

Pure Autonomic Failure: Predictors of Conversion to Clinical CNS Involvement

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Background

Pure autonomic failure (PAF) is a synucleinopathy characterized by orthostatic hypotension, anhidrosis, erectile dysfunction, and bladder involvement. Most patients survive for decades without clinical central nervous system involvement. However, a subset of patients originally diagnosed as PAF ultimately develops extrapyramidal or cerebellar motor symptoms and evolves to multiple system atrophy (MSA), Parkinson's disease (PD) or diffuse Lewy body disease (LBD). The current literature provides little information on findings that may predict future conversion.

Objectives

To identify predictors of conversion of PAF to more sinister synucleinopathies with motor involvement.

Methods

We reviewed patients seen at Mayo Clinic by an autonomic specialist between 7/1/2000 and 7/1/2010, and underwent standardized autonomic reflex testing revealing orthostatic hypotension (OH). OH was defined as a drop in BP of ≥ 30 mmHg systolic or ≥ 15 mmHg diastolic.

1427 patients with 4736 unique visits were identified and each record was reviewed. Patients were included if during their initial evaluation they were diagnosed with neurogenic OH consistent with PAF (possible PAF). Patients with diagnoses of diabetes mellitus, amyloidosis, autoimmune ganglionopathies (positive for nicotinic ganglionic AChR antibodies), small fiber neuropathy, and neurogenic postural orthostatic tachycardia syndrome were excluded. 319 patients fulfilled these criteria.

In order to assess for the presence or absence of progression we identified patients with 3 years or more of in-person follow-up (stable PAF) and/or documented progression to another synucleinopathy (converters). To identify predictors of conversion we assessed relative risk and odds of conversion based on clinical, autonomic, and laboratory variables.

Predictors of Conversion, PAF to MSA	MSA Converters N=22 n (%)	Stable PAF N=41 n (%)	Odds Ratio
1 Vagal CASS score <2	15 (68)	13 (33)	4.3 (1.4-13.1)
2 Preganglionic pattern of sweat loss	14 (78)	15 (45)	4.2 (1.1-15.5)
3 Severe bladder dysfunction	11 (55)	3 (8)	14.7 (3.4-63.8)
4 Supine norepinephrine >100 pg/ml	16 (89)	7 (28)	20.6 (3.7-113.7)
5 Subtle motor signs at presentation	7 (32)	5 (12)	3.4 (0.9-12.3)

