SHORT REPORT

Phenotypic differences between African and white patients with motor neuron disease: a case-control study

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Abstract

There is increasing evidence that race may affect the phenotype in some neurodegenerative diseases. To investigate this in motor neuron disease a retrospective case-control study has been carried out on 15 negroid African and 45 white patients with the disease seen over 8 years. Each African was compared with three age and sex matched white patients with motor neuron disease. There were no statistically significant differences in age of onset or the mean duration of disease in the two groups. The chance of presenting with the "flail arm" variant of motor neuron disease was four times as high in the African group than the white group (odds ratio 4.33, $p=0.05$, 95% confidence interval 0.99-18.92). Although no overall differences in survival were seen between the two groups, in those with the flail arm variant, four out of the six African patients had died whereas all six white arm patients were alive at the censoring date of 1 January 1999 (median follow up 38.5 months). It is concluded that race may influence the phenotype and progression of motor neuron disease.

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Keywords: motor neuron disease; race; phenotype; flail arm variant

There is an increasing body of evidence suggesting that race can affect the clinical phenotype and progression of certain neurodegenerative diseases, including Parkinson's disease and motor neuron disease.¹⁻⁴

In evaluating patients with motor neuron disease in the King's Motor Neuron Disease Care and Research Centre, we had the impression that a syndrome of predominant arm weakness, which we have termed the "flail arm" syndrome⁵ (also known as Vulpian-Bernhardt variant^{6 7}) was more common in people of African descent. To test this hypothesis, we carried out a case-control study on the phenotype of motor neuron disease in patients of African and white origin.

Methods

We performed a retrospective case control study on patients seen at the King's Motor Neuron Disease Care and Research Centre. Patients referred to the specialist clinic between 1 January 1990 and 1 June 1999 (currently 692 patients) were included. We identified 15 African patients originating from West Africa or the Caribbean, and matched each patient with three white motor neuron disease controls. These were consecutive white patients with the disease entered into the database who were matched for age (± 3 years) and sex to the African patients. All participants were classified according to the El Escorial World Federation of Neurology Criteria for motor neuron disease.⁸ The notes of the participants were reviewed and information was entered into a detailed database incorporating key characteristics of the disease. The "flail arm" variant was defined as a predominantly lower motor neuron disorder of the upper limbs, without significant functional involvement of other regions at clinical presentation. Specifically, the wasting and weakness of the arms had to be profound, symmetric, and involve proximal muscle groups ($MRC < 3$).⁵ Follow up for survival data were complete.

STATISTICAL ANALYSES

Logistic regression was used to test whether the probability of having the flail arm variant differed between the ethnic groups. Cox regression was used to compare survival between the groups. Survival was estimated using the Kaplan-Meier curves and expressed as a median survival in months, with 95% confidence intervals (95% CIs) for survival also given in months. The censoring date for survival analysis was 1 January 1999. Other variables tested between the groups included age of onset of disease, disease duration, mode of onset (arm, leg, or bulbar onset) and disease classification defined by El Escorial criteria.⁸ In both the logistic and Cox regression models, robust standard errors were used that took account of the matched groups. The differences between continuous variables were obtained using random effects models with matched groups representing the random

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Table 1 Clinical features of each ethnic motor neuron disease group

	African patients (n=15)	White patients (n=45)
Mean age of onset (SD)	49.9 (13.1) y	50.5 (10.7) y
Mode of onset (n (%))	Upper limb 8 (53) Bulbar 5 (33) Lower limb 2 (13)	Upper limb 22 (49) Bulbar 6 (13) Lower limb 17 (38)
El Escorial criteria (n (%))	Definite 3 (20) Probable 5 (33) Possible 1 (7) Suspected 6 (40)	Definite 11 (24) Probable 17 (38) Possible 10 (22) Suspected 7 (16)
Mean disease duration (SD)	51.4 (53.5) months	42.8 (25.1) months

Table 2 Details of patients with the "flail arm" variant of motor neuron disease

	African group n=6	White group N=6
Male:female	5:1	5:1
Mean age of onset (SD)	50.5 (10.3) y	51.6 (9.4) y
El Escorial criteria (n)	Probable 2 Possible 1 Suspected 3	Probable 1 possible 2 suspected 3

factor. These analyses were carried out using Stata. Means, SD, and proportions were computed using SPSS (release 8). Results are expressed as the mean (SD) and significance was set at the 5% level. Because of the sample sizes, possible confounding factors were not taken into account.

Results

Ten male and five female African patients were identified. The mean age of onset and duration of disease did not differ from the white controls ($p > 0.56$, table 1). No family history of motor neuron disease was identified in the African group. Four patients in the white group gave a positive family history, which is in keeping with the expected frequency of familial motor neuron disease.⁵⁻⁹ One African patient described sensory disturbance in the absence of sensory signs.

Six African patients (40%) and six white patients (13%) presented with the "flail arm" variant of motor neuron disease. The chance of presenting with this variant was four times as high in the African group than the white group (odds ratio 4.33, $p = 0.05$, 95% CI 0.99–18.92). Details of these patients are given in table 2.

