A Deep Dive Into the Neuropathy Work-Up

Jonathan Katz, MD
CPMC
Introduction to Non Evidence Based Medicine

Jonathan Katz, MD
CPMC
When You are in the Trenches, Nothing Makes Sense

Jonathan Katz, MD
CPMC
Let’s Just Agree to Disagree

Jonathan Katz, MD
CPMC
First, a bit of background...
Classic CIDP--TREATABLE
MADSAM/Asymmetric Neuropathy
Chronic Length Dependent Neuropathy - UNTREATABLE
IMPAIRED GLUCOSE TOLERANCE—DOES IT CAUSE NEUROPATHY?

JAMES W. RUSSELL, MD, MS, MRCP,1,2 and EVA L. FELDMAN, MD, PhD1

1 Department of Neurology, University of Michigan, 200 Zina Pitcher Place, Taubman 7500, Ann Arbor, Michigan 48109-0088, USA
2 Geriatric Research and Clinical Center (GRECC), VA Medical Center, Ann Arbor, Michigan

The publication of the Diabetes Control and Complications Trial (DCCT) laid to rest much of the controversy surrounding the role of hyperglycemia in diabetic neuropathy.11,12 This study showed that intensive insulin therapy, coupled with improved glycemic control, reduces the severity of diabetic complications and, more importantly, decreases the risk of developing these complications. This was the first large prospective study to show that careful regulation of blood glucose can prevent development of neuropathy in diabetic patients. Despite the evidence that hyperglycemia is coupled with neuropathy, it has been assumed that neuropathy results only from significant hyperglycemia and is not related to impaired glucose tolerance (IGT). In the presence of mild and episodic hyperglycemia, alternative hypotheses for the development of neuropathy have been proposed, including advanced glycation end products, vitamin deficiency, and lipid abnormalities.13,14

Gluten sensitivity as a neurological illness

M Hadjivassiliou, R A Grünwald, G A B Davies-Jones

Gluten sensitivity

Gluten sensitivity, a jejunal absorption problem, is often underdiagnosed. A recent study of 118 patients referred for evaluation of “unexplained” neurological symptoms found 12 (10.2%) had gluten sensitivity. In 6 these were the first manifestation of neurological symptoms, in 5 secondary signs or symptoms were present. A large number of patients with gluten sensitivity have coeliac disease (CD); this can affect people of any age, and may be associated with neurological symptoms. The most common of these is subacute paresis, which has been described in about 2% of patients. Although the question of a causal relationship between gluten sensitivity and neurological disease remains uncertain, it remains that when neurological symptoms are present in young adults, an association with CD should be considered.

Statins and risk of polyneuropathy

A case-control study

D. Goist, MD, PhD; U. Jeppesen, MD, PhD; M. Andersen, MD, PhD; L.A. García Rodríguez, MD, MSc; J. Hallas, MD, PhD; and S.H. Sindrup, MD, PhD

Abstract—Background: Several case reports and a single epidemiologic study indicate that use of statins occasionally may have a deleterious effect on the peripheral nervous system. The authors therefore performed a population-based study to estimate the relative risk of idiopathic polyneuropathy in users of statins. Method: The authors used a population-based patient registry to identify first-time-ever cases of idiopathic polyneuropathy registered in the 5-year period 1994 to 1998. For each case, validated according to predefined criteria, 25 control subjects were randomly selected among subjects from the background population matched for age, sex, and calendar time. The authors used a prescription register to assess exposure to drugs and estimated the odds ratio of use of statins (ever and current use) in cases of idiopathic polyneuropathy compared with control subjects. Results: The authors verified a diagnosis of idiopathic polyneuropathy in 166 cases. The cases were classified as definite (53), probable (54), or possible (59). The odds ratio linking idiopathic polyneuropathy with statin use was 3.7 (95% CI 1.8 to 7.6) for all cases and 14.2 (5.3 to 38.0) for definite cases. The corresponding odds ratios in current users were 4.6 (2.1 to 10.0) for all cases and 16.1 (5.7 to 45.4) for definite cases. For patients treated with statins for 2 or more years the odds ratio of definite idiopathic polyneuropathy was 26.4 (7.8 to 45.4). Conclusions: Long-term exposure to statins may substantially increase the risk of polyneuropathy.
Conduction Block and Dispersion
What We Do: Tests for Neuropathy Patients

<table>
<thead>
<tr>
<th>Test</th>
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<tbody>
<tr>
<td>B12</td>
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<td>B6</td>
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<td>HIV</td>
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<td>Glucose Tolerance</td>
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<td>Hemoglobin A1C</td>
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<td>Thyroid functions</td>
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<td>CSF testing</td>
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<td>Nerve conduction studies</td>
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<td>Skin Biopsy</td>
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<td>Nerve biopsy</td>
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<td><strong>SPEP or IFE</strong></td>
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Antibodies
Monoclonal Proteins (M Protein):

