Updates in Inherited and Inflammatory Neuropathies: New Treatments in hATTR and What's New in Lumbosacral Radiculoplexus Neuropathies

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Neuromuscular Colloquium

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Disclosure of Speaker

- Has received honorarium from Ionis (Akcea)

P. James B. Dyck

Off Label Usage (experimental studies)

Manufacturer	Product/Device
Ionis, Alnylam	TTR amyloid drugs

Learning Objectives

Inherited:

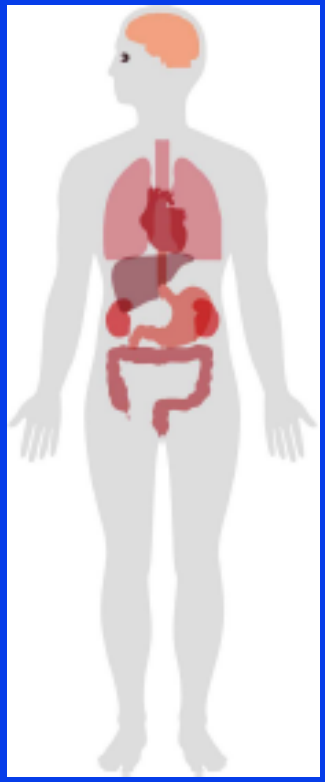
- To review the clinical presentation and disease spectrum of hATTR.
- To discuss the recent clinical trials (including the gene silencing treatment) for hATTR.
  - Inotersen
  - Patisiran

Acquired:

- To discuss the incidence of lumbosacral radiculoplexus neuropathy (LRPN).
- To determine if there is an association of LRPN with diabetes mellitus.

Inherited Neuropathy
hATTR Amyloidosis Is a Rare, Progressive, and Fatal Disease [1-3]

- hATTR is an autosomal dominant disease.
- Characterized by deposition of amyloid fibrils, formed from misfolded transthyretin (TTR).
- Mutations in the TTR gene cause a hereditary form of the disease, known as hATTR.
  - neurological – familial amyloid polyneuropathy
  - cardiology – familial amyloid cardiomyopathy
- Deposition of misfolded mutant TTR occurs in multiple organ systems which interferes with normal function.

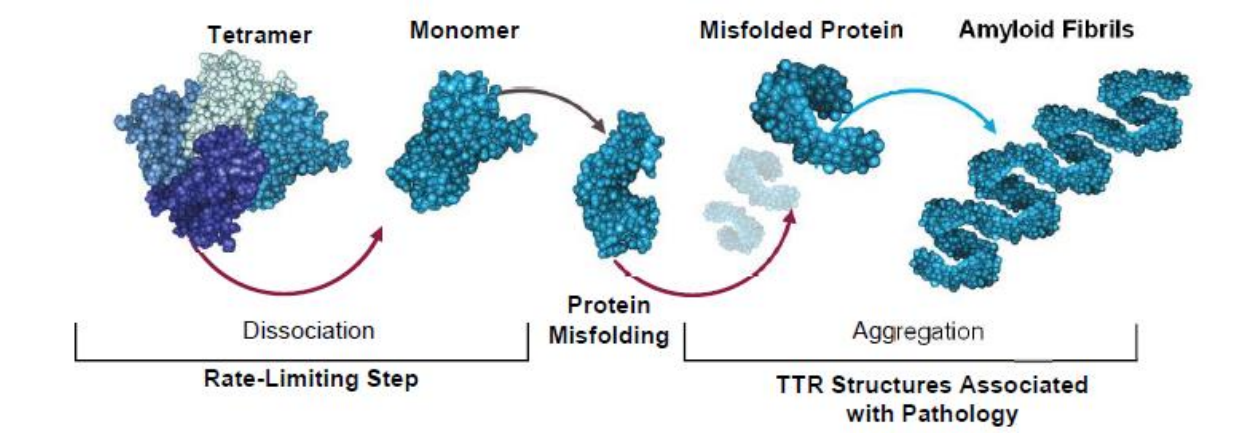


TTR, transthyretin; ATTR, amyloid transthyretin

1.Hawkins P et al. Ann Med. 2015; 47:625-638; 2. Ando Y et al. Orphanet Journal of Rare Diseases 2013, 8:31; 3. Coelho T, et al. A physician's guide to transthyretin amyloidosis. Research Gate Amyloidosis; Foundation, 2008.
https://www.researchgate.net/publication/265490881_A_Physician's_Guide_to_Transthyretin_Amyloidosis_Authored_by. Accessed January 3, 2018

TTR Instability Leads to Fibril Formation

- Transthyretin is a protein, primarily produced in the liver, that comprises four monomers (tetramer) and is involved in the transport of thyroxine and retinol[1].
- TTR gene mutations can result in weaker monomer interactions, leading to dissociation of the tetramer[2,3].
- Monomers can misfold and then aggregate to form amyloid fibrils[2,3].

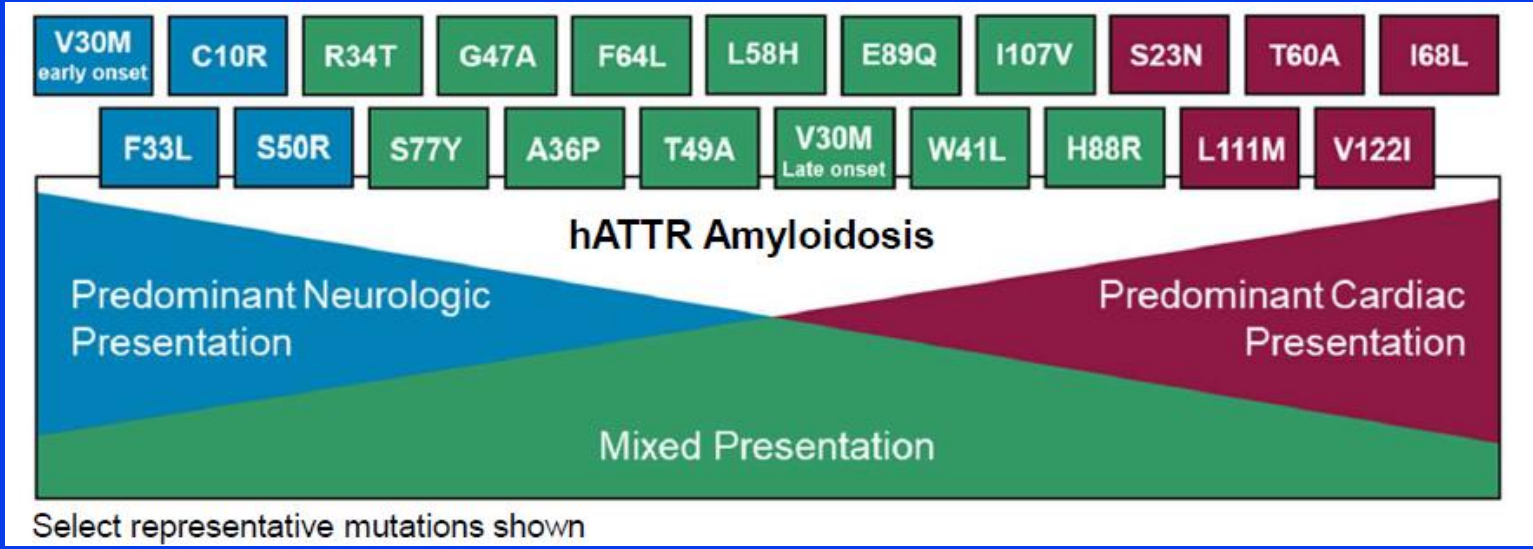


TTR, transthyretin

1. Hawkins P et al. Ann Med. 2015; 47:625-638; 2. Saraiva M. FEBS Letters 2001; 498:201-203; 3. THAOS Disease Background – Transthyretin Amyloidosis. Physician Fact Sheet

Many Genetic Mutations Cause hATTR Amyloidosis

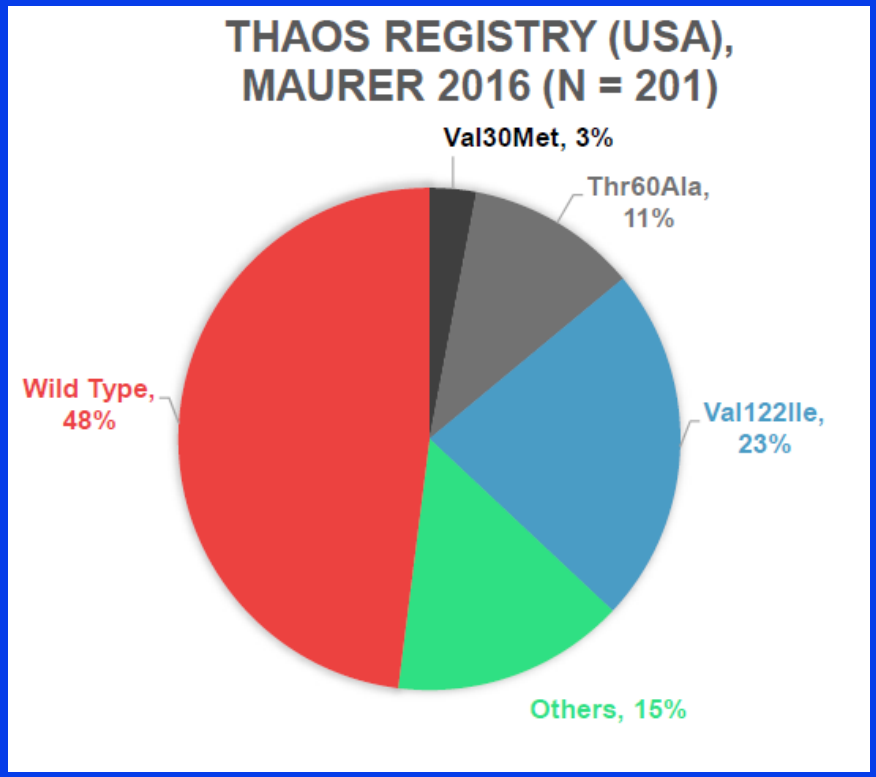
- Hereditary amyloidosis is caused by many gene variants, but TTR mutations account for the majority[1].
- Transmitted in an autosomal dominant manner with variable penetrance[2,3].
- More than 120 TTR mutations have been discovered[1].
- The most common mutation worldwide is Val30Met[4].



hATTR = hereditary amyloid transthyretin; TTR = transthyretin

1. Rowczenio D et al. Human Mutation Database in Brief. 2014;35:E2403–E2412; 2. Coelho T, Maurer M, and Suhr O. CMRO. 2013; 29:63-76; 3. Ando et al. Orphanet Journal of Rare Diseases 2013, 8:31;
4. Gertz. Am J Manag Care. 2017;23:S107-S112. Figure sources: Benson. Am J Pathol. 1996 Feb;148:351-354; Rapezzi et al. Eur Heart J. 2013 Feb;34:520-528; Connors et al. Amyloid. 2003 Sep;10(3):160-84.

