnosis, with a reduced survival (3.4 years) for patients presenting with cardiomyopathy [6–9]. The disease has historically been described according to the predominant phenotype, typically either polyneuropathy impairment (also known as familial amyloidotic polyneuropathy) or cardiomyopathy (also known as familial amyloidotic cardiomyopathy); however, it has become apparent that a large majority of patients exhibit signs and symptoms of both polyneuropathy and cardiomyopathy [3,10,11].

The polyneuropathy signs associated with hATTR amyloidosis were first described by Corino de Andrade in 1952, who noted the rapidly progressive nature of this disease [12]. Subsequent research has confirmed that a range of sensory and motor impairments are reported by patients with hATTR amyloidosis with polyneuropathy, the most common of which include neuropathic pain, altered sensation (i.e. decreased pain sensation), numbness, and tingling, along with muscle weakness and impaired balance which lead to difficulty walking [13–15]. The pathologic process typically involves small-fiber damage early in the disease course, often with subsequent damage to peripheral

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motor and sensory nerves that results in sensorimotor polyneuropathy [12,15]. Autonomic impairment is also frequently observed, and includes nausea and vomiting, changes in gastrointestinal motility, orthostatic hypotension, bladder dysfunction, and erectile dysfunction [8,13]. This spectrum of impairments necessitates a composite measure that captures these different features.

The extent of disability has been a longstanding measure of neuropathic burden in hATTR amyloidosis, typically captured by the Familial Amyloidotic Polyneuropathy (FAP) staging system and/or the polyneuropathy disability (PND) scoring system. FAP staging was developed in an endemic area of Portugal in 1980 [16], and encompasses three stages: FAP stage 1 is defined by unassisted walking, in which patients typically experience mild bilateral neuropathy in the feet and legs [16,17]; stage 2 is defined by the patient requiring assistance walking with crutches or sticks, with neuropathy developing throughout the body [16,17]; and stage 3 is defined by the patient becoming wheelchair-bound or bedridden, with severe neuropathy [16,17]. PND scoring involves a greater separation of disease stages: a score of I indicates sensory disturbance but with preserved walking capacity; II indicates unassisted walking but with difficulty; IIIa indicates one stick or crutch is required for walking; IIIb indicates two sticks or crutches are required for walking; and IV indicates the patient is wheelchair-bound or bedridden [18].

While assessing polyneuropathy in hATTR amyloidosis in this manner can provide a broad indicator of overall disease state, it can take up to 5 years for patients to transition from one FAP stage/PND score to another [17]. As such, these measures are insensitive to tracking disease progression over shorter time periods and are impractical for use as primary outcome measures in clinical trials. Hence, the Neuropathy Impairment Score (NIS), the NIS-lower limb (NIS-LL; a subset of the NIS), and the NIS + 7 (a variation of NIS that includes nerve conduction studies and quantitative sensory and autonomic endpoints) have all been utilized in studies of patients with hATTR amyloidosis [19,20]. These tools were developed, and have been used successfully, across a range of neuropathies [21–23], yet their value for hATTR amyloidosis is limited due to the unique nature of this disease. For example, hATTR amyloidosis with polyneuropathy has a more rapid progression than diabetic polyneuropathy [5,24], and a wider range of impairment (especially sensory and autonomic) compared with chronic inflammatory demyelinating polyneuropathy [13]. To better capture the different features of polyneuropathy in patients with hATTR amyloidosis, and to afford more sensitive detection of disease progression (or even improvement with treatment), these scales have been modified to create the modified NIS + 7 (mNIS + 7) [25–27]. As the primary endpoint in two recent phase III trials, this has become an important measure of polyneuropathy as part of this multisystem disease. This article will discuss the assessment of polyneuropathy in hATTR amyloidosis, the use of NIS and NIS-based scales, and reflect on how and why the different scales have evolved toward the mNIS + 7 iteration.

2. NIS

NIS was designed to provide standard, quantitative, and overall scores of neurologic impairments for the purpose of ongoing evaluation of patients in clinical trials and epidemiologic studies [28]. In addition, it can be used to quantify impairment and progression of neuromuscular conditions at diagnosis and during treatment [28]. It is a composite score of clinical impairments (weakness, reflex loss, and sensory loss) using standard assessment of muscle weakness and groups of muscles, reflexes and sensory modalities at specific sites on both sides of the body (Table 1), and was constructed to provide a balance between these impairments but with the greatest emphasis on weakness [21]. The total NIS is graded on a scale of 0–244, with a higher score indicating greater impairment [29]; a 2-point change is considered the least degree of change a physician could recognize [30]. NIS was developed from two historical approaches to grading neurologic impairment, one from the medical research council (MRC) and the other from the Mayo Clinic (Rochester, MN). The Mayo Clinic grading approach, which measures weakness and sensation loss using a linear scale of severity, was adopted over the MRC approach which was designed for assessment of very severe neurologic damage and only evaluates muscle weakness [28].