- The M-protein may also be benign (just there doing nothing)
- It may attack the nerve (neuropathy)
- It may cause hyperviscosity syndrome (Waldenstrom’s)

Generally indicate an abnormal population of plasma cells
- May be benign (making M-proteins)
- Or malignant (crowding out other cells)
# Paraprotein and Neuropathy

## Differential Diagnosis?

<table>
<thead>
<tr>
<th>Paraprotein Type</th>
<th>Neuropathy Phenotype (and Associated Disease)</th>
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</table>
| IgM              | • Distal (DADS and anti-MAG)  
|                  | • Generalized sensorimotor (CIDP)  
|                  | • Asymmetric neuropathy (vasculitis)  
|                  | • Autonomic/small fiber (amyloid) |
| IgG              | • Any neuropathy (MGUS or monoclonal gammopathy of uncertain significance)  
|                  | • Distal or autonomic (Multiple myeloma and amyloidosis)  
|                  | • Generalized or distal demyelinating (POEMS syndrome)  
|                  | • Generalized (CIDP) |
| IgA              | • Generalized or distal demyelinating (POEMS syndrome) |
# Paraprotein and Neuropathy

<table>
<thead>
<tr>
<th>Relationship of any two findings</th>
<th>DISEASE</th>
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<tbody>
<tr>
<td>UNRELATED</td>
<td>MGUS</td>
</tr>
<tr>
<td>PARAPROTEIN CAUSES NEUROPATHY</td>
<td>DADS, Amyloid</td>
</tr>
<tr>
<td>NEUROPATHY CAUSES PARAPROTEIN</td>
<td>There is no such thing</td>
</tr>
<tr>
<td>ANOTHER PHENOMENON CAUSES BOTH</td>
<td>Vasculitic neuropathy POEMS syndrome CIDP associated with paraprotein?</td>
</tr>
</tbody>
</table>
WAYS FAMOUS PEOPLE DISCUSS NEUROLOGY

Then...
AND NOW...
The Most Common IgM Neuropathy = DADS

- Older age
- IgM only
- Mostly men
- Mostly kappa light chains
- Specific type of slowing on NCS
- Responds poorly to therapies
- Autoantibodies to MAG
IgM Neuropathy - Do we treat it?

Subject: IgM DADS neuropathy

Is anyone actually treating this?
I don’t think it makes sense.
Relatively benign disease versus long term treatment with questionable response. Weighs in favor of staying back.

Jonathan Katz

Director Neuromuscular Research and ALS Clinic, Norris Center
San Francisco, CA
Jon, our group is also becoming more and more conservative with these patients. Unimpressed with Rituximab.

For what it is worth we have not seen DADS with IgM MAG respond to anything so agree with Dave Herrmann and have no problem with not treating them if it is typical sensory symps and signs and ataxia........this just doesn’t get better in our hands. Also in this setting I don’t think heme consult is needed but usually do it out of default and then heme guys have no idea what we in neuro are talking about (“u said DADS?”)

NO!!

Professor & Chairman, University of Kansas Medical Center, Dept of Neurology
Kansas City, KS
As usual I have a slightly different perspective. I’m not advocating widespread use but….I’ve treated over 15 with either anti-MAG or DADS-IgM. I also don’t treat mild cases but not everyone with DADS-M are benign. My experience is that in those that have been very indolent rituximab rarely improves their condition but in long term follow-up most show no progression. Those with more aggressive disease, with motor involvement but still distal and with distal accentuated slowing, they see significant improvement and the NCVs are better. I’ve had some fairly dramatic improvements.

I think the trials (Dalakas and French studies) had less than optimal endpoints. Patient selection is crucial.

Cedars-Sinai Medical Center,

August 28, 2012 at 1:34 pm

Michael Weiss

John, I would generally agree with Richard. I’ve treated about 15 patients with demyelinating PN and monoclonal IgM abs to MAG beginning in 2001 and approximately 50% have had convincing improvement (resolution of their sensory ataxia or foot drop). One patient also had essentially normalization of her NCV and persistent clinical benefit 2 and 1/2 years post treatment (4 weekly infusions). I presented a poster on this at the 2011 AAN meeting. If patients have no or very small CMAPs or a long duration (usually these go together), they are unlikely to benefit. If they have mild symptoms, it may not be worth treating them either but I at least consider a course of therapy in those patients to prevent progression. I should mention that while the drug is fairly benign (the PML risk is there but small), I did have a patient develop a spike in their IgM level and MAG titers and worsening neuropathy transiently, a neurologic equivalent to a well-described phenomenon in Waldenstrom’s called IgM flare syndrome.

August 30, 2012 at 8:03 pm

Jon, As you know I don’t agree with you on this. I have had similar experience as Rich and Michael. The trick is catch them early before these cases become wheelchair bound and before the sensory responses completely go away. I have at least 4/8 who clearly improved in muscle strength and gait disturbance and another who 4 who did not progress. I still treat them with Rituxan and follow both MAG levels (through Wash U) and IgM levels.