Val122Ile, Thr60Ala, and Val30Met Are the Most Common Mutations in the United States[1]

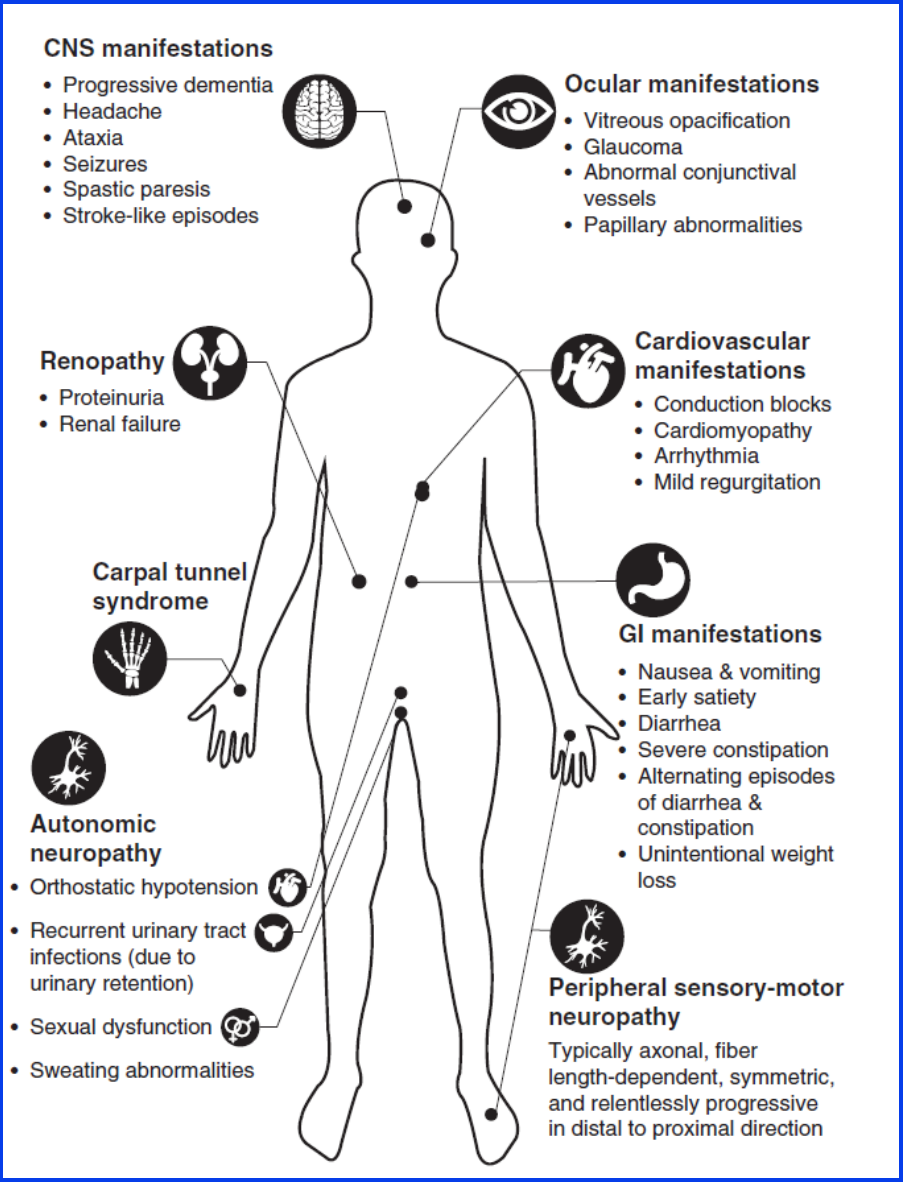


- Val122Ile is most common in cardiomyopathy, may have mild sensory neuropathy[2,3].
- Thr60Ala is a heart and autonomic nerves disease, may have peripheral neuropathy[4].
- Val30Met is the most common form causing polyneuropathy[2,3].

hATTR, hereditary amyloid transthyretin; TTR, transthyretin

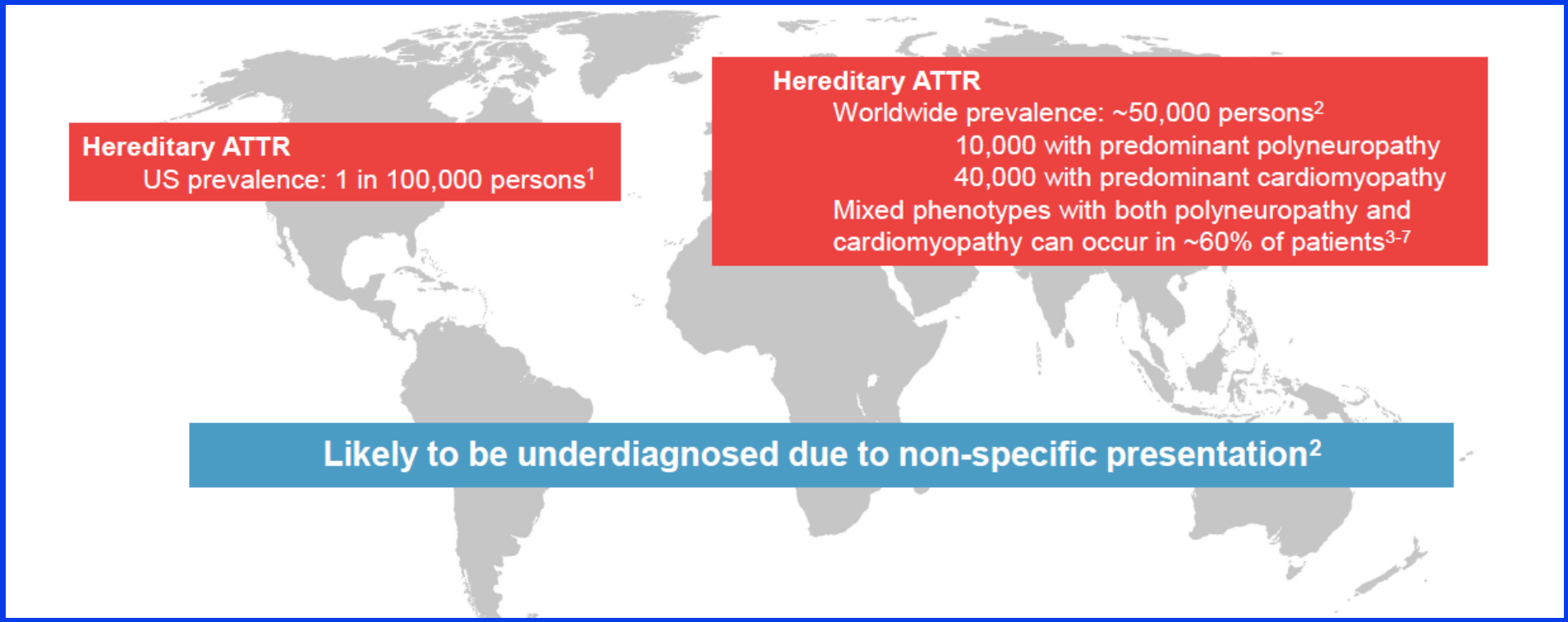
1. Maurer MS et al. J Am Coll Cardiol. 2016;68(2):161-172; 2. Coelho T, Maurer M, and Suhr O. CMRO. 2013; 29:63-76; 3. Hawkins P et al. Ann Med. 2015;47:625-638; 4. Sattianayagam PT et al. Eur Heart J. 2012;33(9):1120-1127

Hereditary ATTR Amyloidosis



Conceicao, JPNS 2016

Rare, but Most Likely Underdiagnosed



ATTR = amyloid ATTR

1. Ando Y, et al. Orphanet J Rare Dis 2013;8:31; 2. Hawkins PN et al. Ann Med 2015;47(8):625-638; 3. Gertz MA. Am J Manag Care. 2017;23:S107-S112; 4. Benson. Am J Pathol. 1996 Feb;148:351-354; 5. Rapezzi et al. Eur Heart J. 2013 Feb;34:520-528; 6. Connors et al. Amyloid. 2003 Sep;10(3):160-84; 7. Wixner J et al. Orphanet J Rare Dis. 2014;9:61.

hATTR Amyloidosis Has a Variable Natural History

- Median age of onset can vary, depending on geographic location[1].
  - United States: 68 years
  - Portugal: 32 years
  - Sweden: 52 years
  - most common TTR mutation in both Portugal and Sweden is Val30Met, whereas in the US, Val122Ile is the most common mutation
- But, even in similar geographic locations, the age range of patients can be fairly wide[2].
- Val30Met Early-onset (age <50 years)[3]
  - progressive sensory-motor and autonomic neuropathy leading to cachexia and death in ~11 years
- Val30Met Late-onset (age ≥50 years)[3]
  - more rapid progression of sensory and motor symptoms
  - median survival is shorter than early-onset at ~7 years

PN, polyneuropathy; hATTR, hereditary amyloid transthyretin

1. Coelho T, Maurer M, and Suhr O. CMRO. 2013; 29:63-76; 2. Parman Y, et al. Curr Opin Neurol. 2016, 29 (suppl 1):S3–S13; 3. Adams D. Ther Adv Neurol Disord. 2013. 6(2): 129–139

TTR-FAP – Liver Transplant

- Untreated, patients exhibit progressive neurological deterioration and death is usually 10 to 15 years after presentation.
- Liver transplantation has been the standard treatment since 1990.
- Liver transplantation eliminates 95% of mutated TTR from the blood.
- The neuropathy often progresses despite liver transplantation (wild-type TTR can still be made into amyloid).
- Alternative treatments needed for TTR-FAP.

