

## *Predicting Neuromyelitis Optica in Patients with Transverse Myelitis*

*Biljana Beretich, MD, MPH  
Department of Neurology  
University of New Mexico*

### *Background*

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- Neuromyelitis Optica (NMO) - rare, but severe, inflammatory disease
- Acute, fulminant attacks of optic neuritis (ON) and transverse myelitis(TM)
- In >90% cases relapsing disease
- Visual acuity worse than 20/200 in >50% pts within 5 years
- Risk of respiratory failure and death

### *Background*

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- NMO - often misdiagnosed as multiple sclerosis (MS), but the course more severe in NMO
- Relapse rate for NMO is 1.3 vs. 0.6 per year in MS, probability of a second attack in the first 2 years is 82% in NMO vs. 62% in MS
- Median time to reach EDSS of 6.0 is 7 years in NMO vs. 9.4 in MS
- Different treatment approaches
- Most of studies designed to differentiate NMO from MS

### *Background*

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- Recently proposed revised diagnostic criteria for NMO require both, ON and TM to be present for diagnosis
- No studies showing early differentiating characteristics between those patients that maintained idiopathic ON/TM diagnosis vs those that went on to develop NMO
- The identification of factors that could predict risk of developing NMO in patients with a new onset of optic neuritis or transverse myelitis would possibly allow earlier and more effective treatment of NMO

### *Hypothesis*

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There are no specific factors (clinical, laboratory or imaging) that allow us to differentiate between NMO and TM earlier than is currently available.

### *Study Design and Methods*

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- Retrospective study, medical chart review
- Subjects:
  - $\geq 16$  years old at onset of symptoms
  - Selected from existing MS clinic database, TM database and UNM patient database
  - Seen through the UNM Hospital and outpatients clinics
  - Categorized into 2 groups: NMO and TM
  - As of today, 17 subjects meet inclusion criteria for NMO, 12 subjects meet inclusion criteria for TM

### Study Design and Methods

- Inclusion criteria by study group:
  - NMO:
    - At least 1 attack of ON and TM
    - 2 supportive criteria: spinal cord MRI lesion involving  $\geq 3$  vertebral segments, brain MRI not meeting diagnostic criteria for MS, or NMO-IgG seropositive status

### Study Design and Methods

- Inclusion criteria by study group:
  - TM:
    - Pts that meet requirements for diagnosis of TM, (diagnosed 5 or more years ago):
      - Gd-enhancing lesions of spinal cord
      - CSF findings (elevated protein and moderate pleocytosis, or elevated IgG index)
      - Acute or subacute motor, sensory and autonomic dysfunction
      - Defined sensory level

### Study Design and Methods

- Exclusion criteria by study group:
  - NMO:
    - Not meeting “revised diagnostic criteria for NMO”
    - Insufficient records to make the diagnosis of definite NMO

### Study Design and Methods

- Exclusion criteria by study group:
  - TM:
    - Attacks of optic neuritis or other neurological symptoms outside of spinal cord involvement
    - Myelopathy related to compression, trauma, malignancies, vascular causes
    - History of previous radiation

### Study Design and Methods

- Demographic and clinical predictor variables in NMO vs. TM study:
  - Age, sex, ethnicity, age of onset, time between events, asymmetric presentation, bladder/bowel dysfunction, autoimmune disease, family history
  - Severity of motor and sensory deficits on presentation

### Study Design and Methods

- Laboratory predictor variables in NMO vs. TM study:
  - Serum: ESR, CRP, ANA titer, RF, ANCA, NMO-IgG
  - CSF: cell count, protein, Ig-G Index, oligoclonal bands
- Imaging predictor variables in NMO vs. TM study:
  - Spinal cord MRI: length of lesion, level, contrast enhancement
  - Brain MRI: number of lesions

### Study Design and Methods

- Analysis:
  - Differences in predictors variables between the groups were evaluated using:
    - Chi square test for nominal data
    - Man-Whitney for ordinal data
    - T-test for interval data
  - Diagnostic value of the tests were expressed as sensitivity, specificity, positive predictive value and positive and negative likelihood ratio

