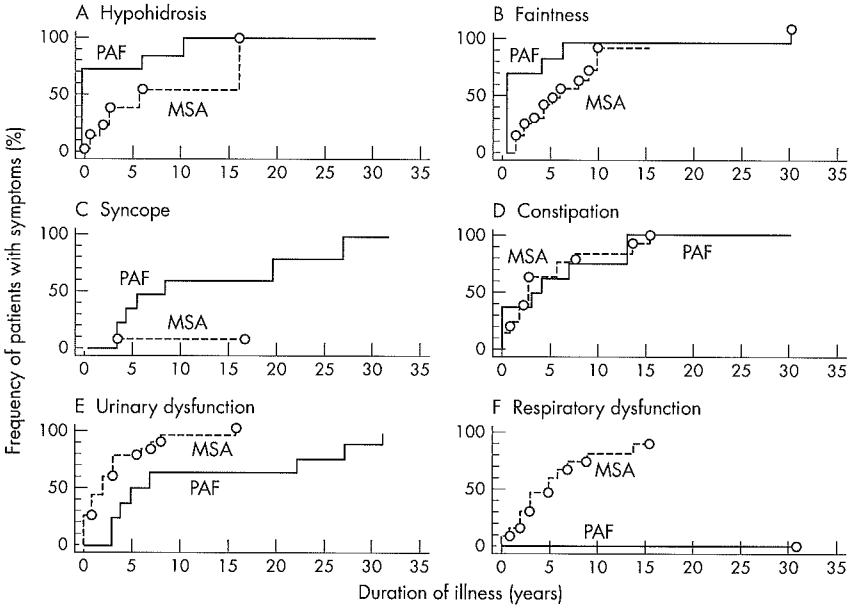

Figure 2 Progression of autonomic symptoms including hypohidrosis (A), faintness (B), syncope (C), constipation (D), urinary dysfunction (E), and respiratory disturbance (F) in patients with pure autonomic failure (PAF) and multiple system atrophy (MSA). Hypohidrosis was an earlier symptom in PAF than in MSA (panel A, $p=0.027$). Faintness and syncope were earlier symptoms in PAF than in MSA (panel B, $p=0.04$; panel C, $p=0.002$). Development of constipation was similar between the two diseases (panel D). Urinary dysfunction was a later symptom in PAF than in MSA (panel E, $p=0.004$). Respiratory disturbance did not occur in our PAF patients, but MSA patients had these problems at an early stage (panel F, $p=0.0004$).

six, 10, 13, and 17 years after the onset of PAF, respectively. Two of the five patients were essentially asymptomatic and had normal study results. Three patients were symptomatic, one of whom had an overactive bladder and the other an underactive bladder; the third had normal results. In our series, all eight patients had urinary dysfunction by 30 years after onset. Thus urinary dysfunction typically emerged in late stage PAF. In contrast, MSA patients developed urinary dysfunction at a very early stage of their disease ($p=0.004$), often as an initial autonomic symptom in about a quarter of the patients. Within five years, more than 75% of MSA patients had urinary dysfunction, especially difficulty in urination. Thus urinary symptoms occurred early and were particularly prominent in MSA.

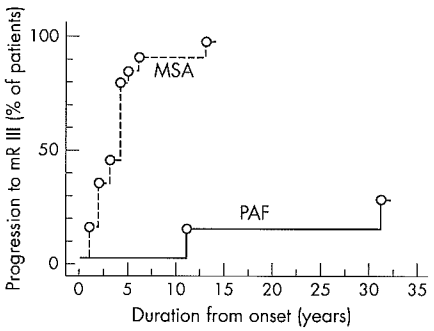

Figure 3 Differences in time remaining independent in activities of daily living (ADL) assessed by the modified Rankin scale between patients with pure autonomic failure (PAF) and multiple system atrophy (MSA). Round symbols represent censored data. Significant differences were seen between PAF and MSA for three ADL milestones and for survival, by Kaplan–Meier analysis and log-rank tests. mR III, modified Rankin scale, grade III (moderate impairment requiring minimal support such as a cane, stair rails, and so on): difference between PAF and MSA significant at $p<0.0001$.