Table 1

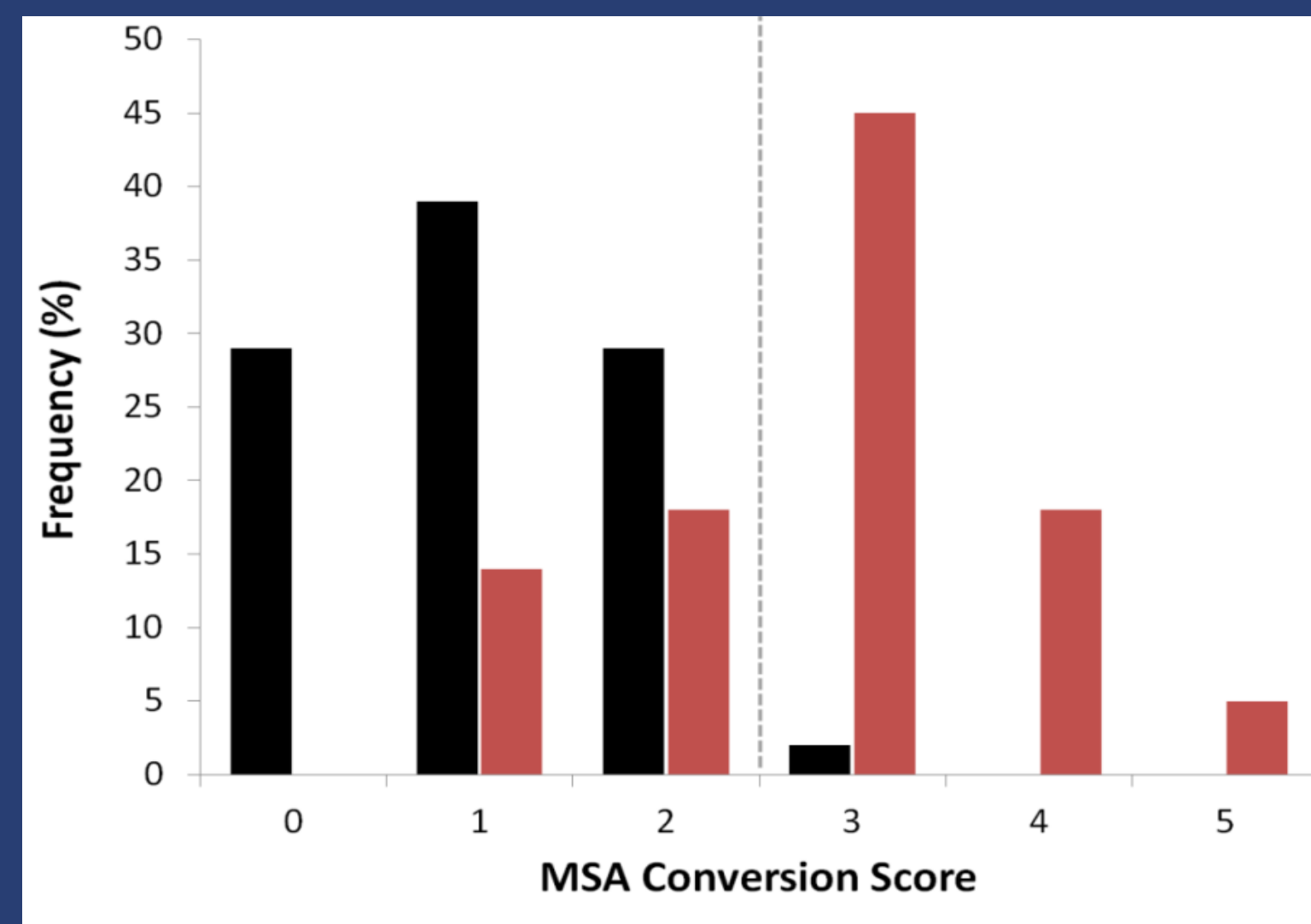


Figure 1: MSA conversion score (total number of predictors present) in stable PAF (black columns) versus MSA converters (red columns). A score >2 is highly predictive of conversion to MSA.

Results

Among 319 patients fulfilling criteria for possible PAF, we identified 41 patients with stable PAF and 38 (12%) converters. Of those who evolved, 22 developed MSA, 11 developed PD or LBD, and 5 remained indeterminate.

The median time to conversion to MSA was 2.4 years, with an intraquartile range of 1.9-3.3 years. This suggests that the majority of PAF to MSA conversion occurs during the first 3 to 4 years after the diagnosis of PAF.

Five variables were identified to be significant predictors of conversion to MSA (Table 1):

- 1) Vagal CASS <2
- 2) Preganglionic pattern of sweat loss
- 3) Severe bladder dysfunction (urinary retention, catheterization, incontinence)
- 4) Supine norepinephrine >100pg/ml
- 5) Subtle motor signs at first presentation

By adding one point for the presence of each of these five variables (Fig. 1), individual predictors were converted into a MSA conversion score, this allowed for prediction of conversion with high accuracy.

A score of 0 to 1 affirms a diagnosis of PAF and is associated with a low risk of conversion to MSA. A score of 2 is intermediate and associated with a moderately increased risk of conversion. A score greater than 2 strongly predicts conversion to MSA with a sensitivity of 68% and specificity of 98%, while a score greater than 3 shows 100% specificity for conversion.

Individuals who converted to LBD or PD had less severe sudomotor involvement than either the stable PAF or MSA conversion group. 10 (91%) PD/LBD converters had a sudomotor CASS ≤ 1 , compared to 16 (40%) of patients with stable PAF ($p=0.003$) and 9 (41%) of those evolving to MSA. Similarly, the fraction of patients with less than 25% sweat loss on thermoregulatory sweat testing was significantly higher in PD/LBD converters than in the other groups. This limited sudomotor involvement along with subtle motor signs at first presentation was predictive of conversion to PD/LBD.

Conclusions

- Over 10% of patients originally diagnosed as PAF eventually evolve to develop clinical CNS involvement, most commonly MSA.
- Utilizing clinical, autonomic, and laboratory data, we have identified 5 variables associated with an increased risk of conversion.
- In combination, these factors allow for prediction of conversion from PAF to MSA with high diagnostic accuracy.

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