To assess the reproducibility of NIS, 12 trained investigators (neurophysiologists and diabetologists) graded 24 masked patients on two occasions with or without varying severities of diabetic polyneuropathy. In this study, in which patients' neuropathic signs were assessed based on individual physicians' usual evaluations, intra- and inter-test variability was high [31]. However, in a repeat study, in which the physicians were asked to grade only unequivocally abnormal neuropathic signs (taking into account variables of age, sex, physical fitness, and physical characteristics), the intra- and inter-test variability was significantly lower [32]. These studies suggest that in clinical trials, NIS should be used only by expert examiners who have preliminary consensus training and surveillance throughout the study.

In controlled clinical trials, using qualified and trained neurologists as examiners, NIS has been used to assess disease progression and response to treatment in a number of polyneuropathies [22,33–35]. In studies of patients with hATTR amyloidosis, NIS has been correlated to various measures of disease impairment, suggesting that the scale is of value for quantitative surveillance of severity of this disease. For example, in the first 100 patients of the phase III trial of the antisense oligonucleotide inotersen in patients with hATTR amyloidosis and polyneuropathy, total NIS was significantly correlated with functional health and disability scores including PND score, Dyck/Rankin score, and Inflammatory Neuropathy Cause and Treatment from Neuropathy Symptoms and Change. Furthermore, in an international natural history study of 283 patients with hATTR amyloidosis and polyneuropathy, NIS was positively associated with FAP staging and PND score [5]. Patients in this study had an estimated NIS increase of 14.3 points per year, suggesting more rapid disease progression than patients with diabetic polyneuropathy for whom the expected increase in NIS is 0.5 points per year [5,24].

NIS was used as a secondary endpoint in a controlled clinical study assessing the effect of diflunisal in patients with hATTR amyloidosis and polyneuropathy, and was able to detect a significant difference ($p < .01$) between treatment and placebo groups at 1 and 2 years (at 2 years, NIS scores increased by 22.8 points in the placebo group compared with 6.7 points in the diflunisal group) [20]. It was also the primary endpoint in a 3-year observational study of tafamidis treatment in 61 patients with hATTR amyloidosis and polyneuropathy, with patients having a mean increase of 15.6 points after 18 months of treatment [36]. In addition, scales based on NIS (NIS-LL, NIS + 7, and mNIS + 7) have been used as the primary endpoints in four placebo-controlled clinical trials (Fig. 1) to assess the effect of pharmacologic treatments on patients with hATTR amyloidosis and polyneuropathy [19,20,26,27].

3. NIS-LL

The NIS-LL is a subset of the NIS using measurements that quantify weakness, reflexes, and sensation in the lower limbs only, and has been primarily utilized in evaluation of length-dependent neuropathies that affect the longer nerve fibers of the lower limbs [21,33,37,38]. The rationale for its use in hATTR amyloidosis is the length-dependent nature of polyneuropathy in this disease, which can be predominant in the lower limbs, particularly in the early stages of the disease [17,25]. NIS-LL was used as a co-primary endpoint to measure the efficacy of tafamidis in the pivotal phase II/III study in patients with early-stage hATTR amyloidosis and polyneuropathy, with an increase of < 2 points at 18 months classified as a “response” (considered the least recognizable degree of change) [19] [30]. Worsening in NIS-LL was observed in the placebo arm of this study (increase of 5.8 points in 18 months),

Table 1
Assessments, grading, and scales of NIS.

	Weakness	Reflexes	Sensation
Assessment	Muscle strength in 24 muscle groups	Muscle stretch reflexes in five muscle groups	Touch-pressure Vibration Joint position Pinprick
Area of body	Cranial (five muscle groups) Upper body (11 muscle groups) Lower body (eight muscle groups)	Biceps Triceps Brachioradialis Quadriceps Ankle[a]	Index finger Great toe
Grading	0: normal 1: 25% weak 2: 50% weak 3: 75% weak 3.25: can just move against gravity 3.50: can move with gravity just eliminated 3.75: muscle contraction can be felt or seen but no visible movement 4: paralysis	0: normal 1: decreased 2: absent	0: normal 1: decreased 2: absent
Scale[b]	0–192	0–20	0–32

NIS Neuropathy Impairment Score.
[a] To account for over-scoring of muscle stretch reflexes in older age groups, decreased and absent reflexes at the ankle are graded 0 and 1, respectively, in patients 50–69 years, and in patients ≥70 years absent ankle reflexes are graded 0.
[b] All assessments are made on both sides of the body.