Endpoints in Neuropathy Subjects

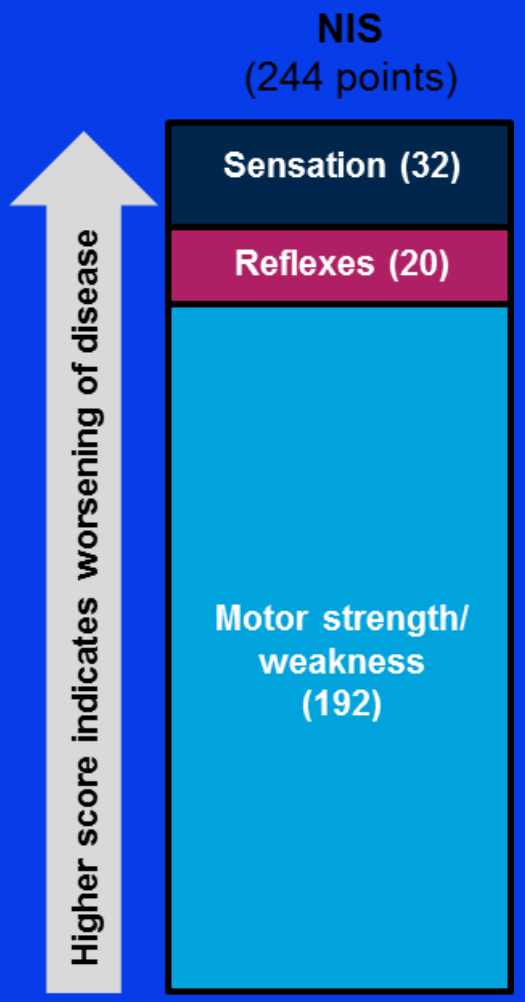
- When designing clinical trials, it is vital that robust endpoints are chosen that are specific for that disease.
- Endpoints for hATTR (TTR-FAP) should emphasize:
  - sensation loss (including small fibers)
  - autonomic
  - motor deficits

Neuropathy Impairment Score (NIS)

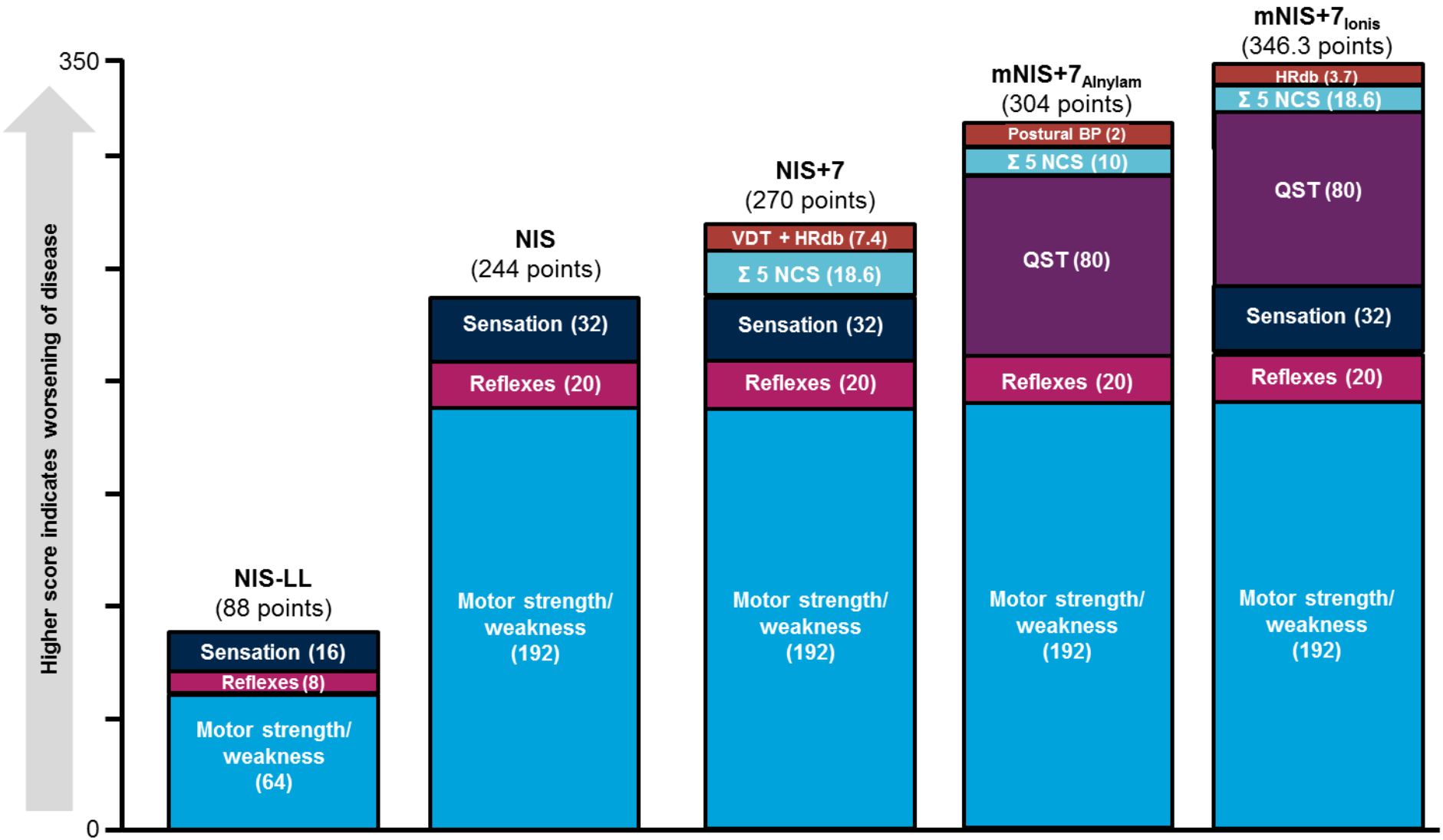
- The Neuropathy Impairment Score (NIS) is a summation of clinical impairments (weakness, decrease in reflexes and sensory loss) using standard groups of muscles, reflexes and sensory modalities and specific sites.
- Weakness is graded by the following scale:
  - 0 = Normal
  - 1 = 25% weak
  - 2 = 50% weak
  - 3 = 75% weak
  - 3.25 = antigravity
  - 3.5 = movement with gravity eliminated
  - 3.75 = muscle contraction without movement
  - 4 = paralyzed

Neuropathy Impairment Score (NIS) Continued

- Reflex abnormality (biceps, triceps, brachioradialis, quadriceps and achilles) graded by the following scale
  - 0 = Normal
  - 1 = Reduced
  - 2 = Absent
- Sensory loss (touch, vibration, pin and joint position sense) is graded at toes and fingers
  - 0 = Normal
  - 1 = Reduced
  - 2 = Absent
- Total scores possible
  - Weakness, 0 – 192
  - Reflexes, 0 – 20
  - Sensory, 0 – 32
  - Total, 0 – 244



Assessment of Neuropathy in TTR FAP: Comparison of Neuropathy Impairment Scores



BP, blood pressure; VDT, vibration detection threshold

Adams et al. *Neurology* 2015;85:675–82; Suanprasert et al. *J Neurol Sci* 2014;344:121–8; Dyck et al. *Muscle Nerve* 2017. Jan 7 [Epub ahead of print]

New Therapies for hATTR

- Gene silencing drugs:
  - Inotersen
  - Patisiran
- Inotersen is an antisense oligonucleotide inhibitor of hepatic production of TTR.
- Patisiran is a hepatically directed small interfering RNA that results in cleavage of the messenger RNA of TTR.

Inotersen in hATTR Neuropathy

Methods

- Trial was done at 24 centers in 10 countries.
- Inclusion criteria:
  - adults (18 – 82 years old)
  - stage 1 (ambulatory) or stage 2 (needing assistance) hATTR neuropathy
  - NIS of 10 to 130 points
  - TTR mutation by genotyping
  - documented amyloid deposits on biopsy (pathology required)
- Exclusion:
  - abnormal laboratory values
  - other causes of the neuropathy
  - liver transplantation

Inotersen in hATTR Neuropathy

Trial Design

- Eligible patients were randomly assigned in a 2:1 ratio to receive 300 mg of subcutaneous (SQ) inotersen or placebo.
- Patients were stratified:
  - Val 30 Met mutation
  - stage 1 or stage 2
  - prior treatment with tafamidis or diflunisal
- Patients received 3 SQ the first week and then weekly SQ injection for 64 weeks.
- 13 doses given at clinical sites at time of visits and the rest at home.

Inotersen in hATTR Neuropathy

End Points

- Primary end points:
  - Modified Neuropathy Impairment Score +7 (mNIS+7, 8 components, -22 to 346 points)
  - Norfolk Quality of Life questionnaire (Norfolk QOL-DN)
- Training:
  - all mNIS+7 assessors were specially trained