Tahseen Mozaffar

I have been a little “out of the loop” lately due to a combination of factors; mainly computer/technical in nature... but NOW I’m back.

I do almost EXACTLY the same thing as Docs Weiss and Mozaffar!

John T Kissel, MD
Who Gets Treated?

- Not indolent with distal motor involvement
- Recent onset with not severe or mild involvement
- Early before they become wheelchair bound
- 50% response rate to Rituximab
Biases?

- The Decision: Relatively benign disease without much progression versus long term on strong (expensive) therapy with partial improvement
- Other Influences:
  - Last case seen
  - Mixed literature
  - What constitutes improvement
- How does one person see 50% of patients improve and another sees none?
Placebo-Controlled Trial of Rituximab in IgM Anti–Myelin-Associated Glycoprotein Antibody Demyelinating Neuropathy

Marinos C. Dalakas, MD, Goran Rakocevic, MD, Mohammad Salajegheh, MD, James M. Dambrosia, PhD, Angelika F. Hahn, MD, Raghavan Raju, PhD, and Beverly McElroy, CNRN


Methods: Twenty-six patients were randomized to four weekly infusions of 375 mg/m² rituximab or placebo. Sample size was calculated to detect changes of ≥1 Inflammatory Neuropathy Course and Treatment (INCAT) leg disability scores at month 8. IgM levels, anti-MAG titers, B cells, antigen-presenting cells, and immunoregulatory T cells were monitored every 2 months.

Results: Thirteen A-MAG-DP patients were randomized to rituximab and 13 to placebo. Randomization was balanced for age, electrophysiology, disease duration, disability scores, and baseline B cells. After 8 months, by intention to treat, 4 of 13 rituximab-treated patients improved by ≥1 INCAT score compared with 0 of 13 patients taking placebo (p = 0.096). Excluding one rituximab-randomized patient who had normal INCAT score at entry, and thus could not improve, the results were significant (p = 0.036). The time to 10 m walk was significantly reduced in the rituximab group (p = 0.042) (intention to treat). Clinically, walking improved in 7 of 13 rituximab-treated patients. At month 8, IgM was reduced by 34% and anti-MAG titers by 50%. CD25⁺CD4⁺Foxp3⁺ regulatory cells significantly increased by month 8. The most improved patients were those with high anti-MAG titers and most severe sensory deficits at baseline.

Interpretation: Rituximab is the first drug that improves some patients with A-MAG-DP in a controlled study. The benefit may be exerted by reducing the putative pathogenic antibodies or by inducing immunoregulatory T cells. The results warrant confirmation with a larger trial.

Ann Neurol 2009;65:286–293
INCAT Score (Month 8)

0 - walking not affected
1 - walking is affected but walks independently outdoors
2 - uses unilateral support (cane, single crutch)
3 - uses bilateral support (cane, crutches)
4 - uses wheelchair but able to stand and walk a few steps with support
5 - restricted to wheelchair.
4/13 treated responded by INCAT (one dramatically)
- Subj. 1 worsened, 7 improved, 5 unchanged
- 0/13 placebo responded
  - Subj. 6 worsened, 7 unchanged
Rituximab Treatment

- Improvement associated with:
  - High anti-MAG antibody titers
  - More severe sensory impairments
- Not associated:
  - Disease duration
  - Age
  - IgM level
  - Electrophysiology
  - Axonal loss
- Repeated nerve conduction studies did not change after therapy
Placebo-controlled trial of rituximab in IgM anti-myelin–associated glycoprotein neuropathy

Abstract

Objective: To determine whether rituximab 375 mg/m² was efficacious in patients with immunoglobulin M (IgM) anti-myelin-associated glycoprotein antibody demyelinating neuropathy (IgM anti-MAG demyelinating neuropathy).

Methods: Fifty-four patients with IgM anti-MAG demyelinating neuropathy were enrolled in this randomized, double-blind, placebo-controlled trial. The inclusion criteria were inflammatory neuropathy cause and treatment (INCAT) sensory score (ISS) ≥4 and visual analog pain scale >4 or ataxia score ≥2. The primary outcome was mean change in ISS at 1.2 months.

Results: Twenty-six patients were randomized to a group receiving 4 weekly infusions of 375 mg/m² rituximab, and 28 patients to placebo. Intention-to-treat analysis, with imputation of missing ISS values by the last observation carried forward method, showed a lack of mean change in ISS at 1.2 months, 1.0 ± 2.7 in the rituximab group, and 1.0 ± 2.8 in the placebo group. However, changes were observed, in per protocol analysis at 1.2 months, for the number of patients with an improvement of at least 2 points in the INCAT disability scale (p = 0.027), the self-evaluation scale (p = 0.016), and 2 subscores of the Short Form-36 questionnaire.