Respiratory disturbances

Respiratory disturbances such as sleep apnoea were uncommon in patients with PAF. Indeed, in our series, no patient had respiratory difficulties in 30 years of follow up. In contrast, respiratory disturbance was one of the most important features in patients with MSA ($p=0.0004$). About half the MSA patients had this complaint within five years, and subsequently the prevalence of respiratory disturbances increased. More than 80% of the MSA patients had respiratory disturbances by 10 years.

Progression of orthostatic hypotension and noradrenaline supersensitivity

Orthostatic hypotension

Orthostatic hypotension (fig 1A) was a major clinical feature in PAF, being marked even in the early stages of the disease. Blood pressure fall varied from 34 to 108 mm Hg at presentation to our hospital, and the extent of orthostatic hypotension progressed markedly in most patients over the next two to 11 years. In seven patients blood pressure fell by more than 50 mm Hg, and most patients experienced syncope.

Noradrenaline supersensitivity

The noradrenaline infusion test estimates denervation supersensitivity at peripheral noradrenaline receptors, suggesting disease involvement of the peripheral sympathetic nervous system. At an early stage, PAF patients all showed excessive rises in blood pressure of 30 mm Hg or more with infusion of a low concentration of noradrenaline (3 or 0.3 μg/min), indicating the presence of denervation supersensitivity (fig 1E). After two to 11 years, however, the extent of blood pressure rise in response to noradrenaline infusion was smaller than at an early stage, suggesting emergence of some compensatory mechanism or secondarily induced insensitivity of noradrenaline receptors.

Activities of daily living and prognosis

PAF patients did not show diminishing capacity for activities of daily living (ADL) up to a late stage (fig 3). In our series three patients died, but they maintained nearly normal ADL throughout their lives. One patient who died at 90 years, 12 years after disease onset, could walk alone without assistive devices until he was 89 years old (modified Rankin scale, 0 to1); rapid deterioration in the last year of life resulted from a subdural haematoma. Another patient who died at 82 years, 32 years after onset, could perform all his daily activities unassisted until he was 81. He was essentially bedridden for the last year of life because of myelodysplastic syndrome. The third patient, who died aged 84 years 12 years after disease onset, remaining healthy and active (modified Rankin scale 0 to 1) until he died suddenly of a severe stroke.

Although both MSA patients and PAF patients have severe autonomic disturbances, functional and survival prognoses[16] were significantly worse in MSA than in PAF. In our series, median time from onset to modified Rankin scale grade III in MSA was four years ($p<0.0001$ *v* PAF); grade IV, seven years ($p = 0.0009$); grade V, nine years ($p<0.0001$); and death, 11 years ($p = 0.003$). In contrast to MSA, PAF carried a relatively good prognosis for function and survival.

DISCUSSION

PAF is a chronic progressive neurodegenerative disease characterised by severe autonomic failure without other neurological deficits. Uniquely, PAF patients can maintain a long healthy life, in contrast to patients with other types of primary autonomic failure. Pathological reports of PAF have described Lewy bodies in the intermediolateral grey columns of the thoracolumbar spinal cord, suggesting that PAF is a form of Lewy body disease.[23–30]

Our study is the first assessment of long term progression of autonomic symptoms and ADL status in PAF, particularly in comparison with MSA. Although a consensus has been reached over the diagnostic criteria for PAF,[8] long term follow up observation of the clinical features is important to identify the differences between PAF and autonomic failure in other neurodegenerative diseases, particularly MSA and Parkinson's disease with autonomic failure.[7 8 12] We investigated clinical features of eight patients with PAF over follow up periods ranging from seven to 32 years.

It is generally accepted that patients with PAF have autonomic failure resulting in peripheral but not central involvement. The results of supine noradrenaline levels, ΔAVP, ^{123}I-MIBG, and the noradrenaline infusion test clearly confirm this. In contrast, patients with MSA have patterns suggesting a predominantly central involvement, although some patients with probable MSA also have low noradrenaline concentrations, increased ΔAVP, a reduced H/M ratio, and raised blood pressure during the noradrenaline infusion test. These neuropharmacological tests would be useful for differentiating PAF from MSA early in the course of the illness. Further studies are needed to clarify their sensitivity, specificity, and positive predictive value.