Inotersen in hATTR Neuropathy

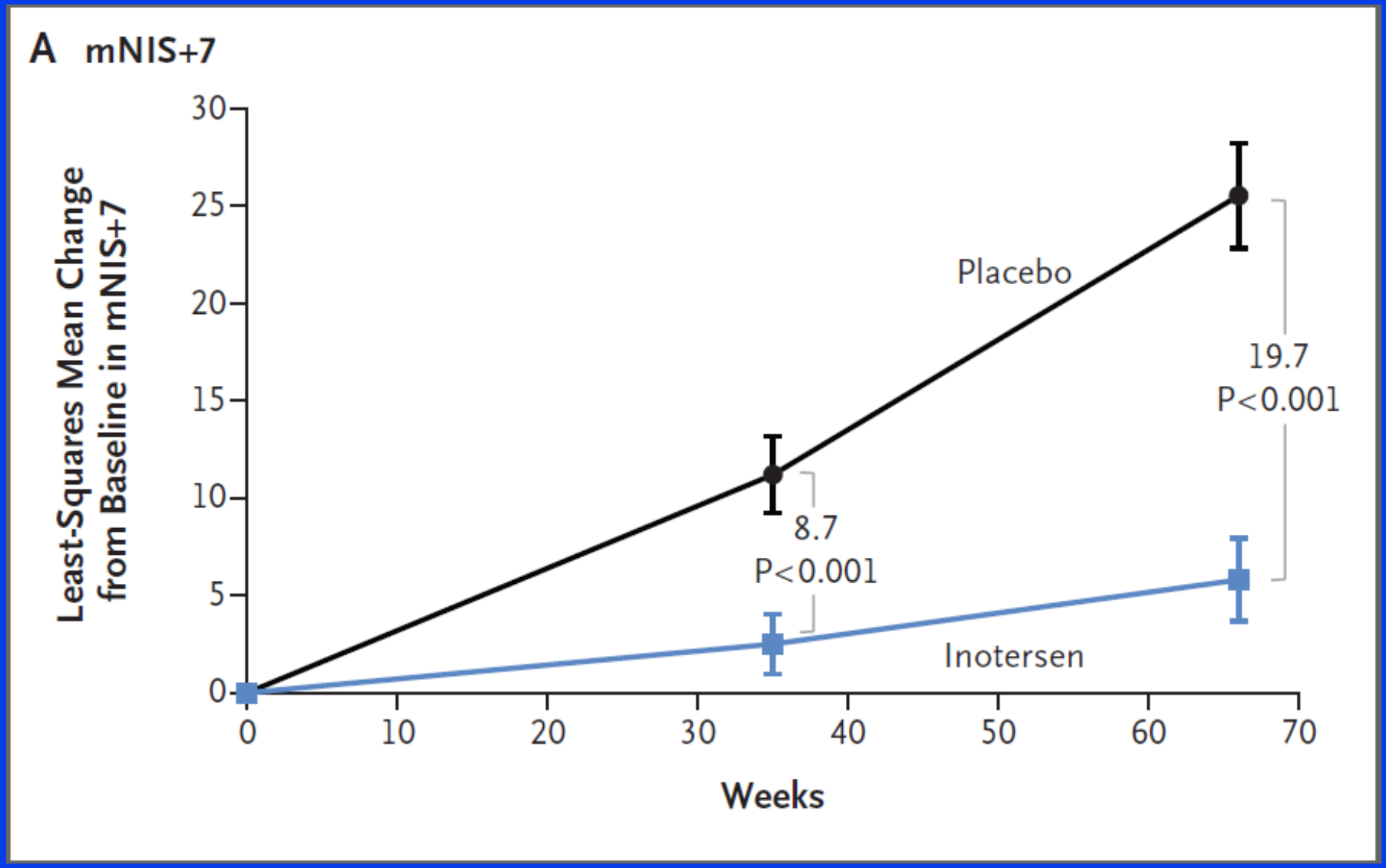
Results - Demographics

- 172 patients of 278 screened received inotersen or placebo in a 2:1 ratio (112 inotersen and 60 placebo).
- Baseline characteristics were well matched.
- Mean age 59 years (69% men).
- Half were Val30Met mutation.
- 67% had stage 1 disease.
- 58% had previously used stabilizers (tafamidis or diflunisal).
- 63% had cardiomyopathy.
- 81% (139/172) completed the 15 month trial.

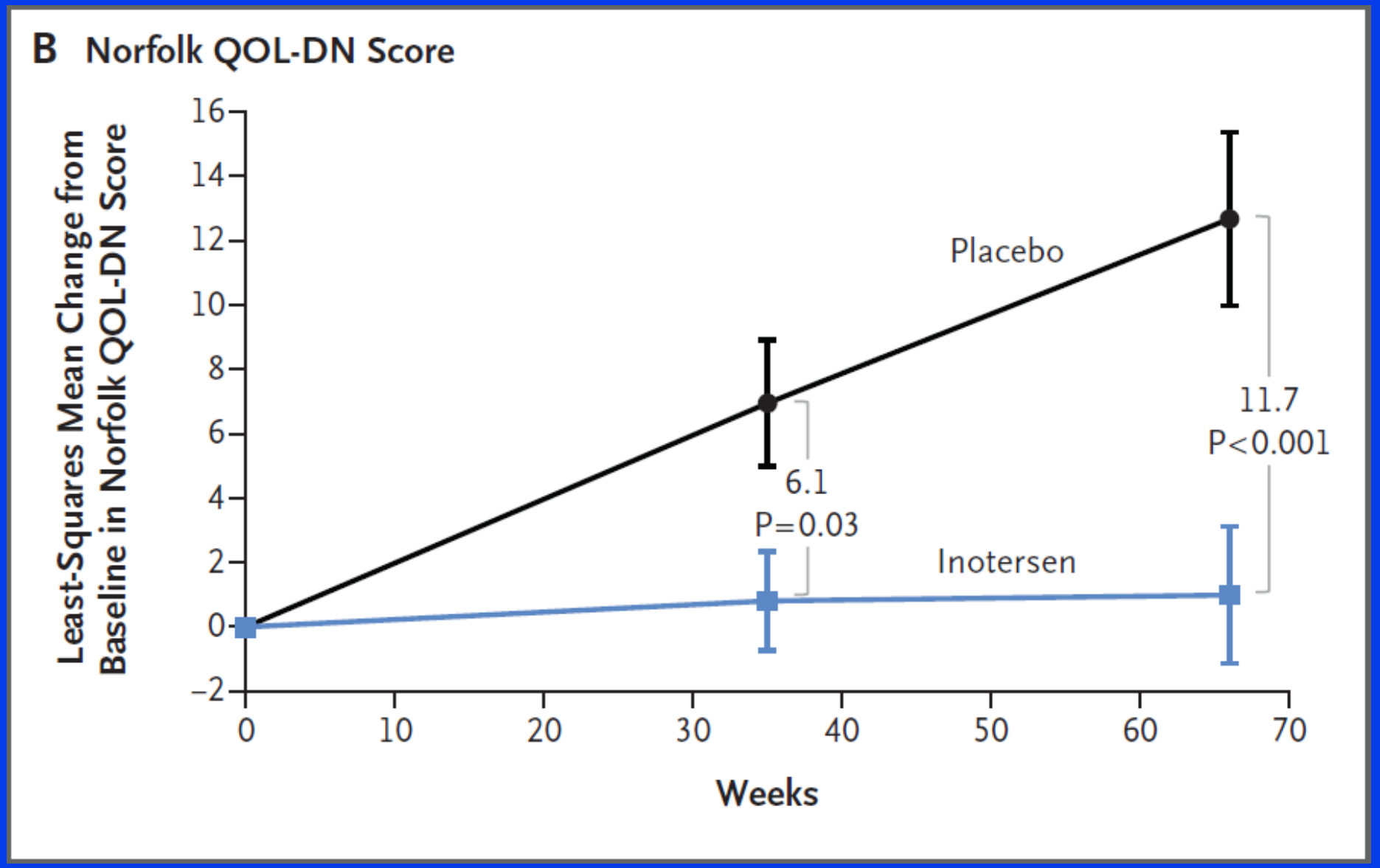
Inotersen in hATTR Neuropathy

Results – Primary End Points

- mNIS+7 showed significant change favoring inotersen at 66 weeks.
  - difference of -19.7 points ($p<0.001$)
- Norfolk QOL-DN score showed significant change favoring inotersen at 66 weeks.
  - difference of -11.7 points ($p<0.001$)
- At interim endpoint (week 35) there was an -8.7 points mNIS+7 difference ($p<0.001$) and a -6.1 points Norfolk QOL-DN difference ($p=0.04$).
- 36% of inotersen had improvement of mNIS+7 and 50% had improvement of Norfolk QOL-DN (many patients improved).



Benson, M., et al, NEJM 2018; 379:22-31



Benson, M., et al, NEJM 2018; 379:22-31

Inotersen in hATTR Neuropathy

Subgroup Analysis

- Significant benefit for subgroups was seen for inotersen compared to placebo in both mNIS+7 and Norfolk QOL-DM. These included:
  - Val30Met mutation or non-Val30Met mutation
  - stage 1 neuropathy or stage 2 neuropathy
  - previous treatment with tafamidis or diflunisal or no previous treatment
  - presence of cardiomyopathy or no evidence of cardiomyopathy
- Serum levels of TTR in the inotersen group reached a median reduction of 79% (weeks 13 to 65).

Inotersen in hATTR Neuropathy

Safety

- There were 5 deaths (all in inotersen group).
  - 4 from disease progression (2 cachexia, 1 intestinal perforation, 1 congestive heart failure)
  - 1 patient had fatal intracranial hemorrhage associated with platelets less than 10,000/mm^3
- Glomerulonephritis occurred in 3 patients (inotersen group).
  - all 3 renal biopsy showed crescentic glomerulonephritis superimposed on background amyloidosis
  - 1 patient successfully treated with glucocorticoids
- 54% of inotersen group had platelets <140,00/mm^3.
  - platelets <25,000/mm^3 occurred in 3 people
  - in 2 of 3 they returned to normal with stopping inotersen and giving steroids (third person had intracranial hemorrhage and died)
  - no cases of severe thrombocytopenia occurred after platelet monitoring.

Inotersen in hATTR Neuropathy

Conclusions

- An international, randomized, placebo-controlled trial of, weekly SQ inotersen showed significantly alteration of the disease course. Both primary endpoints showed benefit.
  - mNIS+7
  - Norfolk QOL-DN score
- The benefits were independent of TTR mutation type, disease stage and cardiomyopathy.
- The principal safety concerns for inotersen were thrombocytopenia (3 patients <25,000/mm^3) with one death to intracranial bleed (before monitoring) and 5 deaths in inotersen and none in placebo.
- After increased monitoring, no severe thrombocytopenia occurred.

Patisiran in hATTR Neuropathy

Methods

- Trial was done in 44 sites in 19 countries
- A multi-centered, international, randomized, double-blinded placebo-controlled, phase 3 study with patisiran in hATTR neuropathy.
- Inclusion criteria:
  - adults (ages 18 – 85)
  - a pathological mutation in TTR
  - hATTR neuropathy
  - NIS from 5 to 130 points
  - good liver and renal function
  - pathological diagnosis not required
- Exclusion criteria:
  - prior liver transplantation
  - New York Heart Association class III or IV

Patisiran in hATTR Neuropathy

Trial Design

- Patients were randomized in 2:1 ratio to receive IV patisiran (0.3 mg/kg) or placebo once every 3 weeks.
- Randomization was stratified by:
  - NIS less than 50
  - early onset disease (<50 years) with Val30Met
  - previous use of TTR stabilizer (diflunisal or tafamidis)
- Primary endpoint was mNIS+7
- Secondary endpoints included:
  - Norfolk QOL-DN questionnaire
  - Rasch-built Overall Disability Scale (R-ODS)
  - 10 meter walk test, with speed measured
  - BMI
  - Autonomic Symptom Scale
- Endpoints assessed at baseline, 9 and 18 months.