During the follow up period of median 38.5 months (range 10–218 months), for the two groups, seven African patients and 15 white patients died. Using Kaplan-Meier analysis, the median survival for the African group was 34 months (95% CI 18.8–49.2), compared with 38 months for the white group (95% CI 32.1–43.8). These were not significantly different in the Cox regression ($p = 0.89$). However, reviewing only the patients with the flail arm variant showed that four out of six African patients had died during follow up compared with none of the six white patients ($p = 0.01$).

Discussion

This study, which must be regarded as preliminary in view of the few African subjects available, is to our knowledge the first to

systematically compare the motor neuron disease phenotype in different ethnic groups. The main findings were that significantly more African patients had upper limb onset with "flail arm" phenotype than white patients. There were no statistically significant differences in age of onset, mean duration of the disease, or survival in the groups as a whole. However, in patients with the "flail arm" variant, four out of six African patients had died during the follow up period whereas all six white patients were alive.

Although the white control group included four patients with a family history of amyotrophic lateral sclerosis, whereas there were no patients in the African group with known familial disease, we think that this is unlikely to influence our results as the clinical course of familial patients is indistinguishable from that of sporadic patients.

Several studies on motor neuron disease have been reported in Africa.^{4, 10-12}

The first case report was from Nairobi in 1955 by Harries, who described two men aged 26 and 30 years, with features of progressive bulbar palsy, progressive muscular atrophy, and amyotrophic lateral sclerosis.¹⁰ A study of 13 Rhodesian African patients with motor neuron disease seen between 1967 and 1971 disclosed a similar clinical picture to white patients with typical amyotrophic lateral sclerosis predominating.¹¹ A larger prospective study of 92 Nigerian patients with motor neuron disease described simultaneous initial involvement of both right and left arms as the most common presentation, but the weakness was predominantly distal in this cohort.¹²

The age of onset of motor neuron disease in Rhodesian Africans was younger (mean 36 years, range 24–55) than the age of onset described in Europe and the United States, and there was a greater male preponderance (10 men, three women).¹¹ Osuntokun *et al* also showed a male:female ratio of 3:1 with an age of onset of 37.6 years.¹² Although the male:female ratio of Africans in our study (2:1) exceeded the generally quoted white ratio of 1.5:1,⁵⁻⁹ only a few patients were involved. However, the age of onset of disease in the African population in our study was older than in these previous studies,^{11, 12} and did not differ from the white controls. This difference may be influenced in part by the lower mean age of the population and lower life expectancy in African countries, and on selection bias. No information is available from the previous studies on the demographics of the patient populations, and it is possible that older patients in Africa at that time were less likely to be referred to specialist centres. However, the influence of genetic and environmental factors on these differences is unknown.

We found no difference in survival between the total African and white groups. In the study of Nigerian Africans, although 73/92 patients had the amyotrophic lateral sclerosis variant, the duration of disease exceeded 6 years in 54%, 10 years in 29%, and 15 years in 8%.¹² Patients with a younger onset of disease tend to have a longer survival, and this may account in

part for the prolonged survival in their study. There may also be a lack of specificity in the diagnosis in the Nigerian study, as investigations were limited. Mortality from motor neuron disease among the white population of South Africa was found to be half that in England and Wales.¹³ These findings suggest that there may be an environmental influence on the development and course of the disease.

The “flail arm” syndrome is characterised by a relatively symmetric and proximal involvement of both arms progressing to severe wasting and functional disability, with little or no weakness of the leg or bulbar muscles at presentation.⁵ We were able to support our hypothesis that the “flail arm” variant was more common in the African group. A similar clinical pattern in Sudanese patients with motor neuron disease has been noted by Abdulla *et al*, who found that simultaneous involvement of both arms was the commonest presentation in 28 patients with amyotrophic lateral sclerosis seen between 1993 and 1995.⁴ We described the “flail arm” syndrome in 39 out of 395 (10%) patients with amyotrophic lateral sclerosis seen at the King’s Motor Neuron Disease Care and Research Centre over an 8 year period.⁵ The male to female ratio was 9:1 in the “flail arm” group and in keeping with this it was 5:1 in our African patients with “flail arm”. The median survival in the total flail arm group, which included some of the African patients, was 57 months (95% CI 45–69). Katz *et al* also described a similar syndrome, which they termed amyotrophic brachial diplegia, with isolated atrophy and weakness of cervical innervated muscles and rapid early progression but limited progression thereafter, and a more favourable prognosis.¹⁴ In our present study, the median survival for the African group was 34 months (95% CI 18.8–49.2). Four out of six (67%) AfroCaribbean patients with “flail arm” died by the censoring date, whereas none of the six white patients with “flail arm” variant had died. This difference was significant ($p=0.01$) and suggests that the “flail arm” variant is not

a benign syndrome in African patients, whereas in white patients it may have a slightly better prognosis.^{5, 14}

This pilot study suggests that there are differences between African and white patients with motor neuron disease in the phenotype and progression of the disease. The influence of genetic and environmental factors on these differences remains unclear.

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