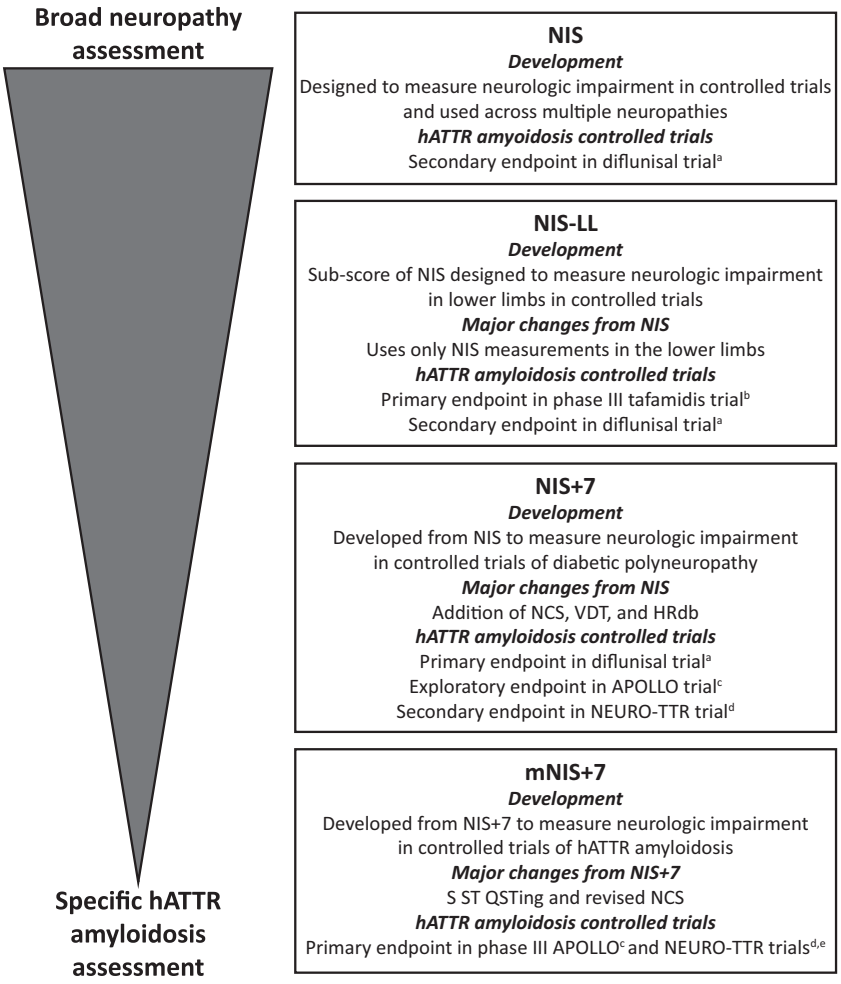

Fig. 1. The evolution of NIS to mNIS + 7 for hATTR amyloidosis. [a]Berk et al. [20]. [b]Coelho et al. [19]. [c]Adams et al. [26]. [d]Dyck et al. [49]. [e]Individual components of mNIS + 7_{Ionis} are secondary endpoints in the NEURO-TTR trial. *hATTR amyloidosis* hereditary transthyretin-mediated amyloidosis, *HRdb* heart rate with deep breathing, *mNIS + 7* modified Neuropathic Impairment Score + 7, *NCS* nerve conduction studies, *NIS* Neuropathy Impairment Score, *NIS + 7* Neuropathy Impairment Score + 7, *NIS-LL* Neuropathy Impairment Score-lower limb, *S ST QST* smart somatotopic quantitative sensation testing, *VDT* vibration detection threshold.

fitting with the known disease course [19]. However, the NIS-LL progression was reduced in patients treated with tafamidis, and the proportion of responders was significantly higher in the tafamidis arm compared with the placebo arm for the efficacy-evaluable population (patients who completed the study as per protocol), although not the intent-to-treat population [19]. Since this trial, the two points change in NIS-LL has been used as a surrogate for response/progression in several additional studies, both of tafamidis and other agents [36,39,40].