Patisiran in hATTR Neuropathy

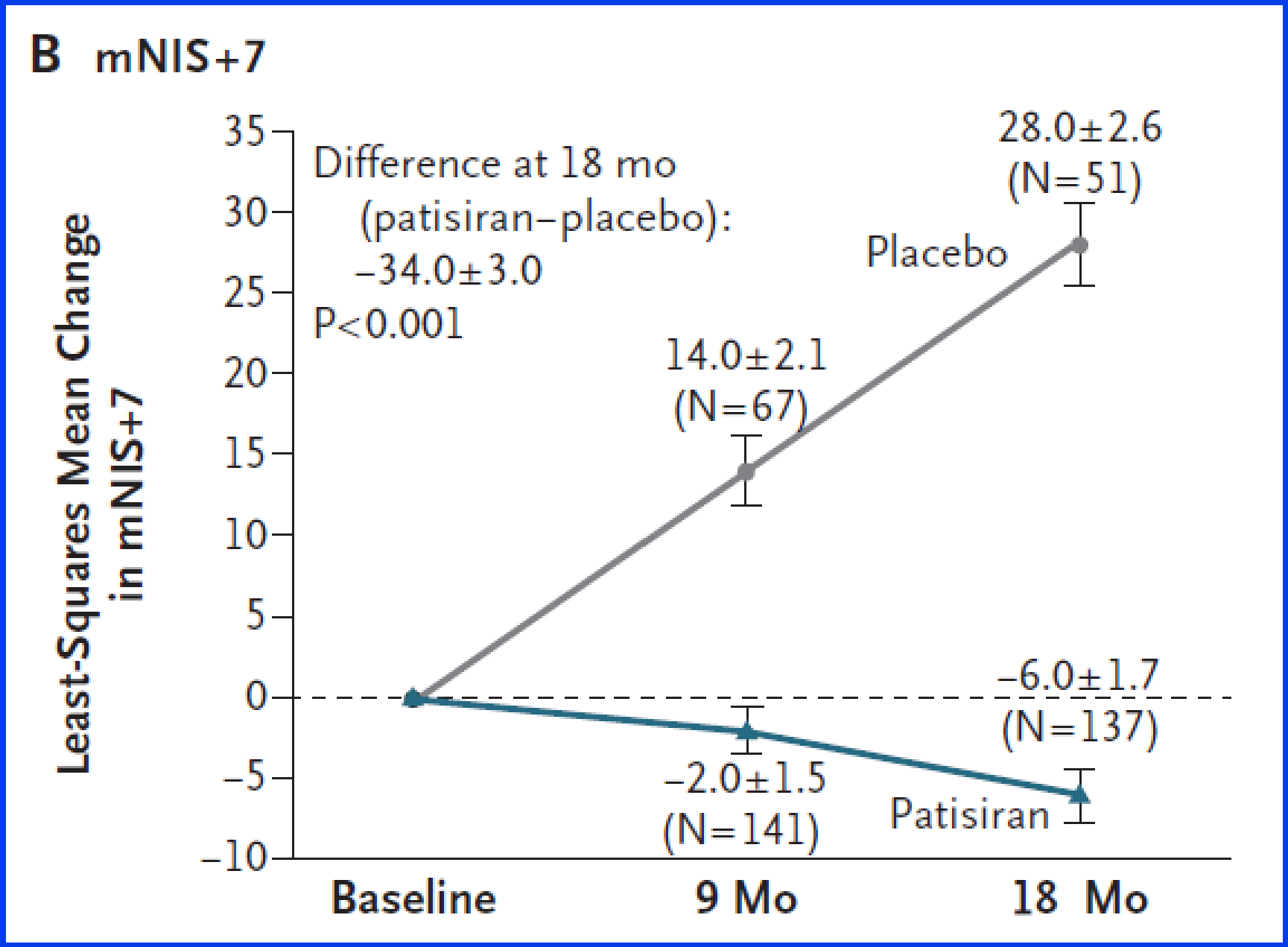
Results - demographics

- From Dec. 2013 through Jan.2016, 225 patients were randomized to receive patisiran (148) or placebo (77).
- The groups were well balanced in regards to:
  - age
  - sex
  - race
  - TTR genotype
  - prior use of stabilizers
  - FAP stage
  - New York Heart Association class
- 126 patients (56%) had cardiac disease with more in the patisiran group (61% vs. 47%).
- 93% of patisiran and 71% controls completed the study.

Patisiran in hATTR Neuropathy

Results - Efficacy

- The median serum TTR reduction over the 18 months was 81%.
- The primary endpoint, difference in mNIS+7 was positive both at 9 and 18 months.
  - at 18 months, -34.0 points difference
  - at 9 months, -16.0 points difference
- The treatment effect was significant for all subgroups and components of mNIS+7.
- At 18 months, 56% of patisiran patients had an improvement in mNIS+7 (compared to 4% placebo) (many patients improved).

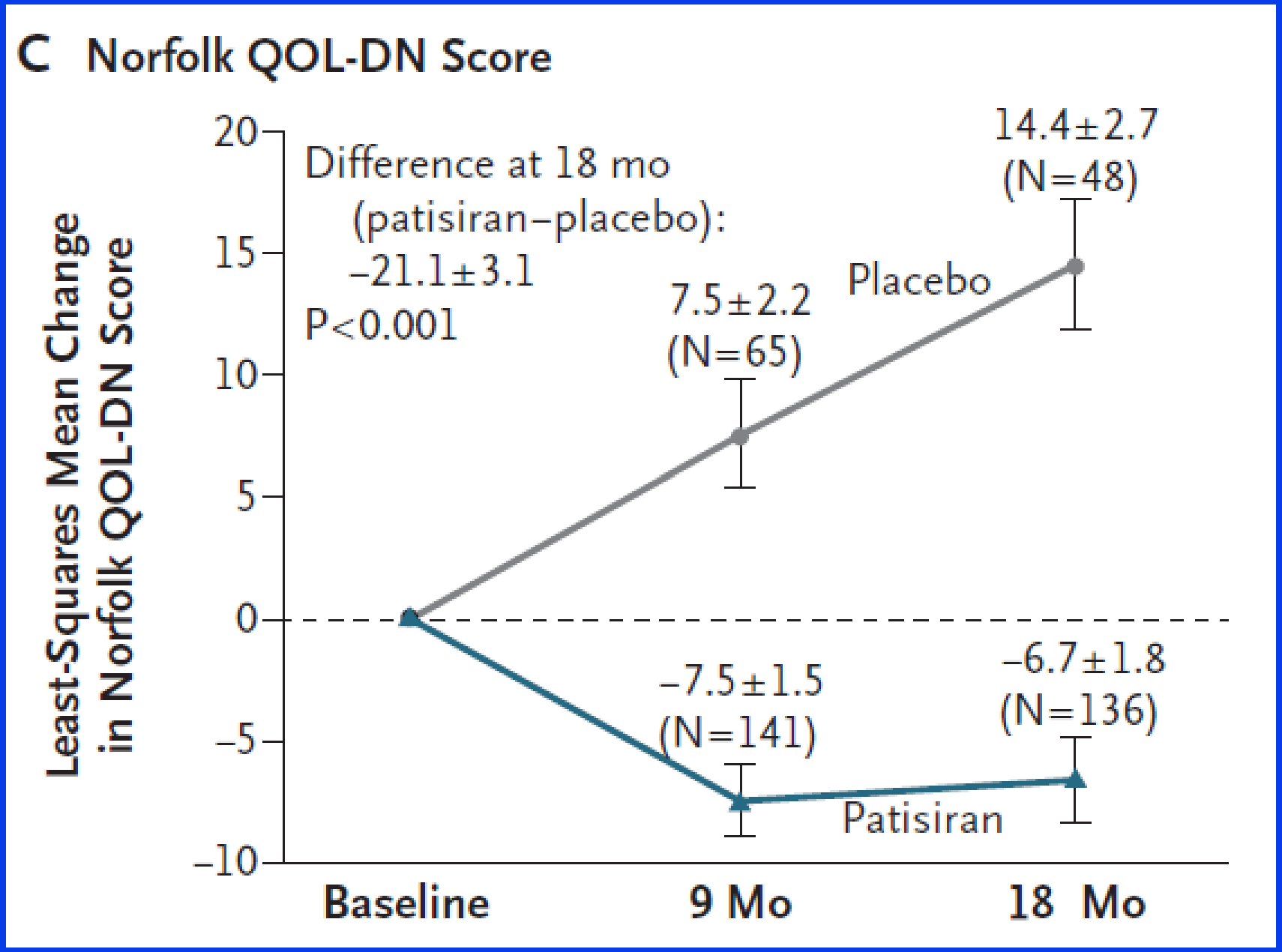


Adams, D., et al, NEJM 2018; 379:11-21

Patisiran in hATTR Neuropathy

Results – Secondary Endpoints

- The Norfolk QOL-DN showed a significant difference between patisiran and placebo groups.
  - the difference was -21.1 points ($p<0.001$)
- The scores were improved across all subgroups in favor of patisiran.
- The gait speed for 10-m walk test improved in 53% patisiran vs. 13% placebo.
- The NIS-weakness (motor strength) was improved in 40% patisiran vs. 1% placebo.



Adams, D., et al, NEJM 2018; 379:11-21

Patisiran in hATTR Neuropathy

Safety of Patisiran

- 97% in patisiran and placebo report adverse events, most of which were mild.
- Severe adverse events occurred in similar frequencies (28% patisiran and 36% placebo).
- Adverse events leading to discontinuing were more frequent in placebo (14%) than in patisiran (5%).
- Death occurred in 5% (7) in patisiran and 8% (6) in placebo patients and were predominantly cardiovascular and in keeping with hATTR.
- Infusion related reactions were more common in patisiran (19% vs. 9%).
- No changes in laboratory values (liver, kidney or platelets) were seen in patisiran.

Patisiran in hATTR Neuropathy

Conclusions

- Patisiran, a small interfering RNA, in an international, randomized, placebo-controlled, trial, given intravenously at 0.3 mg/kg once every 3 weeks for 18 months modified the disease course.
- The effects extended across sensory, motor and autonomic domains.
- The secondary endpoints including quality of life measures showed improvement.
- The principal safety concerns were infusion related reactions.
- hATTR has a rapidly progressive course, highlighted by the worsening in the placebo group (38% discontinuation of placebo vs. 7% in patisiran).

hATTR Neuropathy Conclusions

1) hATTR is an autosomal dominant inherited neuropathy causing pain, numbness, weakness and autonomic dysfunction that is progressive and often fatal.

2) Subcutaneous inotersen, an antisense oligonucleotide TTR inhibitor, showed significant benefit in hATTR neuropathy (mNIS+7 and Norfolk QOL-DN).

3) IV patisiran, a small interfering RNA showed also significant benefit in hATTR neuropathy (mNIS+7 and Norfolk QOL-DN).

hATTR Neuropathy Conclusions

4) Both gene silencing drugs worked very well and there is a place for both drugs.
   - both drugs are very expensive
   - Inotersen needs monitoring (especially platelets)
   - Inotersen has advantage of being SQ
   - Patisiran has fewer side effects but is given IV
   - choice should be made on patients needs

5) hATTR amyloid may be mistaken for CIDP.
   - probably due to CIDP being overdiagnosed than TTR-FAP resembling CIDP

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Inflammatory Neuropathy
Lumbosacral Radiculoplexus Neuropathy: Incidence and Association with Diabetes Mellitus

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(authors have nothing to disclose)

Radiculoplexus Neuropathies

- Conditions involving roots, plexus and peripheral nerves:
  - Cervical (CRPN)
  - Thoracic (TRN)
  - Lumbosacral (LRPN)
- These conditions can involve people with diabetes mellitus (DM) (DRPN) or without DM (non-DRPN).