### Results

Characteristic	NMO	TM	p – values
Patient #	17	12	
Females # (%)	12 (70.6%)	9 (75%)	.8
Male # (%)	5 (29.4%)	3(25%)	.8
Mean Age at Onset	34.29	40	.46
NMO IgG	7/12 (58% positive)	0/2 (0% positive)	
Bowel/Bladder Dysfunction	8/13 (61.5%)	7/10 (70%)	

### Results

Variable	Eligible n (%)	NMO	TM	False positive rate, % (95% CI)	Positive LR (95% CI)
Clinical presentation (asymmetric)	25/29 (86)	14/15 (93)	3/10 (30)	18 (0-88)	3.11 (1.2 - 8.1)
ANA Positive	17/29 (59)	5/10 (50)	1/7 (14)	17 (0-39)	3.5 (0.51 - 23.8)
CSF protein (high)	22/29 (75)	4/12 (33)	4/10 (40)	50 (9-91)	0.83 (0.28 - 2.51)
CSF IgG (high)	21/29 (72)	5/12 (42)	1/9 (11)	17 (0-39)	3.75 (0.53 - 26.77)
CSF IgG synthesis rate (high)	19/29 (66)	3/10 (30)	0/9 (0)	0	6.36 (0.37 - 108.57)
IgG Index (high)	19/29 (66)	2/10 (20)	2/9 (22)	50 (0-100)	0.9 (0.16 - 5.13)
Oligoclonal bands (positive)	20/29 (69)	2/12 (17)	1/8 (13)	50 (0-100)	1.33 (0.14 - 12.37)
Myelin basic protein (high)	18/29 (62)	4/9 (44)	4/9 (44)	50 (9-91)	1.0 (0.35 - 2.81)

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### Results

Variable	Eligible n (%)	NMO	TM	False positive rate, % (95% CI)	Positive LR (95% CI)	Negative LR (95% CI)
C-spine only	26/29 (90)	5/17 (29)	3/9 (33)	38 (0-79)	0.88 (0.27 - 2.87)	1.06 (0.61 - 1.84)
T-spine only	20/29 (69)	0/13 (0)	5/7 (71)	100	0.05 (0.003 - 0.82)	3.086 (1.1 - 8.67)
C + T-spine	19/29 (66)	12/13 (92)	4/6 (0.67)	25 (0-100)	1.39 (0.77 - 2.49)	0.23 (0.026 - 2.07)
≥ 3 segments cord lesion	27/29 (93)	14/16 (88)	9/11 (82)	39 (18-60)	1.07 (0.77 - 1.49)	0.69 (0.11 - 4.17)
Bilateral myelitis	26/29 (90)	10/14 (71)	9/12 (75)	47 (23-71)	0.95 (0.6-1.52)	1.14 (0.32 - 4.12)
≥ 2 cord lesions	29/29 (100)	9/17 (53)	0/12 (0)	0	13.72 (0.88 - 215.28)	0.49 (0.29 - 0.81)

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### Discussion

- Difficulties encountered during the study:
  - Small, unbalanced number of study subjects
  - No control over selection of subjects
  - Data and records not complete
  - Difficulty in generalizing the findings
  - Inconsistent availability of relevant tests

### Conclusion

Preliminary results of the study are encouraging. Some of the variables investigated showed positive predictive value for an earlier diagnosis of Devic's disease. These predictors might be used alone or in combination with each other. Continuation of this study would be needed to get firmer evidence that these predictors are in fact more statistically reliable. In addition, increasing the number of study subjects may reveal other predictors that have not yet manifested.

### Recommendations

- Prospective studies would be necessary, preferably involving large medical centers or multicenters, with a longer follow up of patients with optic neuritis and transverse myelitis
- National databases needed
- Standardized approach needed for the evaluation of patients with NMO, TM and ON

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