Conclusions: Although primary outcome measures provide no evidence to support the use of rituximab in IgM anti-MAG demyelinating neuropathy, there were improvements in several secondary outcomes in per protocol analysis.

Level of Evidence: This study provides Class I evidence that rituximab is ineffective in improving ISS in patients with IgM anti-MAG demyelinating neuropathy. Neurology® 2013;60:1-9

Glossary

AE = adverse events; BAFF = B-cell activating factor; IgM = immunoglobulin M; INCAT = inflammatory neuropathy cause and treatment; ISS = inflammatory neuropathy cause and treatment sensory score; MAG = myelin-associated glycoprotein; RCT = randomized controlled trial; RIMAG = Rituimab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy; SF-36 = Short Form-36; UPRICRB = Unit of Clinical Research and Biostatistics; VAS = visual analog pain scale.
Included patients n=54

Placebo n=28

Withdrawal n=1
Causes:
1 withdrawal of consent at M3

Evaluation of main outcome – per protocol population n=27

Rituximab n=26

Withdrawal n=6
Causes:
2 withdrawal of consent at D14 and M3
1 clinical worsening at M3
1 ECG abnormality before infusion at D1
1 serious adverse event at D1
1 loss to follow-up at M6

Evaluation of main outcome – per protocol population n=20

Intention to treat population n=28

Intention to treat population n=26
Table 3  Results for the main analysis (first row) and other analyses of inflammatory neuropathy cause and treatment sensory score in the intention-to-treat population and in the per protocol population: Rituximab vs Placebo in Polyneuropathy Associated With Anti-MAG IgM Monoclonal Gammopathy (RIMAG) study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group (n = 28)</th>
<th>Rituximab group (n = 28)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between day 0 and month 12</td>
<td>1.0 ± 2.8</td>
<td>1.0 ± 2.7</td>
<td>0.92(^a)</td>
</tr>
<tr>
<td>Mean percent change in ISS ± SD</td>
<td>10.0 ± 33.7</td>
<td>11.3 ± 38.3</td>
<td>0.90(^a)</td>
</tr>
<tr>
<td>ISS improvement ≥20% with respect to baseline, n (%)</td>
<td>12 (42.9)</td>
<td>11 (42.3)</td>
<td>0.97(^b)</td>
</tr>
<tr>
<td>ISS improvement ≥4, n (%)</td>
<td>6 (21.4)</td>
<td>4 (15.4)</td>
<td>0.73(^c)</td>
</tr>
<tr>
<td>ISS improvement ≥2, n (%)</td>
<td>11 (39.3)</td>
<td>8 (34.6)</td>
<td>0.72(^b)</td>
</tr>
<tr>
<td>Median change in ISS for the lower limbs (IQR)</td>
<td>0.0 (−1.0; 1.0)</td>
<td>0.0 (−1.0; 2.0)</td>
<td>0.39(^d)</td>
</tr>
<tr>
<td>Per protocol population</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Between day 0 and month 12</td>
<td>1.0 ± 2.8</td>
<td>1.3 ± 3.0</td>
<td>0.68(^a)</td>
</tr>
<tr>
<td>Mean percent change in ISS ± SD</td>
<td>10.4 ± 34.3</td>
<td>15.5 ± 42.2</td>
<td>0.64(^a)</td>
</tr>
<tr>
<td>ISS improvement ≥20% with respect to baseline, n (%)</td>
<td>12 (44.4)</td>
<td>10 (50.0)</td>
<td>0.77(^b)</td>
</tr>
<tr>
<td>ISS improvement ≥4, n (%)</td>
<td>6 (22.2)</td>
<td>4 (20.0)</td>
<td>1.00(^c)</td>
</tr>
<tr>
<td>ISS improvement ≥2, n (%)</td>
<td>11 (40.7)</td>
<td>8 (40.0)</td>
<td>0.95(^b)</td>
</tr>
<tr>
<td>Median change in ISS for the lower limbs (IQR)</td>
<td>0 (−1.0; 1.0)</td>
<td>1.0 (−0.5; 3.0)</td>
<td>0.15(^d)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR = interquartile range; ISS = inflammatory neuropathy cause and treatment sensory score; n' = number of available data when lower than n for the group.

\(^a\) Student t test.

\(^b\) \(\chi^2\) test.

\(^c\) Fisher exact test.