3.1. Limitations of NIS and NIS-LL in hATTR amyloidosis

While NIS and NIS-LL have been used successfully in clinical trials of patients with hATTR amyloidosis, there is some variability inherently associated with the use of examiner-based assessments [26]. By comparison, assessments of motor and sensory nerve conduction are more objective, quantitative, and referenced. Using expert electromyographers, pre-training instruction, and certification, appropriately chosen attributes of nerve conduction can provide highly validated measures of neuropathy in hATTR amyloidosis with polyneuropathy [25,41].

A further limitation of the use of NIS-LL in hATTR amyloidosis is that polyneuropathy often occurs in the upper limbs, forearms, fingers, and in severe disease, even the trunk; these changes are not captured by lower limb assessments [13,26]. Assessment of sensation is also limited to specific body sites (great toe [both scales] and the index finger [NIS only]), although sensation loss can occur over the body's surface in this disease. In addition, autonomic dysfunction is not measured by either scale, even though it has been commonly observed in patients with hATTR amyloidosis and can have a significant impact on quality of life [42].

4. NIS + 7

The NIS + 7 scale uses the same weakness, reflexes, and sensation measures as the NIS, combined with seven additional assessments that were included to better characterize and quantitate neuropathic impairment [30]. Five of these additional assessments are nerve conduction studies (NCS), focused on 3 nerves in the lower limbs: tibial nerve distal motor latency; peroneal nerve compound muscle action potential amplitude, distal motor latency and conduction velocity; and sural sensory nerve action potential amplitude [20,25]. These NCS data measurements should be acquired using a uniform protocol and reviewed at a central center to ensure reproducibility [43]. The additional two components of the NIS + 7 are vibration detection threshold (VDT), a sensory measure taken at the great toe, and heart rate response to deep breathing (HRdb), which serves as a measure of autonomic dysfunction. Both are highly standardized and referenced tests [25,44,45].

The NIS + 7 was developed and validated as an endpoint for clinical trials in diabetic sensorimotor polyneuropathy, which typically features milder neuropathic impairment than hATTR amyloidosis [30,46]. However, NIS + 7 was the primary endpoint in a controlled clinical study assessing the effect of diflunisal in patients with hATTR amyloidosis and polyneuropathy, and was able to detect a significant difference between treatment and placebo groups at 1 and 2 years (at 2 years, NIS + 7 scores increased by 26.3 in the placebo group, and by 8.7 points in the diflunisal group) [20].

One potential concern of adding neurophysiologic tests (such as NCS studies) to the measures of clinical signs already included in NIS (such as muscle weakness), is an overlap between clinical measurement of weakness of a muscle group and a neurophysiologic measurement of a component of the same muscle group. However, including both testing types allows for the capture of a broad range of polyneuropathy dysfunction and provides the benefit of having both the more objective neurophysiologic tests and direct assessments of patient symptoms provided by the clinical signs testing. The neurophysiologic tests can also be used as an independent confirmation of the clinical signs measurements.

4.1. Limitations of NIS + 7

To test the suitability of the scale for patients with hATTR amyloidosis, a retrospective analysis of 97 patients was performed [25]. While NIS + 7 adequately assessed weakness and muscle stretch reflexes, ceiling effects (patients at the maximal or minimal score available for their evaluation) were detected for sensation loss, nerve conduction abnormalities, and autonomic dysfunction. For example, the tests performed could not differentiate between a patient who had a loss of sensation only at the toes and a patient with loss of sensation from the knee downward. Large-fiber sensory dysfunction is also emphasized over small sensory fiber dysfunction, and sensation loss is underemphasized as NIS + 7 is weighted toward weakness (71% of total score). Assessment of the five NCS suggested they were not ideally suited for studying hATTR amyloidosis as attributes were often unevaluable (for example, because amplitudes were zero). Finally, autonomic dysfunction was not adequately assessed by only using HRdb [25].

5. mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis}

Incorporating the recommended changes to NIS + 7, two recently completed phase III trials in hATTR amyloidosis with polyneuropathy have used modified versions of the NIS + 7 as their primary endpoints. The APOLLO trial assessing the RNAi therapeutic patisiran used the mNIS + $7_{Alnylam}$, whereas the NEURO-TTR trial assessing inotersen used a slightly different version termed the mNIS + 7_{Ionis} [26,27]. These scales were designed to assess a broad range of abnormality, ranging from mild to severe, and are the first to be developed specifically for detecting polyneuropathy progression in clinical trials of patients with hATTR amyloidosis and polyneuropathy.

The mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis} scales both employ the same weakness and reflex assessments and scoring as the NIS, and include NCS measures that are revised from the NIS + 7. Both tools discard VDT in sensation assessment, and instead include smart somatotopic quantitative sensation testing (S ST QST) [26,27]. However, the mNIS + $7_{Alnylam}$ uses only S ST QST for sensory loss, whereas the mNIS + 7_{Ionis} also retains the NIS sensation measure (Table 2). Finally, the mNIS + $7_{Alnylam}$ uses an alternative measure of autonomic dysfunction (postural hypotension), whilst the mNIS + 7_{Ionis} maintains HRdb (Table 2). The differing components of the NIS + 7, mNIS + $7_{Alnylam}$, and mNIS + 7_{Ionis} are shown (Fig. 2) and described in more detail below [26,27].

5.1. Changes from NIS + 7: sensation

Both the mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis} scales employed S ST QST to measure sensation loss, which are computer-controlled (smart) and standardized (results are compared with reference values taken from a healthy population) quantitative sensation tests [46,47]. They have been shown to provide accurate assessment of sensation loss in length-dependent polyneuropathies and minimize intra- or inter-test differences, making them useful for multicenter trials [47]. In S ST QST, up to 10 unilateral anatomic sites distributed across the body are tested for both touch pressure (TP) and heat as pain (HP) [46]. TP is assessed using graded nylon monofilaments and HP is assessed using graduated heat pulses, with the patient describing detection of the TP stimulus, and detection and degree of severity for the HP stimuli [46,48]. Due to the length-dependent nature of polyneuropathy in hATTR amyloidosis [25], tests are initially performed at the lateral leg and forearm, then at more distal sites if sensation is detected or more proximal sites if sensation is not detected. Only one side of the body (left side) is tested, as sensation loss is assumed to be symmetrical, as observed in 87% of

Table 2
Assessments, grading, and scoring of mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis}.

	mNIS + $7_{Alnylam}$ APOLLO Trial (patisiran)			mNIS + 7_{Ionis} NEURO-TTR Trial (inotersen)		
	Assessment	Grading	Scoring	Assessment	Grading	Scoring
Muscle Weakness	Assessed in 24 muscle groups (both sides)	*Judged by examiner* 0: normal 1: 25% weak 2: 50% weak 3: 75% weak 3.25: can just move against gravity 3.50: can move with gravity just eliminated 3.75: muscle contraction can be felt or seen but no visible movement 4: paralysis	Points 0–192	Assessed in 24 muscle groups (both sides)	*Judged by examiner* 0: normal 1: 25% weak 2: 50% weak 3: 75% weak 3.25: can just move against gravity 3.50: can move with gravity just eliminated 3.75: muscle contraction can be felt or seen but no visible movement 4: paralysis	Points 0–192
Reflexes	Assessed in 5 muscle groups (both sides)	*Judged by examiner* 0: normal 1: decreased 2: absent	Points 0–20	Assessed in 5 muscle groups (both sides)	*Judged by examiner* 0: normal 1: decreased 2: absent	Points 0–20
Sensation	S ST QST Assessed at up to 10 sites (left side only)	*Compared to RV*[a,b] 0: normal 10: mildly reduced 20: very reduced	Points 0–80	S ST QST Assessed at up to 10 sites (left side only) + Touch pressure, vibration, joint position, pinprick Assessed at 2 sites	*Compared to RV*[a,b] 0: normal 10: mildly reduced 20: very reduced + Judged by examiner 0: normal 1: decreased 2: absent	Points 0–80 + Points 0–32
NCS	5 nerve assessments: ulnar motor tibial motor peroneal motor ulnar sensory sural sensory	*Compared to RV*[a,b] 0: normal 1: mildly reduced 2: very reduced	Points 0–10	5 nerve assessments: ulnar motor tibial motor peroneal motor ulnar sensory sural sensory	*Compared to RV*[a]	Normal deviates[c] 0–18.6
Autonomic	Postural hypotension	*Compared to RV*[a,b] 0: normal 1: mildly reduced 2: very reduced	Points 0–2	HRdb	*Compared to RV*[a]	Normal deviates[c] 0–3.7
TOTAL			304			346.3

HRdb heart rate with deep breathing, mNIS + 7 modified Neuropathy Impairment Score + 7, *NCS* nerve conduction studies, *NIS* Neuropathy Impairment Score, *RV* reference values, *S ST QST* smart somatotopic quantitative sensation testing.

[a] RV from a healthy study population and matched for age.

[b] Normal < 95th percentile, mildly reduced ≥95th to < 99th percentile, very reduced ≥99th percentile.

[c] To express scores as normal deviates, scores are normalized to indicate how many standard deviations they are from the mean of a healthy reference population.

patients [25,26].