In our study, orthostatic hypotension and related faintness and syncope were the most important clinical features of PAF, and developed at a very early stage. Furthermore, orthostatic hypotension worsened gradually as the disease progressed in spite of medical treatment for hypotension. In contrast, MSA patients were less likely to have syncope than PAF patients. Progression of MSA is relatively rapid,[16] so MSA patients are often wheelchair bound or nearly bedridden before showing severe hypotension with syncope.[16] About half the patients with MSA noted faintness by four years after onset, at a time when most of them were wheelchair bound and spent a considerable amount of their waking time lying down. This may limit the exposure of MSA patients to syncope.

Another important autonomic abnormality observed in PAF was sudomotor impairment. Hypohidrosis or anhidrosis was a major complaint in patients with PAF. Emergence of orthostatic hypotension, sometimes with loss of consciousness, and sudomotor dysfunction at a very early stage were striking characteristic features in PAF, in contrast to MSA where these symptoms were absent in the early phase of the disease.

A striking clinical characteristic of PAF was the absence of respiratory dysfunction such as sleep apnoea until a very late phase of disease. This feature again contrasted with MSA, where respiratory dysfunction was a major problem, threatening life in the later phase of disease.

Constipation and urinary dysfunction are among the characteristic symptoms of primary autonomic failure syndrome including PAF, MSA, and Parkinson's disease with autonomic failure.[30 31] Urinary problems have been documented in the past to some extent,[9 11 12] representing a characteristic feature of PAF, especially in the late phase. Sakakibara *et al*[32] reported that all six of their patients with PAF who complained of urinary disturbances showed abnormalities on urodynamic studies. In our series, five of eight patients underwent urodynamic evaluation, and two with urinary symptoms showed a hyperactive or underactive bladder. However, the severity of the urodynamic abnormalities and associated symptoms was mild, in agreement with the previous report.[32] In contrast, patients with MSA have severe urinary dysfunction, especially difficulty in urination[33] and nocturnal urinary frequency, with residual urine, detrusor hyperreflexia, low compliance, and detrusor sphincter dyssynergy on urodynamic studies. Intermittent self catheterisation is often required even early in the course of the illness.

On the basis of these observations, we can assume that orthostatic hypotension and sudomotor dysfunction precede urinary dysfunction and particularly respiratory dysfunction in the development of autonomic disturbances in PAF, while in MSA urinary dysfunction precedes orthostatic hypotension and sudomotor dysfunction, and respiratory dysfunction is a serious problem even at an early stage. Modes of progression of autonomic symptoms seem to be an important way of distinguishing between PAF and MSA.

The evolution of the change in blood pressure during the noradrenaline infusion test in PAF is difficult to explain. While the clinical features became worse over the course of several years in PAF patients, in contrast the degree of blood pressure elevation during the test became smaller with time. The same method was used for the test on each occasion, and no previous reports provide an explanation for this phenomenon. Age related changes such as atherosclerosis or changes in drug treatment might have contributed, but further study is necessary.

Patients with PAF had a better prognosis than those with MSA. Even the three patients with PAF who died during follow up lived independently until one or two years before they died all died of concurrent diseases. Various factors contributed to this advantage in ADL and long term prognosis. First, patients with PAF did not have severe urinary disturbances, which would lessen the risk of recurrent urinary infections, and they also did not have life threatening respiratory failure. Second, while management of orthostatic hypotension remains challenging late in the course of illness, administration of plasma volume expansion fluids, fludrocortisone, and sympathomimetic agents can be effective in ameliorating symptoms and preventing faintness and syncope with resulting head injuries or bone fractures which could compromise ADL and survival. Third, patients

with PAF in this study showed no motor or cognitive impairment. No parkinsonism or dementia, which would have affected daily activities or required additional treatment, was evident during the course of their illness. Further studies are needed to evaluate the significance of the pathological background for temporal features of autonomic, motor, and cognitive involvements.

The precise epidemiology of PAF has not been assessed, either in Japan or in Western countries. To our knowledge, relatively few cases of PAF have been studied or described, and necropsy reports are far less common than for MSA. In our Japanese series, more than 200 patients with MSA were referred to hospital during the course of the study, but only eight patients with PAF were diagnosed during the same period. Although physician referral patterns may have on influence, PAF appears to be uncommon in Japan compared with MSA. Further studies should be undertaken to clarify the incidence and prevalence of PAF worldwide.

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