\(^d\) Mann-Whitney test.
### Table 4
Results for secondary analysis for clinical evaluation (change from D0 to M12), functional scores (evaluated at M12), and SF-36 scores (change from D0 to M12) in the per protocol population: Rituximab vs Placebo in Polynuropathy Associated With Anti-MAG IgM Monoclonal Gammapathy (RIMAG) study

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group (n = 27)</th>
<th>Rituximab group (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median change in INCAT disability scale score (D0-M12) (IQR)</td>
<td>0.0 (−1.0; 0.0) (n’ = 27)</td>
<td>0.0 (−1.0; 1.0) (n’ = 20)</td>
<td>0.22&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Improvement in INCAT disability score ≥2, n (%)</td>
<td>0 (0.0)</td>
<td>4 (20.0)</td>
<td>0.027&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Improvement in INCAT disability score ≥1, n (%)</td>
<td>4 (14.8)</td>
<td>8 (40.0)</td>
<td>0.0503&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean change in NIS (D0-M12) ± SD</td>
<td>1.8 ± 5.1 (n’ = 26)</td>
<td>1.1 ± 6.0 (n’ = 19)</td>
<td>0.89&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Median change in MRC score (D0-M12) (IQR)</td>
<td>0.0 (−3.0; 0.0) (n’ = 27)</td>
<td>0.0 (−1.5; 1.5) (n’ = 20)</td>
<td>0.17&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean change in 10-meter walk time, s (D0-M12) ± SD</td>
<td>0.1 ± 2.7 (n’ = 24)</td>
<td>0.3 ± 3.2 (n’ = 18)</td>
<td>0.84&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Ataxia (2-3), n (%)</td>
<td>17 (65.4) (n’ = 26)</td>
<td>13 (65.0) (n’ = 20)</td>
<td>0.98&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean change in VAS score for pain ± SD</td>
<td>−0.07 ± 1.7 (n’ = 24)</td>
<td>0.61 ± 2.3 (n’ = 17)</td>
<td>0.26&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mean functional score at M12 ± SD</td>
<td>14.8 ± 4.3 (n’ = 25)</td>
<td>12.0 ± 5.5 (n’ = 17)</td>
<td>0.07&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Self-evaluation scale at M12</td>
<td>(n’ = 25)</td>
<td>(n’ = 19)</td>
<td>0.016&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Improvement, n (%)</td>
<td>1 (4.0)</td>
<td>5 (26.3)</td>
<td></td>
</tr>
<tr>
<td>Stabilization, n (%)</td>
<td>9 (36.0)</td>
<td>10 (52.6)</td>
<td></td>
</tr>
<tr>
<td>No effect, n (%)</td>
<td>15 (60.0)</td>
<td>4 (21.0)</td>
<td></td>
</tr>
<tr>
<td>SF-36 scores, absolute change (D0-M12)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical component summary scales (mean ± SD)</td>
<td>−0.5 ± 4.1 (n’ = 15)</td>
<td>3.1 ± 6.6 (n’ = 14)</td>
<td>0.08&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mental component summary scales (mean ± SD)</td>
<td>0.4 ± 9.2 (n’ = 15)</td>
<td>3.2 ± 8.9 (n’ = 14)</td>
<td>0.41&lt;sup&gt;d&lt;/sup&gt;</td>
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<tr>
<td>SF-36 subscores, absolute change (D0-M12)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Physical functioning (mean ± SD)</td>
<td>−3.9 ± 9.8 (n’ = 20)</td>
<td>11.6 ± 19.6 (n’ = 17)</td>
<td>0.0063&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Role-physical (median, IQR)</td>
<td>0.0 (0.0; 25.0) (n’ = 23)</td>
<td>0.0 (−25.0; 25.0) (n’ = 16)</td>
<td>0.76&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Role-emotional (median, IQR)</td>
<td>0.0 (−33.3; 16.7) (n’ = 24)</td>
<td>33.3 (0.0; 66.7) (n’ = 18)</td>
<td>0.02&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Mental health (mean ± SD)</td>
<td>−2.1 ± 12.8 (n’ = 24)</td>
<td>4.5 ± 9.9 (n’ = 17)</td>
<td>0.08&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Vitality (mean ± SD)</td>
<td>−1.4 ± 13.1 (n’ = 24)</td>
<td>2.1 ± 13.7 (n’ = 19)</td>
<td>0.40&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Social functioning (median, IQR)</td>
<td>0.0 (−31.2; 12.5) (n’ = 20)</td>
<td>12.5 (0.0; 12.5) (n’ = 18)</td>
<td>0.07&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bodily pain (median, IQR)</td>
<td>0.0 (−10.5; 9.0) (n’ = 23)</td>
<td>9.0 (0.0; 11.0) (n’ = 17)</td>
<td>0.09&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>General health (median, IQR)</td>
<td>0.0 (−11.0; 8.5) (n’ = 24)</td>
<td>5.0 (0.0; 15.0) (n’ = 17)</td>
<td>0.12&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Abbreviations: INCAT = inflammatory neuropathy cause and treatment; IQR = interquartile range; n’ = number of data available when lower than n for the group; MRC = Medical Research Council; NIS = neurologic impairment score; SF-36 = Short Form-36; VAS = visual analog pain scale.

<sup>a</sup>Mann-Whitney test.
<sup>b</sup>Fisher exact test.
<sup>c</sup>χ² test.
<sup>d</sup>Student t test.
Cochrane Votes NO (but is anybody listening?)