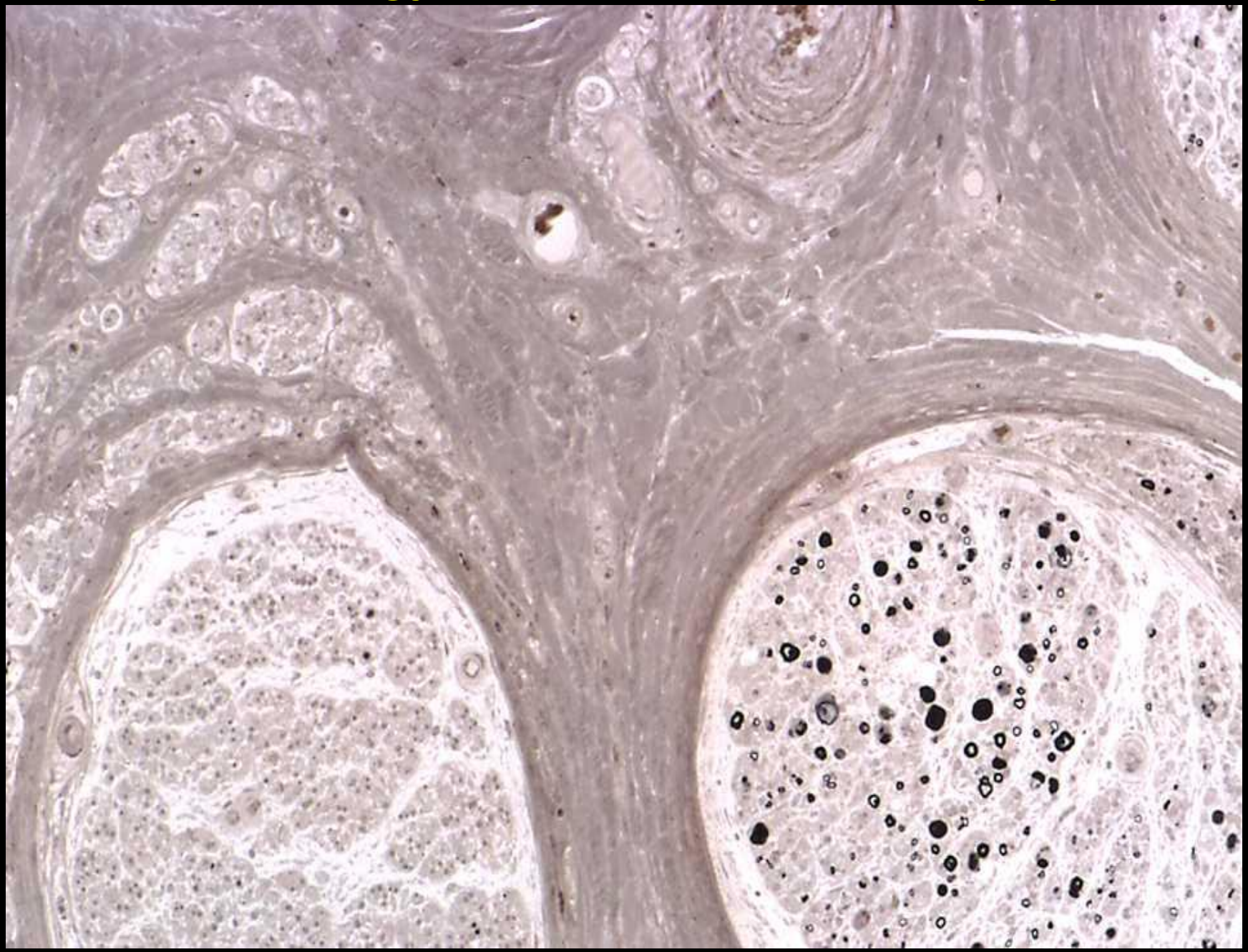
Synonyms for DLRPN

- Neuritic paralysis, Bruns, 1890.
- Paralytic neuropathy, Leyden, 1893.
- Diabetic myelopathy, Garland, et al., 1953.
- Diabetic amyotrophy, Garland, 1955.
- Diabetic femoral - sciatic neuropathy, Skanse, et al., 1956.
- Diabetic femoral neuropathy, Calverley, et al., 1960.
- Diabetic mononeuropathy multiplex, Raff, et al., 1968.

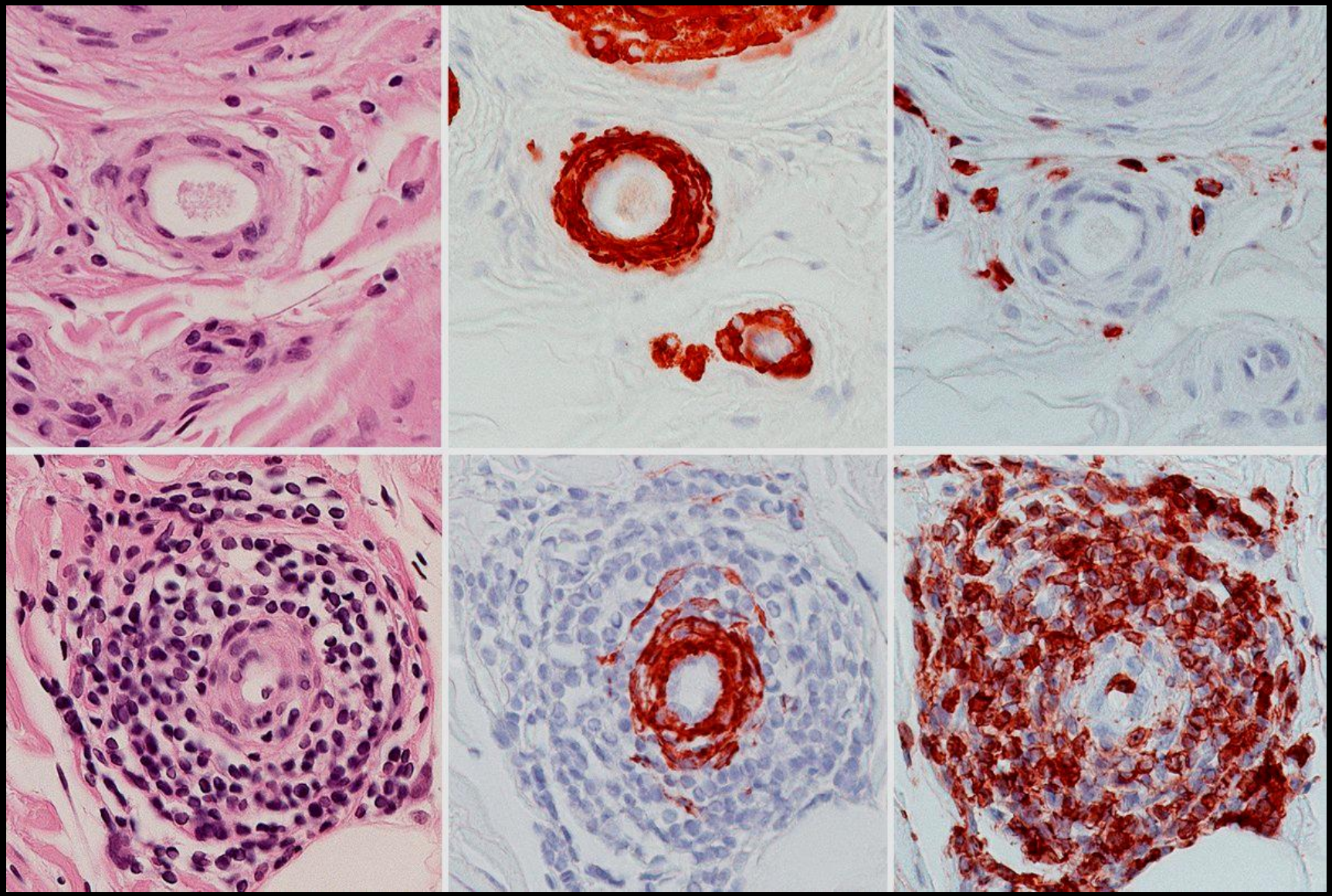
Synonyms for DLRPN (continued)

- Proximal diabetic neuropathy, Williams, et al., 1976 and Asbury, 1977.
- Bruns-Garland syndrome, Chokroverty, et al., 1977 and Barohn et al., 1991.
- Diabetic polyradiculopathy, Bastron and Thomas, 1981.
- Painful lumbosacral plexopathy, Bradley, et al., 1984.
- Diabetic chronic inflammatory demyelinating polyradiculoneuropathy, Krendel, et al., 1995.
- Diabetic lumbosacral radiculoplexus neuropathy, Dyck, et al., 1998.
- Multifocal diabetic neuropathy, Said, et al., 2003.

Pathology: Ischemic Nerve Injury



Microscopic Vasculitis in DLRPN



Incidence of Lumbosacral Radiculoplexus Neuropathy and Role of DM

Objective

- To assess the incidence of LRPN in Olmsted County MN.
- To assess the frequency of DM among the LRPN cohort.
- To compare LRPN patients to a gender and age matched cohort from Olmsted County to see if the rate of DM is different.

Incidence of LRPN

Methods

- All possible LRPN cases during a 16 year period (Jan. 1, 2000 – Dec. 31, 2015) living in Olmsted County were identified.

Inclusion criteria

1. A clinical syndrome of LRPN
   - subacute to chronic onset of weakness, numbness or pain in lower limbs
   - usually begin focally or unilaterally in lower limbs and progresses to involve both proximal and distal segments and be bilateral
   - the neurological examination shows motor, reflex or sensory abnormality beyond a single root or peripheral nerve distribution

Incidence of LRPN

Inclusion Criteria (continued)

2. Neurophysiology
   - NCS/EMG show an axonal disorder involving at least 2 different lumbosacral root levels from at least 2 different peripheral nerves and may involve paraspinal muscles (a lumbosacral radiculoplexus neuropathy)
3. Specialty assessment:
   - all included cases were evaluated by a neurologist
   - other potential causes of lumbosacral syndromes were excluded through laboratory testing or imaging (CT or MRI)

Patients were grouped into definite or probable groups.

- definite had all 3 criteria (1, 2 and 3)
- probable had 2 criteria (1 or 2 and 3)

Methods

Exclusion Criteria

- Other structural causes of LRPN were excluded.
  - large disks, tumors, masses, hematoma or dural AV fistula were excluded
- Other possible explanations for LRPN were excluded.
  - infection, radiation, multifocal CIDP, sarcoidosis, peripheral nerve lymphoma and other conditions

Methods

Selection of control patients

- 3 aged and gender matched control patients from Olmsted County were identified for each LRPN patient.
- This group served as a comparison group for the presence of diabetes mellitus (DM) or impaired glycemia.