Scoring of sensation is based on comparison to reference values obtained from a study of healthy subjects, and categorized on a points scale (from percentiles) as normal, mildly reduced, or very reduced [26,27]. To ensure accuracy and reproducibility, identical and automated instruments are used, along with standardized computer algorithms for testing, threshold finding, and comparison to reference values [47]. Although the implementation of these measures makes S ST QST time-consuming [46,47], they are necessary to assess sensation loss somatopically and accurately [26,27]. Compared to the previous

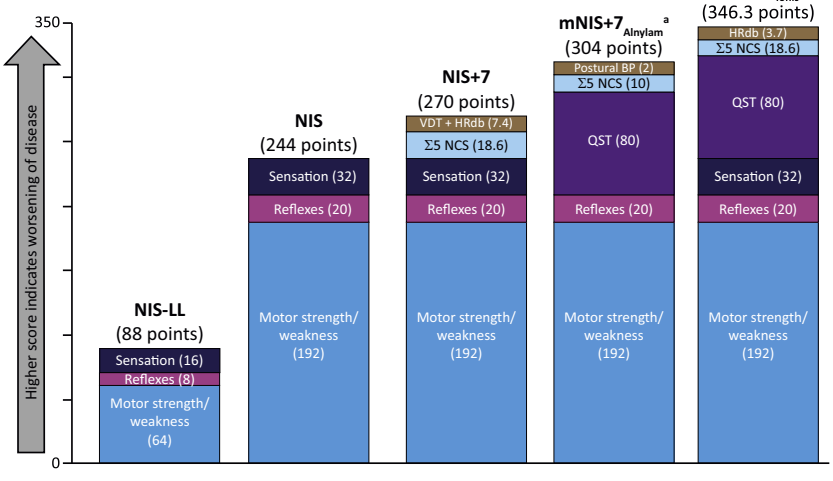

Fig. 2. Composition and maximum scores of NIS and NIS-based scales. [a]NCS and postural BP are graded as points. [b]NCS and HRdb are expressed as normal deviates. *BP* blood pressure, *HRdb* heart rate with deep breathing, *mNIS + 7*, modified Neuropathy Impairment Score + 7, *NCS* nerve conduction studies, *NIS* Neuropathy Impairment Score, *NIS + 7* Neuropathy Impairment Score + 7, *QST* quantitative sensation testing, *VDT* vibration detection threshold.

NIS scales, the use of S ST QST as part of mNIS + 7 provides a better balance between measurement of large and small sensory fibers, and estimates sensation loss over the surface of the body rather than just at distal sites. Furthermore, this measure is considered less subjective and ceiling effects have not been observed [25].

5.2. Changes from NIS + 7: NCS

In NIS + 7 NCS, conduction velocity and distal latency measurements were often unmeasurable in patients with hATTR amyloidosis and acted as less direct measurements of muscle weakness or sensory loss [25]. Replacement of these with upper and lower limb amplitudes of motor and sensory nerve conductions (i.e. action potential amplitudes) in mNIS + 7 (Table 2) allowed for a better measurement of progression of hATTR amyloidosis with polyneuropathy as this disease has a mainly axonal pathophysiology [25,26]. This change in NCS measurement markedly improved the correlation of mNIS + 7 with overall NIS and all three subsets of NIS (weakness, reflexes, and sensation) [25]. In mNIS + $7_{Alnylam}$, the five NCS are scored by comparison to standardized reference values (from a healthy study population) in the same way as S ST QST [26]. However, in the mNIS + 7_{Ionis}, each NCS is expressed as a normal deviate from percentile reference values, again taken from a healthy study population [49]. The use of normal deviates can account for changes in severity within the normal range of values, although this may provide noise which could be prevented by the use of the points-based approach.

5.3. Changes from NIS + 7: autonomic dysfunction

Autonomic dysfunction is measured and scored in the mNIS + 7_{Ionis} using HRdb. However, this assessment is not always measurable in patients with hATTR amyloidosis (e.g. due to cardiac arrhythmia or electronic pacing) [25,27,50]. To account for this, the measurement of postural hypotension was instead included in the mNIS + $7_{Alnylam}$. The drawback of postural hypotension is that it is treatable with medical interventions (such as fludrocortisone) and this should be taken into account when it is assessed [26]. To ensure standardization, both endpoints were scored in the same manner as NCS in their relevant mNIS + 7 scales.