Conclusions

In conclusion, the seven published RCTs of immunotherapy in anti-MAG IgM paraproteinaemic neuropathy were all either too small, too short or too flawed to draw confident conclusions about the efficacy of individual treatments or comparisons between them. More large, carefully constructed, collaborative studies are required to identify which treatments are effective. These will need to last long enough to demonstrate meaningful clinical changes and start treatment early enough in the disease to be able to reverse deficits before they become ‘fixed’. Responsive outcomes will need
Is this a matter of phenotypes?

- CIDP cases can have IgM paraproteins and are likely to respond to therapies
With CIDP phenotype rather than typical MAG phenotype, would treat as CIDP, eg, IVIG.

Phoenix Neurological Associates, Phoenix, AZ

Michael, while anti-MAG neuropathy is thought to be primarily a distal demyelinating neuropathy, it does progress more proximally over variable amounts of time so this presentation (proximal and distal weakness), while unusual, could certainly occur. You could do a treatment trial (like 3 months) with IVIG, but if he doesn’t respond, which is very possible, I would treat with rituximab.

Associate Professor, University of Washington Medical Center
Seattle, WA

Thanks

Professor, UCLA
Los Angeles, CA
PLEX/Ritux IgM Responder

Almost length dependent:
Motor (left/right): Deltoids 4+/4+, biceps 4-/4-, triceps 4-/4-, wrist extensors 4-/4-, wrist flexors 4+/4-, finger extensors 2/2, finger flexors 2/2, iliopsoas 3/3, quadriceps 3/3, hamstrings 4-/3, dorsiflexors 0/0, plantar flexors 0/0.

Sensory: Absent proprioception at ankles and wrists bilaterally.
-Absent vibratory sense to knees and elbows bilaterally.
-pinprick loss to the knees and elbows bilaterally.

No reflexes.
Distal acquired demyelinating symmetric neuropathy

J.S. Katz, MD; D.S. Saperstein, MD; G. Gronseth, MD; A.A. Amato, MD; and R.J. Barohn, MD

**Article abstract—Objective:** To characterize an acquired, symmetric, demyelinating neuropathic variant with distal sensory or sensorimotor features. **Background:** Classic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients have prominent proximal and distal weakness. However, chronic demyelinating neuropathies may present with different phenotypes. An approach that distinguishes these disorders primarily according to the pattern of weakness may be useful to the clinician. **Methods:** A total of 53 patients with acquired symmetric demyelinating polyneuropathies were classified primarily according to the pattern of the neuropathy and secondarily according to the presence and type of monoclonal protein (M-protein) in this retrospective review. The authors distinguished between patients with distal sensory or sensorimotor involvement, designated as distal acquired demyelinating symmetric (DADS) neuropathy, from those with proximal and distal weakness, who were designated as CIDP. **Results:** M-proteins were present in 22% of patients with CIDP. There were no features that distinguished clearly between CIDP patients with or without an M-protein, and nearly all of these patients responded to immunomodulating therapy. In contrast, nearly two-thirds of the patients with DADS neuropathy had immunoglobulin M (IgM) kappa monoclonal gammopathies, and this specific combination predicted a poor response to immunomodulating therapy. Antimyelin-associated glycoprotein (anti-MAG) antibodies were present in 67% of these patients. **Conclusion:** Distinguishing acquired demyelinating neuropathies by phenotype can often predict the presence of IgM kappa M-proteins, anti-MAG antibodies, and responses to immunomodulating therapy. **Key words:** Chronic inflammatory demyelinating polyradiculopathy—Distal acquired demyelinating symmetric neuropathy—Monoclonal gammopathy of uncertain significance—Terminal latency index—Myelin-associated glycoprotein.

NEUROLOGY 2000;54:615–620
Table 3 Treatment response

<table>
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<tr>
<th>Characteristic</th>
<th>DADS-M</th>
<th>DADS-I</th>
<th>CIDP*</th>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Any subjective improvement, n (%)</td>
<td>3/10 (30)</td>
<td>4/5 (80)</td>
<td>20/21 (95)</td>
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</tr>
<tr>
<td>Objective motor response, n (%)</td>
<td>0/8 (0)</td>
<td>2/3 (67)</td>
<td>20/21 (95)</td>
<td>0.001†‡</td>
</tr>
</tbody>
</table>

* Includes patients with and without a monoclonal protein.
† The comparison between DADS-M and DADS-I is significant.
‡ The comparison between DADS-M and CIDP is significant.
More Phenotypes

Anti-MAG

Subject: Anti-MAG

I saw a 51 yo woman with subacute asymmetrical-onset bilateral foot paresthesias/numbness, has a small IgM monoclonal protein and vary high titer MAG ab. Normal NCS and skin biopsy. Would you treat? Further testing?

Thanks!