Determination of DM

- The medical records of the LRPN cases and controls were reviewed to identify those with prevalent DM.
- Definition of DM:
  - ongoing treatment with diabetic medication
  - a coded diagnosis of DM in the medical record
  - American Diabetes Association criteria for DM before the index date

Incidence of LRPN

Results - Demographics

- 1,892 potential LRPN cases over 16 years in Olmsted County were identified.
- 59 cases (52 definite and 7 probable) met criteria for LRPN.
  - 33 males and 26 females
  - median age at diagnosis was 70 years (range 24 – 88 years)
- 3 people had recurrent episodes of LRPN.
  - 62 episodes in the study period

Incidence of LRPN

Results - Incidence

- The overall annual incidence of LRPN adjusted for age and sex is 4.16/100,000 (95% C.I. 3.13 to 5.18).
- Annual incidence of DLRPN is 2.79/100,000 (95% C.I. 1.94 to 3.14).
- Annual incidence of non-DLRPN is 1.27/100,000 (95% C.I. 0.71 to 1.83).

Incidence of LRPN

Results – Trends Over Time

- We divided incidence into 4 groups each lasting 4 years.
  - 2000 – 2003, 5.75/100,000 (95% C.I. 3.05 to 8.45)
  - 2004 – 2007, 4.07/100,000 (95% C.I. 1.92 to 6.22)
  - 2008 – 2011, 4.54/100,000 (95% C.I. 2.38 to 6.70)
  - 2012 – 2015, 3.26/100,000 (95% C.I. 1.49 to 5.04)
- The incidence did not seem to vary over the course of the study.

Role of DM in LRPN

Results – Diabetic State

- The majority of LRPN cases had DM (39; 66.1%).
  - 3 were diagnosed with DM at the time of presentation of LRPN
- Half of the non-DLRPN cases had prediabetes (10 of 20, 50%).
  - A1C between 5.7 to 6.4%
  - fasting blood sugars between 100 mg/dL and 125 mg/dL
- 37 of DLRPN were type 2 DM and 2 were type 1 DM.
- Mean HgA1C of DLRPN was 8.0% and mean fasting glucose was 181.5 mg/dL.
- Mean HgA1C of non-DLRPN was 5.6% and mean fasting glucose was 101.9 mg/dL.

Role of DM in LRPN

Results – DM in the Controls vs. LRPN

- The rates of DM and prediabetes were high in the control group.
  - 35 of 177 control patients (19.8%) had DM
  - 55 of 142 control patients (38.7%) were pre-DM
- DM was more prevalent in LRPN when compared to controls.
  - 39/59 (66.1%) vs. 35/177 (19.8%), $p < 0.001$
- Pre-DM was not different than controls.
  - 10/20 (50.0%) vs. 55/142 (38.7%), $p = 0.336$
- Odds ratios:
  - the calculated univariate OR of LRPN in DM was 7.91 (95% C.I. 4.11 to 15.21)
  - the calculated univariate OR of LRPN in pre-DM was 1.006 (95% C.I. 1.004 to 1.012)

Epidemiology of LRPN

Clinical Features of LRPN

- Median age of diagnosis was 70 years (24 – 88 years).
- Median time from onset to diagnosis was 2 months (range 1 to 72 months).
- 57 of 62 (92%) presented with pain.
- 5 (8.1%) presented as painless episodes.
- Syndrome was bilateral at time of evaluation in 23 (37.1%) and 6 were symmetrical.
- Most were asymmetrical on neurological examination and on electrophysiological testing.
- LRPN was recurrent in 3 DM cases with the contralateral lower limb involved (12 to 15 months after the initial episode).

Epidemiology of LRPN

Clinical Pattern of Involvement

- Pure proximal involvement in 20 (32.3%).
- Proximal equal to distal in 16 (25.8%).
- Proximal greater than distal in 10 (16.1%).
- Distal greater than proximal in 9 (14.5%).
- Isolated distal in 4 (6.5%).
- Predominantly sensory in 3 (4.8%).
- 10 (6 DM and 4 non-DM) had involvement in beyond the lumbosacral segment (a broader radiculoplexus neuropathy).
  - 9 had thoracic radiculopathies ipsilateral to the LRPN
  - 1 had bilateral cervical radiculoplexus neuropathy

Incidence of LRPN Compared to Other Inflammatory Neuropathies

- The incidence of 4.16/100,000/year is more frequent than other inflammatory neuropathies studied in the same population.
  - Guillain-Barré syndrome = 1.7/100,000 in Olmsted County
  - Brachial plexopathy = 1.64/100,000 in Olmsted County
  - CIDP = 1.6/100,000 in Olmsted County
- The frequency of LRPN as an inflammatory neuropathy is likely underappreciated by most experts and physicians.
- We did not estimate the prevalence of LRPN as it is a monophasic illness lasting only months.

Role of DM in LRPN

- The occurrence of DM is increased in LRPN.
  - patients with DM are 8 times more likely than those without DM to develop LRPN
- This increase in DM occurs in spite of the high rate of DM in the control group (19.8%).
- The high rate of DM in control patients is similar to the reported prevalence rate of DM above the age of 65 years of 20.8% in the U.S.A. by Nation Diabetes Statistics Report.

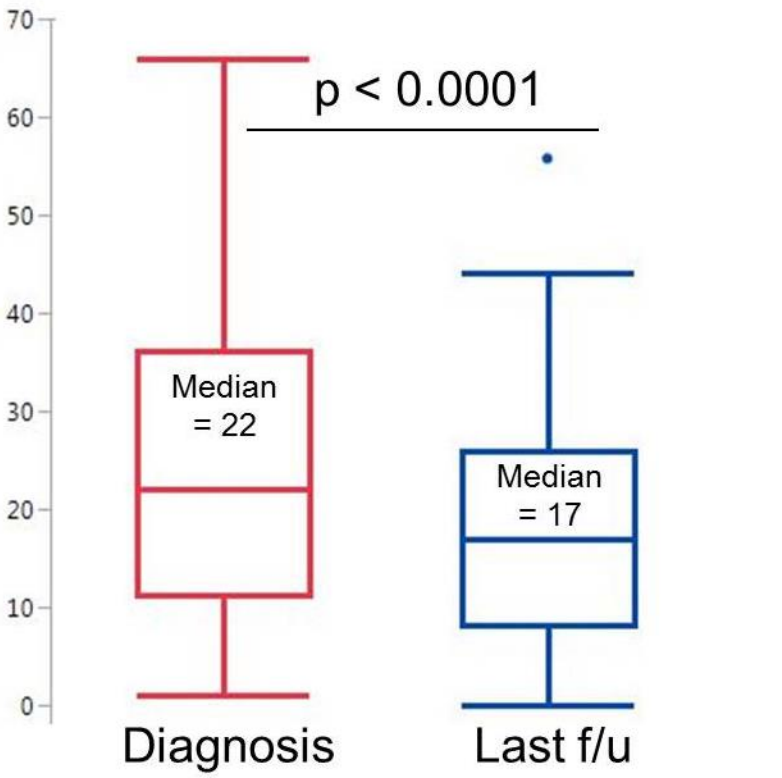
Atypical Presentations of LRPN Do Occur

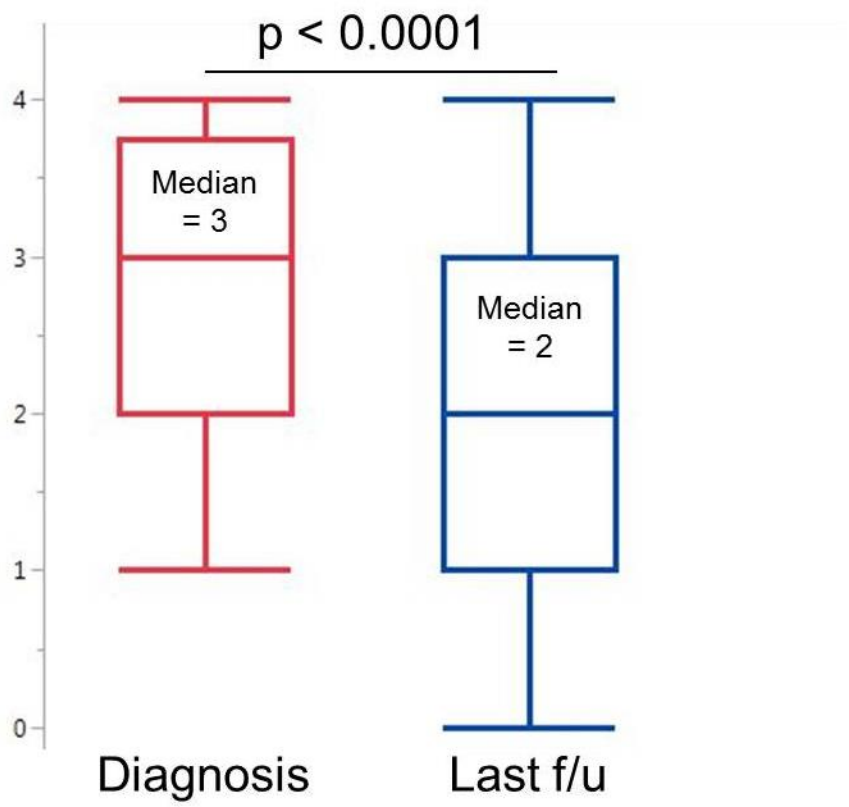
- Painless form (5/62, 8.1%, 2 DM and 3 non-DM)
  - these have been described in DLRPN as having a more insidious and widespread course due to ischemic injury and microvasculitis (Garces-Sanchez et al, 2011)
- Sensory predominant (3/62, 4.8%)
  - only sensory involvement was identified on exam but EMG showed widespread motor involvement

Other Neurological Segments Involved In LRPN

- Most cases of LRPN were isolated to the lower limb.
- Thoracic radiculopathy occurred occasionally.
  - 9/62, 14.5%
- Cervical radiculoplexus neuropathy occurred rarely.
  - 1/62, 1.6%
- This co-existence of lumbosacral, thoracic and cervical neuropathies together provides support for the concept of a more diffuse radiculoplexus neuropathy.