5.4. Assessment of the mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis} in hATTR amyloidosis

Test/re-test reproducibility of the mNIS + 7_{Ionis} was assessed in the first 100 patients of the NEURO-TTR trial, with duplicate evaluations performed within a few days of each other by the same examiners. High reproducibility values were observed for NIS, NCS, and HRdb (Krippendorff α coefficient ≥ 0.93), although the reproducibility value for S ST QST (Krippendorff α coefficient = 0.57) was lower, especially for TP sensation [27]. As assessment of neuropathic measures is subject to variability between investigators, extensive training was provided to support the use of a standardized and validated methodology and ensure that scoring was as consistent and accurate as possible for both the APOLLO and NEURO-TTR trials [26,27]. In terms of the mNIS + 7 scales' linearity, the mNIS + $7_{Alnylam}$ was able to detect differences between treatment and placebo groups across different ranges of baseline polyneuropathy severity in the APOLLO study [51]. However, the impact of a specific change in mNIS + 7 score in a patient with minimal polyneuropathy may not be the same as an equal change in score in a patient with severe polyneuropathy. Comparability therefore depends on matching placebo versus treatment groups by the level of severity.

Published data suggest both mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis} can provide robust assessment of disease impairment and progression. Baseline data from 225 patients with hATTR amyloidosis in the phase III APOLLO trial showed an association between mNIS + $7_{Alnylam}$ score, FAP stage, and PND score [26]. In addition, an analysis of the baseline data of the first 100 patients in the phase III NEURO-TTR trial showed that mNIS + 7_{Ionis} score was significantly correlated with total NIS, Norfolk QOL-DN, PND score, and the 36-Item Short Form Health Survey [27]. Furthermore, scored neuropathy signs (e.g. NIS, NIS-W) correlated with quantitative measures of the mNIS + 7 (NCS, touch pressure S ST QST), supporting the adequacy of the neurologic examination that investigators were trained for. Finally, the results of both the APOLLO and the NEURO-TTR trials showed mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis} could detect significant differences between the placebo and intervention groups [52,53]. In the APOLLO trial, mean mNIS + $7_{Alnylam}$ score in placebo-treated patients increased by 28.0 points at 18 months, compared with a decrease of −6.0 points in patisiran-treated patients [52]. In the NEURO-TTR trial, mean mNIS + 7_{Ionis} score in placebo-treated patients increased by 25.5 points at 15 months, compared with an increase of 5.8 points in inotersen-treated patients [53].

6. Discussion

Polyneuropathy is one of the most common progressive manifestations of hATTR amyloidosis, yet sensitively measuring the multiple manifestations of neurologic dysfunction associated with this disease is challenging. FAP staging and PND scoring have been the hallmark of clinical neuropathy assessment in hATTR amyloidosis, yet while these scales have the advantage of being simple and transparent, they only take into consideration broad changes in status and may fail to capture small but meaningful alterations in neuropathic function. In addition, patients often experience transitions between stages/scores rather than abrupt changes (e.g. using a walking aid occasionally) and these subtleties are not captured with disability-based scoring systems. To better describe the progression of all aspects of the polyneuropathy, clinical trials have instead utilized NIS-based composite scoring scales which maximize the chance of capturing a treatment effect.

Fig. 2 shows a comparison of the measures and scoring used across NIS and NIS-based measures in hATTR amyloidosis clinical trials. Across all scales, weakness evaluation is the main contributor to the total score (55.7–78.7%), as it is likely the most reliable sign of neuropathic disease. Sensation loss is the second highest (13.1–32.3%) measure in NIS-based scales, with the importance of this measure based on the observation that neuropathy is usually combined with small-fiber loss of function. Muscle reflex loss is weighted below weakness and sensation as the third highest contributor to the total score (5.8–9.1%), as it does not generally produce clinical symptoms. For the +7 scales, NCS is fourth highest contributor (3.3–6.9%) and autonomic dysfunction (0.7–1.4%) is the smallest contributor. Although postural hypotension is an improved measure of autonomic function compared with HRdb, which is not always measurable in patients with hATTR amyloidosis, the opportunity to improve assessment of dysautonomia in the current mNIS + 7 remains.

The use of these scales in hATTR amyloidosis with polyneuropathy has evolved to reflect the type of neuropathy impairment experienced by patients, and the setting in which they are used. The validation of NIS for use in diabetic neuropathy, another axonal degenerative neuropathy [21], provided the initial justification for adopting the NIS scale for use in hATTR amyloidosis trials, and NIS was shown to correlate with FAP stage, PND score, Norfolk QOL-DN, and disease duration [5,54,55]. Furthermore, NIS-LL and NIS + 7 demonstrated the positive effect of treatment in the phase II/III tafamidis trial [19] and the phase III diflunisal trial, respectively [20]. However, further investigation suggested these scales had limitations for hATTR amyloidosis, with evaluation of sensory loss, NCS, and autonomic dysfunction considered inadequate [25].