Andrea

May 15, 2012 at 4:58 am

Would try because pt is so very young (younger than me) ...but it won't work R

Richard Barohn

May 15, 2012 at 5:41 am
Hi RRNMF,

I saw a 51 yo woman with subacute asymmetrical-onset bilateral foot paresthesias numbness, has a small IgM monoclonal protein and very high titer MAG ab. Normal NCS and skin biopsy. Would you treat? Further testing?

Thanks!
Andrea

Univ of Iowa, Dept of Neurology
Iowa City, IA
May 15, 2012 at 5:41 am

Would try because pt is so very young (younger than me) ....but it wont work R

Richard Barohn

Professor & Chairman, University of Kansas Medical Center, Dept of Neurology
Kansas City, KS

May 15, 2012 at 5:51 am

Probably would because of age IF she has objective sensory loss. Agree with rick it will probably not work.

John T Kissel, MD
Treat What? With What?

She has subjective symptoms without objective abnormalities (normal NCS). This is not typical anti-MAG neuropathy (i.e., DADS).

I would tell the patient the following:
(1) There is no scientific evidence that this small monoclonal protein has anything to do with her subjective numbness.
(2) There is no convincing evidence that Rituxan or any other immunotherapy is beneficial even in typical anti-MAG neuropathies (sorry but anecdotal stories of subjective improvement in a few patients just does not sway me).
(3) We have even less evidence that these medications are helpful in non-DADs IgM MAG cases)
(4) There are though known risks associated with use of Rituxan (e.g., PML), which although probably quite low, could kill her.

This way the patient truly will give their “informed consent” regarding treatment.

May 15, 2012 at 12:27 pm

Agree 100% with Tony.

Aziz

Clinical Associate Professor of Medicine, Baylor College Of Medicine
Houston, Tx
I agree with Rich. We have had considerable success with Rituxan but the trick is to use it early before the sensory nerve disappears. We have had patients, similar to Rich, who went into "remission".

However, agree that I am not sure what I am treating with Andrea’s patient. Are we sure this is not a pre-ganglionic pathology, i.e. spine or spinal cord related? Normal nerve conductions, normal skin biopsy and asymmetry would lead me away from an IgM (kappa, I assume) related MAG pathology and would look for other considerations. Not willing to treat yet.

Tahseen

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May 15, 2012 at 8:57 am

YES ANDNO!!!
RESEARCH REPORT

Amyloid-like IgM deposition neuropathy: a distinct clinico-pathologic and proteomic profiled disorder

Juan J. Figueroa¹, E. Peter Bosch², P. James B. Dyck¹, Wolfgang Singer¹, Julie A. Vrana³, Jason D. Theis³, Ahmet Dogan³, and Christopher J. Klein¹

¹Departments of Neurology and Pathology, Mayo Clinic, Rochester, MN; ²Department of Neurology, Mayo Clinic, Scottsdale, AZ; ³Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
Abstract  Some patients with immunoglobulin paraproteinemnic neuropathy have intra-nerve deposits that morphologically mimick amyloid, but do no stain with Congo red. Patients with amyloid-like deposits were identified. The nerve amyloid-like aggregates were studied by laser microdissection and dual mass spectrometry. Three male patients, all with IgM gammopathy, and neuropathy were identified. Follow-up, disease duration was 5, 19, and 7 years, respectively. All had progressive asymmetric sensory-onset distal axonal polyneuropathy with late motor involvement. Autonomic symptoms occurred in only one after 13 years of symptoms. None had clinical cardio-renal involvement. One had skin papules with dermal amyloid-like deposits. Endoneurial amyloid-like deposits had granulo-fibrillar ultrastructure. Mass spectrometry of laser-dissected deposits identified IgM pentameric macroglobulin (heavy, light, and joining chains) without amyloid-associated proteins including absent apolipoprotein E and serum amyloid P-component. Amyloid-like neuropathy has distinct clinical, pathologic, and proteomic features which expand the spectrum of IgM neuropathies. Patients have favorable survival, relative absence of autonomic features, and distinct proteomic profiles of the infiltrative protein in nerve.
IgM MGUS Neuropathy

I have a pt with IgM MGUS who has a progressive axonal neuropathy. He has failed IVIg and Rituxan. Wondering if anyone has used cyclophosphamide 500 mg for 4 days and prednisone 60 mg for 5 days every 28 days for 6 mo? Or any other ideas?
there are a lot of posts on paraproteinemic neuropathies and many of them involve “treatments” that are seemingly chance, ie, the evidence base is nil or less. the group should have a systematic approach to these. All patients should be evaluated or at least reviewed with an oncologist interested in paraproteins. Bone marrow, etc. should be available for difficult cases esp. if vitamin R is planned. Treatments should follow the Oncology diagnosis as the evidence base is greater than the small and likely biased case series from neurologists (I always worry about anyone who repeatedly publishes case series where every patient improves). More often than not biopsy should be considered or done (could this case be amyloid and therefore not respond?). For IgM we should know anti-MAG status and results of CT chest/abd/pelvis to r/o lymphoma while for other Igs we should know if myeloma or plasmacytoma has been ruled out. Thus in this case there is lots more to know before we start giving advise for serious Rx.
great article david
suraj i agree onc needs to look hard to make sure this is not WM.
assuming it is not, we have had no success in making these idiopathic patients better with cytoxan or far that matter with anything very much. For the deymelinating IgM with our without MAG I often dont even try anymore. For the axonals its even worse!