Longitudinal Results
Last follow-up with Neurologist





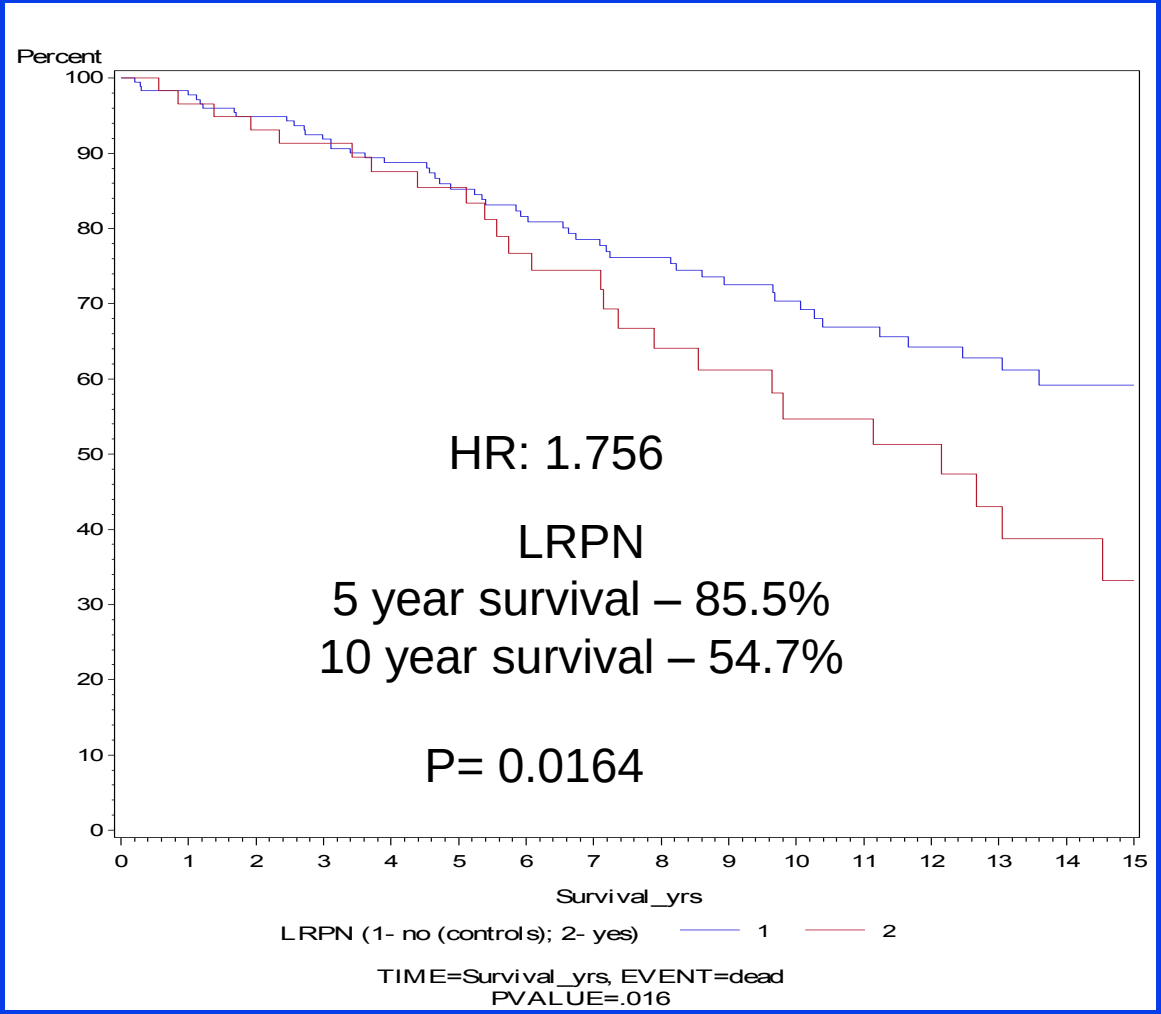
- Patients with LRPN improve over time in regards to NIS and mRankin scores.

Longitudinal Results
Last follow-up with Neurologist

- NIS
  - NIS improved ≥ 4 points in 56%
  - NIS worsened ≥ 4 points in 6%
- mRankin
  - mRankin improved ≥ in 45%
  - Most recent mRankin 0 or 1 in 29%
- Wheel-chair dependent
  - Initially 24%
  - Follow-up 12%

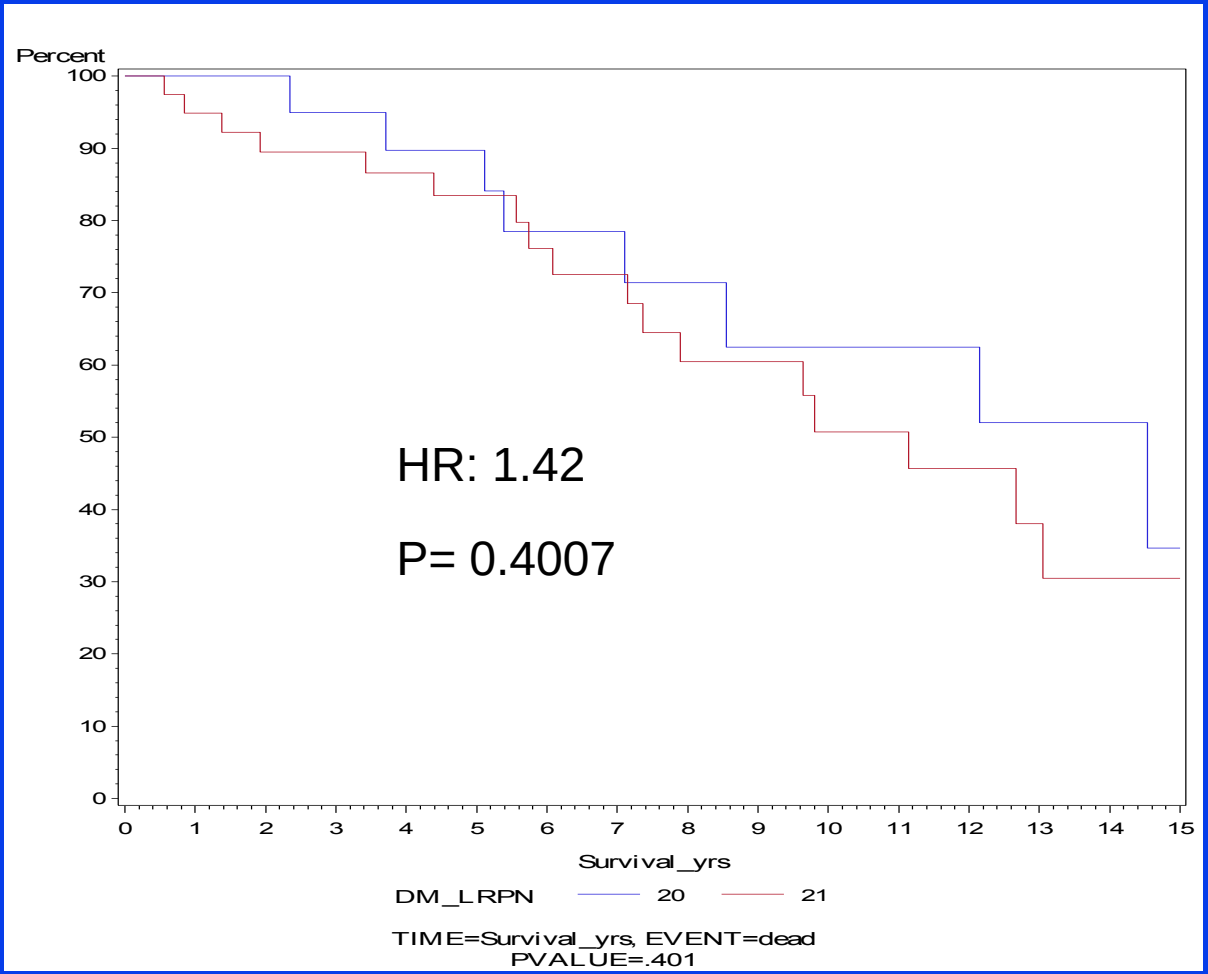
Survival Results
Control vs LRPN

Control = Blue
LRPN = Red



Survival Results
Non-Diabetic LRPN vs Diabetic LRPN

Non-diabetic LRPN = Blue
Diabetic LRPN = Red



Survival Results
Mortality Risk Factors

- Univariate logistic regression:
  Age, LRPN, History of cancer and Cardiovascular risk factors were all associated with increased mortality

Variables	HR	95% CI		Pr > chisq
Female	0.547	0.343	0.874	0.0116
Age	1.087	1.063	1.112	<.0001
Renal Dysfunction	5.418	3.054	9.612	<.0001
Hypertension	2.296	1.446	3.646	0.0004
Diabetes	2.512	1.603	3.937	<.0001
Coronary artery disease	4.998	3.097	8.066	<.0001
Heart failure	4.035	2.205	7.383	<.0001
Stroke/TIA	3.917	2.002	7.664	<.0001
Peripheral artery disease	5.94	2.554	13.818	<.0001
Dyslipidemia	1.86	1.187	2.914	0.0068
Cancer	3.534	2.199	5.679	<.0001
LRPN	1.756	1.102	2.799	0.0179

Survival Results
Mortality Risk Factors

- Multivariate logistic regression

	Variables	P value	HR	95% CI of HR	
Model 1	Age	<.0001	1.072	1.047	1.097
	Diabetes	0.0198	1.746	1.092	2.789
	Chronic Kidney Disease	0.0325	1.928	1.056	3.52
	Stroke/TIA	0.0033	2.814	1.411	5.61
	Coronary_artery_dise	0.006	2.101	1.237	3.567
	Peripheral_artery_di	0.0031	3.716	1.556	8.875

	Variables	P value	HR	95% CI of HR	
Model 2	Age	<.0001	1.065	1.039	1.091
	Diabetes	0.0134	1.804	1.13	2.879
	Stroke/TIA	0.0021	2.943	1.478	5.859
	Cancer	0.046	1.671	1.009	2.766
	Coronary artery disease	0.002	2.291	1.353	3.88
	Peripheral artery disease	0.0036	3.719	1.538	8.994

	Variables	P value	HR	95% CI of HR	
Model 3	Age	<.0001	1.084	1.059	1.11
	Chronic Kidney Disease	0.0047	2.323	1.294	4.169
	Dyslipidemia	0.0454	1.612	1.01	2.574
	Diabetes	0.0065	1.876	1.193	2.95
	Stroke/TIA	0.0328	2.096	1.062	4.134

- In multivariate analysis age, diabetes, kidney disease, coronary artery disease among others are mortality risk factors.

Conclusions

1. We have shown in a northern U.S.A. population that LRPN is a common form of inflammatory neuropathy (incidence = 4.16/100,000/year).
2. LRPN is three times more frequent than other common inflammatory neuropathies (including AIDP and CIDP) in our population and probably should receive more attention from experts.
3. Diabetes mellitus is a risk factor for the development of LRPN (LRPN occurs 8 times more frequently in diabetic patients).

Conclusions

4. The syndrome of LRPN presents very similarly in diabetic and non-diabetic patients but its strong association with DM makes the continued classification of diabetic and non-diabetic forms reasonable.
5. Atypical presentations such as painless and sensory predominant forms should be recognized as subtypes of LRPN.
6. People with LRPN have an increased risk of mortality but this is secondary to diabetes mellitus and other co-morbidities rather than the neuropathy (LRPN) itself.

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