Early Clinical Features Differentiate Cerebellar Variant MSA and Sporadic Ataxia

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Multiple system atrophy (MSA) is a neurodegenerative disorder that can be characterized by cerebellar dysfunction, autonomic dysfunction, pyramidal signs and parkinsonism[1]. Patients with MSA can be classified as having primarily parkinsonian features (MSA-P) or cerebellar features (MSA-C) according to the current MSA consensus criteria[2].

Early diagnosis of patients who will go on to develop MSA-C presents a challenge to clinicians. In MSA-C, symptom onset and progression are variable. Furthermore, it is difficult to differentiate MSA from Sporadic Ataxia (SA) since these two conditions share numerous symptoms but represent distinct clinical entities. A definite diagnosis of MSA can only be achieved by neuropathological examination at autopsy. Quick, accurate and early diagnosis of MSA-C is vital for informing patients and families regarding early treatment, care of patients, and prognosis.

The probability of developing MSA-C after initial clinical presentation of SA has been estimated to be approximately 25%-29% within five years of cerebellar symptoms[3]. In a previous study, using the 1999 consensus criteria, the two clinical features that were helpful in predicting the transition of SA to MSA-C were genitourinary dysfunction and a narrow-based, unsteady gait.[4]

The current study was performed to investigate whether there are clinical characteristics at initial clinical presentation that lead to early differentiation of MSA-C and SA using the 2008 consensus criteria. To address this question we performed a retrospective chart review and diagnosed patients as having MSA-C or Sporadic Ataxia. The clinical features at time of presentation were recorded and analyzed.

Methods

Patients

We retrospectively examined the medical records of 145 patients who presented with cerebellar symptoms to a Neurology Clinic at the University of British Columbia Hospital between 2000 and 2009. All patients were seen by the same Neurologist (SDS) specializing in cerebellar ataxia. Patients seen at the Neurology Clinic during this time were given annual follow-ups for regular clinical care and monitoring disease progression. Fifty-six consecutive patients with cerebellar symptoms fulfilled the following inclusion criteria: 1. Negative family history of a similar disorder or neurodegenerative disease 2. No dementia 3. No established symptomatic cause (no alcohol abuse, no chronic use of anticonvulsants, no gluten sensitivity, no infectious disease, no Multiple Sclerosis (MS), no paraneoplastic disease or neoplasm, no ischemia or hemorrhage, normal levels of Vitamin E/B12, normal thyroid function, Veneral Disease Research Laboratory Test (VDRL) negative) 4. Negative testing for Wilson's disease, SCA 1,2,3,6,7 and 8, Friedrich's ataxia, Ataxia Telangectasia, and Autosomal Recessive Ataxia with Oculomotor Apraxia type I and II.

Classification

Clinical charts were reviewed by SDS and ALS and patients were divided into the following categories: 1. Multiple System Atrophy of Cerebellar Type (MSA-C): Patients who fulfilled the criteria of the 2008 International Consensus Statement for possible or probable MSA-C and 2. Sporadic Ataxia (SA): Patients who had cerebellar ataxia but did not fulfill the criteria for MSA-C. The characteristics and clinical features of the patients' at time of presentation were recorded (Table).

Statistical Analysis

Controlling for age of onset and gender, a univariate logistic regression analysis was initially performed comparing each of the clinical variables at time of presentation in patients with MSA-C versus patients with SA.Variables significant at $P <= 0.2$ in the univariate regressions were then analyzed jointly in a step-wise forward and step-wise backward multiple logistic regression, and resulting significant variables at $P<0.05$ were retained. Using the logistic regression function an ROC curve was derived.

Results

Patient Characteristics

Twenty-five patients fulfilled the diagnostic criteria for MSA-C. Thirty-one patients had Sporadic Ataxia. The characteristics and clinical features are presented in the Table. The age at symptom onset was not significantly different between the two groups (mean age MSA-C=54 and SA=51, $p=0.075$). In addition, the age at clinical examination was not significantly different between MSA-C and SA patients (mean

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Table: Clinical characteristics of patients with Multiple System Atrophy cerebellar variant compared to Sporadic Ataxia (total n = 56)