As a result, the mNIS + $7_{Alnylam}$ and mNIS + 7_{Ionis} scales, the first designed specifically to assess impairment in hATTR amyloidosis clinical trials, were created and have been used as the primary endpoint in two recent phase III trials (Table 2). In both trials, the mNIS + 7 scales

were able to detect improvements in polyneuropathy symptoms for treatment compared with placebo at the first time point assessed (8 months in NEURO-TTR; 9 months in APOLLO) and at the end of the treatment period (15 months in NEURO-TTR; 18 months in APOLLO) [52,53]. The scales and their components also had strong correlations with other assessments used in hATTR amyloidosis such as PND score and Norfolk QOL-DN, increasing confidence in their suitability. These measures are well suited for use in hATTR amyloidosis because they capture a high degree of the varied impairment of hATTR amyloidosis, which ranges from a length-dependent, small-fiber sensory-motor polyneuropathy in early-onset disease, to a more severe, multisystem disease that can affect all fibers in late-onset disease [56,57]. However, it should be noted that the mNIS + 7 scale does not capture disease involvement across all systems, as gastrointestinal symptoms and cardiomyopathy are not assessed by this measure. Instead, the mNIS + 7 scale is focused specifically on polyneuropathy impairments, with the sensitivity of these measures providing a detailed insight into disease progression, and whether treatment can arrest or improve features of this. Furthermore, interrogation of the separate elements of the $mNIS + 7_{Alnylam}$ and $mNIS + 7_{Ionis}$ scales allows investigators to pinpoint how individual neuropathic signs are affected [52,58].

A potential drawback of a composite scale such as mNIS + 7 is assigning a degree of clinical meaning to a specific change in overall score. The variation in symptoms and disease severity also presents a challenge to relating an improvement in score to the benefits in a particular patient. However, it should be noted that for specific domains, for example muscle groups, the meaning of a 1-point change does reflect a known difference in muscle weakness or reflexes (Table 2). For overall score, changes in the mNIS + 7 scale have been associated with changes in other measures directly related to patient functioning (e.g. ambulation as assessed by PND score [26]), demonstrating its clinical relevance. Furthermore, the fact that this scale was able to detect significant differences between treated and untreated patients in phase III clinical trials supports its sensitivity [52,53].

This detailed disease characterization is valuable in clinical studies but requires extensive training to ensure proficiency and minimize variability between centers and investigators. Experts should be trained to use only clear disease-associated abnormalities rather than more traditional criteria and not grade signs of concomitant diseases; this approach has been shown to reduce variability [31,32]. When measuring NCS, consistency and reproducibility can be enhanced with specialist training, standardized reference values, and evaluation of tracings at a central reading center [41,59]. S ST QST variability can be reduced by using identical equipment, standardized algorithms, and reference values, along with specialized training and standardized protocols [47]. This is particularly important based on recent concerns on test/re-test reproducibility of the TP element of S ST QST [27]. These demands are necessary if neuropathy impairment is to be assessed accurately, and data generated by differing investigators/centers are to be comparable.

7. Summary

The various neuropathic impairments and variable progression have presented challenges to developing a comprehensive measure for assessing polyneuropathy in hATTR amyloidosis. While the initial use of disability assessments to categorize the disease in stages proved useful, more detailed measures were needed to track progression and compare treatment arms in controlled clinical trials. The NIS was therefore adopted from other neuropathies and has provided the basis for the primary endpoints of all major placebo-controlled trials in patients with hATTR amyloidosis and polyneuropathy. Testing of the NIS scores specifically in this disease has driven their evolution, with the mNIS + 7 scales used as the primary endpoint in the most recent phase III trials designed to reflect the unique nature of polyneuropathy in hATTR amyloidosis.

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Declaration of Competing Interest

PJBD and AGD have no conflict of interest. LO has received speaker fees from Alnylam Pharmaceuticals and Pfizer. MP received consulting fees and fees for a study site from Alnylam Pharmaceuticals; compensation for study site and travel support from Ionis Pharmaceuticals; recipient of a grant and received consulting honoraria from Pfizer; received consulting honoraria from Vertex Pharmaceuticals, Biogen, and Chromocell. JFW received clinical trial funding from Alnylam Pharmaceuticals. IA is an employee of Alnylam Pharmaceuticals. WJL had institutional contracts to train investigators and for quality control of data from Alnylam Pharmaceuticals and Ionis Pharmaceuticals. PJD received industry support for teaching and quality assurance of a therapeutic trial in transthyretin amyloidosis from Alnylam Pharmaceuticals and Ionis Pharmaceuticals.

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