Professor & Chairman, University of Kansas Medical Center, Dept of Neurology
Kansas City, KS
Clinical and pathological heterogeneity in a series of 31 patients with IgM-related neuropathy

M. Luigetti a,*, A. Conte a, N. Montano b, A. Del Grande a, F. Madia a, M. Lo Monaco a, L. Laurenti c, M. Sabatelli a

a Institute of Neurology, Catholic University of the Sacred Heart, Rome, Italy
b Institute of Neurosurgery, Catholic University of the Sacred Heart, Rome, Italy
c Institute of Haematology, Catholic University of the Sacred Heart, Rome, Italy
3.2.1. Classic phenotype
The classic phenotype was observed in 18 of 31 patients (58%). Age at onset varied from 50 to 73 years (mean 62.77, median 62.5, SD ± 6.14). The ratio of men to women was 5:1. The mean follow-up period was 87.4 months (range 24–324 months). Clinically all patients revealed sensory ataxia, paraesthesias with stockings-and-glove distribution and absence of tendon reflexes; in 8 patients slight strength impairment (graded 4 on the MRC scale) was detected in distal muscles of upper and lower limbs (#14, 15, 17, 22, 24, 25, 28, 29).

Anti-MAG essay was performed in 13 cases and proved positive in 9 (Table 1). Seven patients with classical phenotype (#14, 15, 20, 26, 27, 29, 31) were treated with Rituximab, according to standard protocol [15], with a good response in four (#14, 27, 29, 31). They had not been treated with other immunosuppressant or immunomodulatory therapies. The remaining 11 patients were treated only with palliative therapies aimed at symptom control.

3.2.2. Atypical phenotype
An atypical phenotype was observed in 13 of 31 patients (42%). Age at onset ranged from 42 to 79 years (mean 64.61, median 68, SD ± 11.96). The ratio of men to women was 0.86:1. The mean follow-up period was 62.3 months (range 24–168 months).

Three main phenotypes were observed in this group of patients. Multiple mononeuropathy was observed in 5/13 patients, with predominant involvement of the upper limbs in three (#1, 6, 7) and of cranial nerves in the other two (#2, 8). Symmetric polyneuropathy with predominant motor impairment was observed in 7/13 patients (#3, 4, 5, 9, 10, 11, 13). The remaining one patient (#12) had painful neuropathy, characterized by shooting pain and burning in her lower limbs and hands, due to predominant small-fibre involvement, as previously described [16].
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<th>Case</th>
<th>Phen</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Age at onset</th>
<th>Median nerve</th>
<th>Sural nerve</th>
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<th>Serum IgM titre (g/dL)</th>
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<td>SCV (m/s)</td>
<td>SNAP (μV)</td>
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Age, age at last examination; yr, years; Phen, clinical phenotype; C, classical; A, atypical; MCV, motor conduction velocity; DL, distal latency; CMAP, compound muscle action potential; SCV, sensory conduction velocity; SNAP, sensory nerve action potential; NP, not performed; BTU, Buhlmann titer units. In bold patients with an atypical phenotype.
Three Atypical Phenotypes of IgM

- **Multiple mononeuropathy**
  - 5/13 total
  - 4/5 had MAG
  - Predominant involvement of the upper limbs in three (#1, 6, 7) and of cranial nerves in the other two (#2, 8)

- **Symmetric polyneuropathy with predominant motor impairment**
  - 7/13 patients (#3, 4, 5, 9, 10, 11, 13)
  - 3 of 5 had MAG

- **Painful neuropathy**
  - Shooting pain and burning in lower limbs and hands, due to small-fibre involvement (Patient #12)
Atypical Cases Respond to Steroids

- We treated with glucocorticoids 10/13 patients (#2, 4, 5, 6, 7, 9, 10, 11, 12, 13), all of whom reported symptomatic improvement except for one (#12, who had a distal painful neuropathy) who responded poorly, as we have previously reported.

- Of the remaining 3/13 patients, two refused therapy (#1, 3) and one (#8) was treated with chemotherapy for an underlining WM with a good response.
Conclusions About “IgM” Neuropathy

- Think phenotype
- Difference in response observations may be from distinct clinical presentations
- Caution grouping cases into a single ANTIBODY SYNDROME
- Different phenotypes may not be same disease:
  - Frank IgM deposition, asymmetric sensory
  - Amyloid (small chains)
  - Vasculitis (presumably M-protein and Vasculitis both from third factor)
  - Classic: Widened lamillae