	Patients with MSA-C n (%); n=25	Patients with SA n (%); n=31	*p*-value
Age at clinical examination, mean (range)	57 (46-78)	55 (33-83)	0.499
Age at onset, mean (range)	54 (35-72)	51 (13-71)	0.075
Disease duration at presentation, mean (range)	3 (0-11)	5 (0-34)	0.163
Cerebellar signs and symptoms			
Oculomotor abnormalities	18 (72)	18 (58)	0.394
Gaze-evoked horizontal nystagmus	9 (36)	14 (45)	0.420
Double vision	0 (0)	5 (16)	0.806
Dysphagia	6 (24)	9 (29)	0.721
Dysarthria	19 (76)	21 (68)	0.403
Saccade dysmetria	3 (12)	8 (26)	0.163
Dysmetria/intention tremor of upper limb	24 (96)	21 (68)	**0.034**
Asymmetric Onset	13 (52)	11 (35)	0.530
Abnormal heel-shin test	22 (88)	23 (74)	0.297
Asymmetric Onset	9 (36)	7 (23)	0.623
Ataxic gait	24 (96)	26 (84)	0.211
Impaired tandem walking	25 (100)	28 (90)	**0.001**
Pyramidal symptoms			
Brisk reflexes	11 (44)	12 (39)	0.505
Pyramidal weakness	2 (8)	1 (3)	0.959
Extensor plantar hyperreflexia	8 (32)	5 (16)	0.162
Extrapyramidal symptoms			
Rest tremor	1 (4)	1 (3)	0.804
Cog-wheel rigidity	2 (8)	2 (6)	0.996
Bradykinesia	2 (8)	3 (9)	0.736
Dystonia	0 (0)	0 (0)	0.860
Peripheral neuropathy			
Decreased or absent reflexes	4 (16)	7 (23)	0.334
Impaired sensory	8 (32)	8 (26)	0.932
Autonomic symptoms			
Urinary urgency	16 (64)	3 (9)	**0.002**
Urinary frequency	14 (56)	3 (9)	**0.003**
Incontinence	6 (29)	1 (3)	0.080
Erectile dysfunction	7 (19)	3 (23)	0.146
Postural drop	9 (36)	2 (6)	0.301

Note: MSA-C = Multiple System Atrophy Cerebellar Variant, SA = Sporadic Ataxia, SD = Standard Deviation

age MSA-C=57 and SA=55, p=0.499). The mean disease duration at time of evaluation was not significantly different (MSC-C=3 and SA=5 p=0.163). The mean annual follow up duration was not significantly different (MSA-C=5.6 years and SA=7.8 years, p=0.430)

Clinical Features

Controlling for age of onset and gender, a univariate logistic regression analysis was performed comparing each of the clinical variables at time of presentation in patients with MSA-C versus patients with SA. The four variables which were significant at P<=0.2 in the univariate analysis dysmetria/intention tremor of the upper limb (p=0.034), urinary urgency (p=0.002), urinary frequency (p=0.003), and tandem walking (p=0.001) - were analyzed jointly in a step-wise forward and step-wise backward multiple logistic regression. Dysmetria/intention tremor of the upper limb (p<0.015) and urinary urgency (p=0.001) were more common clinical findings at time of initial presentation in patients with a final diagnosis of MSA-C.

The logistic regression function derived was: logit P=log P/(1-P)=-7.47 + 0.038 (age of onset) + 0.73 (sex, female=1) + 4.19 (dysmetria/intention tremor) + 4.11 (urinary urgency).

Using this function, a receiver operating characteristic (ROC) curve was plotted (Figure 1). From the ROC curve a specificity of 80% could be achieved with a corresponding sensitivity of 80%. The area under the curve (AUC) was 0.894 with a 95% confidence interval of 0.815 to 0.974 (Figure).

Comment

The present study used the recently revised 2008 consensus criteria[2] to diagnose patients as having either MSA-C or SA. Our study has identified statistically significant differences in clinical features at presentation and supports the hypothesis that MSA-C and SA represent two distinct disorders. Our results are in accordance with previous research which used the 1999 consensus criteria[1] suggesting that MSA-C and SA have different clinical presentations. Using the 1999 consensus criteria Burk et al[5] found that bladder dysfunction was characteristic of patients with MSA-C (p=0.01). Although not significant, Burk et al[5] also found a trend towards MSA-C

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patients presenting more frequently with intention tremor (p=0.07). In support of this, another study by Litvan et al[6] used the 1999 consensus criteria and identified that the best predictors in MSA at the first clinical visit were early severe autonomic failure, early cerebellar symptoms, and gait problems. In a different study by Abele et al[3], dysphagia and bladder dysfunction and ataxia of the upper limb were significantly more frequent in patients with MSA as compared to unexplained ataxia using 1999 consensus criteria.

