Epidemiology of multiple system atrophy

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Abstract Multiple system atrophy (MSA) is a form of atypical parkinsonism with unknown etiology. The epidemiological studies conducted up to now on this disease are scarce. The incidence rate is about 0.6 cases per 100 000 persons per year. The prevalence rates show 4-5 cases per 100 000 persons. In Italy, about 4900 prevalent cases have been estimated. The mean onset age is about 54 years; the median survival is 7-9 years. Only one case-control study has been performed on this disease. This study showed an increased risk of MSA associated with occupational exposure to organic solvents, plastic monomers and additives, pesticides and metals. Smoking habits seem to be less frequent in MSA cases (as in Parkinson’s disease cases) than in healthy controls. Quinn’s clinical criteria and those of the Consensus Conference promoted by the American Academy of Neurology are in fair agreement. We have performed a case-control study on 73 MSA cases, 146 hospital controls and 73 population controls.

Introduction

Multiple system atrophy (MSA) includes striatonigral degeneration (SND), Shy-Drager syndrome (SDS), and sporadic olivopontocerebellar atrophy (OPCA). MSA is characterized clinically by signs of pyramidal, extrapyramidal, cerebellar and autonomic involvement in various combinations [1].

Pathologically, MSA is characterized by the presence of oligodendroglial cytoplasmic inclusion (GCIs) in the motor systems and supraspinal autonomic sections. GCIs are also abundant in the putamen, pallidum and lateral part of caudate nucleus. GCIs are considered to precede the neuronal alterations. The substantia nigra shows cellular de
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Descriptive epidemiology

The descriptive epidemiological studies on this disease are quite scarce, probably because of the recent nosological classification. The crude incidence rate is 0.6 cases per 100 000 persons per year. In the age group > 50 years, the estimate increases to 3 cases per 100 000 persons [3, 4].

The standardized prevalence rates indicate 4-5 cases per 100 000 persons. In the age group > 55 years, 17-29 cases per 100 000 persons have been observed [3, 4]. In Italy, 4900 prevalent cases have been estimated on the basis of Bower et al.’s study [3]: 81.5% of these are concentrated in the age band 60-79 years, while only 9.8% and 8.7% concern the age bands 50-59 years and >80 years, respectively. Epidemiological descriptive studies on MSA are based on some units of observed cases. For this reason, some factors such as clinical criteria adopted, recruitment methods of cases (e.g. door-to-door, practitioners, hospital records of cases), and time lag between symptomatology onset and diagnosis may influence remarkably the epidemiological estimates related to this disease. Therefore, it is necessary to carry out studies with strict epidemiologic methods and on wide populations.
This disease is more frequent in men (1.3:1), the mean onset age is about 54 years, and the median survival is about 7-9 years [2, 3].

Analytical epidemiology

Only one case-control study has been performed up to now on 60 MSA cases and 60 controls, enrolled in the period 1978-1988, before the introduction of the Quinn’s classification in 1989 and most used by the scientific community [5]. That study revealed a higher risk of disease onset associated with occupational exposure to organic solvents (OR=2.41; \(p<0.05\)), plastic monomers and additives (OR=5.25; \(p<0.05\)), pesticides (OR=5.8; \(p<0.05\)), or metals (OR=14.75; \(p<0.05\)). These hypothetical risk factors present wide confidence intervals and are based on data gathering defined by the same authors as limited [5].

Moreover, a higher frequency of symptoms and neurological diseases has been observed in first relatives of MSA cases compared with controls (23% in MSA cases vs. 10% in controls) [5]. This last information suggests the hypothesis of a genetic predisposition to neurological diseases but, in literature, no family has been reported with MSA cases.

As regards smoking habits, the only study carried out up to now reveals that MSA cases present the same pattern as Parkinson’s disease cases. In fact, an odds ratio inferior to 1 has been observed (OR=0.56; 95% CI, 0.29-1.06), with a dose-response trend in the categories moderate (OR=0.64; 95% CI, 0.31-1.32) and heavy smokers (OR=0.47; 95% CI, 0.21-1.05) [6]. Although it is necessary to conduct further case-control studies, only a perspective study (such as that carried out on Parkinson’s disease) will be able to determine whether smoking is a protective factor in MSA onset.

Some studies have shown no association between MSA and polymorphisms at the ApoE/CYPIID6 loci. One small study has reported an association between MSA and a mutant allele at CYPIID6 locus [7].

No epidemiological analytical study has been performed up to now to examine the relationship between genotype and environment. In particular, it is necessary to estimate for multifactorial pathologies (as parkinsonisms seem to be) the possible risk of disease onset associated with the interaction of genetic factors of individual susceptibility (cytochrome P450, N-acetyltransferase, ApoE) and the exposure to possible environmental neurotoxins (e.g. solvents, pesticides, metals).

Clinical epidemiology

The clinicopathologic study has revealed that the criteria for the diagnosis of MSA realized by Quinn and commonly used present good specificity (79% for possible MSA and 97% for probable MSA, at the first visit), but low sensitivity (53% for possible MSA and 44% for probable MSA, at the first visit), with a positive predictive value of 30% for possible MSA and 68% for probable MSA [8]. These values suggest that it is necessary to identify criteria for the clinical diagnosis of MSA in accordance with the pathological criteria. New clinical criteria have been proposed during a Consensus Conference promoted by the American Academy of Neurology [9]. In a subsequent study, the clinical concordance degree between Quinn’s criteria and those of the Consensus Conference has been evaluated, in a series of 45 patients with diagnosis of MSA according to Quinn’s criteria. In particular, the concordance was moderate (k=0.59) for possible MSA and substantial (k=0.64) for probable MSA [10]. Moreover, 4 MSA cases (9% of the whole case record) diagnosed according to Quinn’s criteria could not have been considered to be affected by MSA, if the criteria of the Consensus Conference had been applied. This type of study has to be promoted because it allows controlling the variability derived from the application of different clinical criteria, especially in the management of pharmacological trials.

An evaluation of the natural history of MSA shows that the SND form has a mean disease duration inferior to the OPCA form (4 vs. 9.1 years) and that autonomic disturbances precede motor deficit in 63% of patients. In the early phase of disease, the response to treatment with levodopa was moderate in 20%-30% of MSA cases.

No follow-up study has monitored onset and progression of symptomatology for the whole course of disease. In this way, it would be possible to identify subgroups of patients and to try specific pharmacological treatments on them.

ESGAP study

In this epidemiologic context, we have performed a case-control study. Seventy-three MSA cases (42 M, 31 F), 146 hospital controls (84 M, 72 F) and 73 population controls (42 M, 31 F) matched for sex, age (± 3 years) and province of residence were enrolled consecutively at seven neurologic clinics from 1 January 1994 to 31 July 1998. Quinn’s clinical criteria for the diagnosis of MSA were adopted.

Hospital and population controls were inpatients with neurological diseases, except neurodegenerative diseases, and healthy relatives of patients without neurological diseases, respectively.

MSA patients were examined by at least one neurologist and all diagnoses were confirmed independently by two neurologists from different centers, who reviewed the charts of the patients and analyzed videotapes.

Information on education, smoking, hobbies, family, history of neurological diseases and occupational history was collected by means of a face-to-face interview, using a structured questionnaire. Each occupational history of the subjects included in the study was classified according to standardized codes adopted in Italian occupational epidemiology.