A study by Abele et al[7] recorded the clinical findings of 27 consecutive patients with Sporadic Ataxia. They reported that 93% of patients with Sporadic Ataxia presented with dysmetria and intention tremor of upper limbs. In addition, this study found that 33% of patients with SA complained of bladder urgency. Although this study suggested an overlap in the clinical features of sporadic ataxia patients and MSA patients, the diagnoses in their study were based on the 1999 MSA consensus criteria and it is possible that those patients who were diagnosed with sporadic ataxia who had bladder symptoms may now be diagnosed with possible MSA–C if the new criteria were applied. Furthermore this study did not have a longitudinal follow-up component to it and it is likely that a percentage of these patients would go on to develop MSA-C. In support of this hypothesis, Osaki et al[8] applied the 2008 MSA consensus criteria to 59 MSA patients who had previously been reported using the 1999 consensus data. The updated classification yielded higher sensitivity and positive predictive value (PPV) of possible MSA at first clinic visit when compared to the old consensus classification.

To our knowledge this is the first study to use the 2008 second consensus statement on the diagnosis of Multiple System Atrophy to look for predictive clinical features which distinguish MSA-C from SA. We have identified dysmetria/intention tremor of the upper limb (p=0.015) and urinary urgency (p=0.001) at initial clinical presentation as features which are significantly more common in patients who go on to develop MSA-C. With a combination of the four variables (older age of onset, female sex, dysmetria/intention tremor of the upper limb, and urinary urgency) the ROC curve demonstrated that a specificity of 80% with a sensitivity of 80% could be obtained in predicting the clinical diagnosis of MSA-C.

Although SA has a longer disease course than MSA-C, there was no significant difference in disease duration at the time of presentation (p=0.163) indicating that most patients will present early in the disease course regardless of the cause of their ataxia. Interestingly, unlike Parkinson Disease and Parkinsonism, in which asymmetric onset can be an early distinguishing feature, asymmetry of finger nose testing (p=0.530) and heel shin testing (p=0.623) did not differentiate MSA and SA.

There are three limitations to the present study that warrant acknowledgement. Firstly, this is a retrospective study based on patients' clinical findings at first time visit at a university neurology clinic. Future research following both subsets of patients longitudinally is required in order to shed light on the variable disease progression of both MSA-C and SA and the proportion of patients with SA that go on to develop MSA-C. A second limitation is the absence of autopsy results. Thus, a diagnosis of MSA-C was based on clinical symptoms only. A third limitation is that the sample size is small and the data was collected from a single clinical center. Consequently,

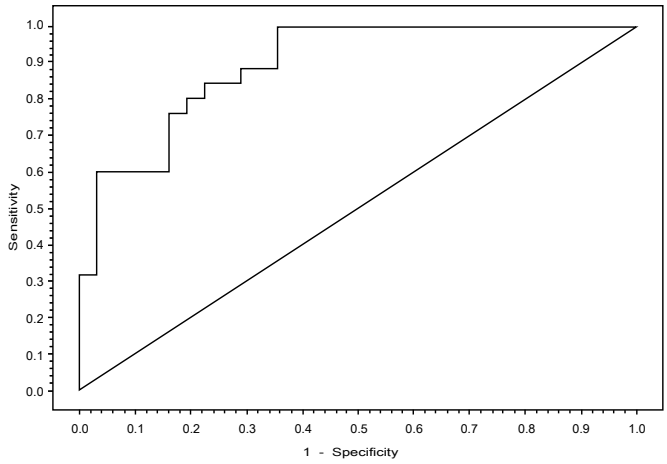

Figure: ROC curve of sensitivity plotted against 1-specificity to distinguish Multiple System Atrophy Cerebellar Variant from Sporadic Ataxia patients. *The ROC curve based on the logistic regression function. The combination of the variables (older age at onset, female sex, dysmetria/ intention tremor of the upper limbs and urinary urgency) achieved a specificity of 80%, with a sensitivity of 80%. The AUC was 0.894 with a 95% confidence interval of 0.815 to 0.974.*

applicability of the results must be made with caution. However, the University Outpatient Clinic includes the Ataxia Clinic and has a large catchment area as patients are referred from all over the province to this center. Although the sample size is small and may have limited some clinical symptoms from reaching statistical significance, MSA-C is a rare neurological condition and a sample of 25 is consistent with a clinic of our size.

These findings demonstrate there are clinical features which lead to early differentiation of MSA-C and SA and support the hypothesis that MSA-C and SA represent two distinct disorders. Future research involving close follow-up of these two subsets of patients is needed in order to elucidate the disease-specific progression of both MSA-C and SA.

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