

The present results do not support the theory of increased synthesis of renal venopressor PGF_{2α} in black hypertensive patients.

Further studies are necessary to confirm the possibility of ethnic pattern in renal PG synthesis.

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Duchenne and Becker muscular dystrophy prevalence in South Africa and molecular findings in 128 persons affected

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A genetic service for Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) was initiated in Cape Town in 1987. Of the 143 DMD patients diagnosed during the period 1987-1992, 66 had a familial pattern of inheritance and 77 were apparently sporadic. Twenty BMD patients were identified, of whom 12 had other affected relatives and 8 were sporadic. Overall minimum prevalence rates of 1/100 000 for DMD and 1/755 000 for BMD were calculated. A markedly low DMD prevalence in the indigenous black population (1/250 000) contributed to the overall low DMD prevalence in South Africa when compared with that in the UK (1/40 000).

By means of molecular methods, the diagnosis in 42% of the affected DMD males was confirmed by detection of deletions in the dystrophin gene. Deletions were identified in 50% of Indian, white and mixed ancestry patients. In contrast, only 22% of blacks had identifiable deletions.

DMD appears to be underrepresented in the black population; the low deletion frequency in this group suggests that unique mutations not detectable by methods used in this study may be more frequent in these patients than in the other populations. The increased DMD frequency in Indians corroborates findings reported from the UK.

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Duchenne muscular dystrophy (DMD) is the most common heritable muscle disorder¹ and is transmitted as an X-linked recessive trait. Affected boys characteristically exhibit progressive muscle weakness and pseudohypertrophy of the calf muscles.² The disorder has an inexorable progressive clinical course culminating in death in the teenage years. A similar but milder condition, Becker muscular dystrophy (BMD), occurs less commonly. Those with this disorder are less severely affected and are usually able to procreate.³

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The diagnosis of DMD or BMD is suggested by their typical clinical presentation in males and can be confirmed by demonstration of raised muscle serum enzyme levels together with histological findings in muscle biopsy specimens. In addition, molecular techniques now allow exact identification of mutations in the gene which is located on the short arm of the X-chromosome (Xp21).⁴

A previous article provided details of a national molecular genetics service for the diagnosis of DMD/ BMD based at the Department of Human Genetics molecular laboratory in Cape Town.⁵ The relative prevalences of DMD are remarkably dissimilar in different ethnic groups in South Africa, as are the intragenic molecular defects.

The implications of these findings for health care planning and community-orientated genetics services form the basis of this article.

Patients and methods

A national diagnostic service for DMD and BMD was initiated in South Africa in 1987. Efforts were made to identify affected boys by means of a letter circulated to paediatricians, general practitioners, genetics nurses of the Department of National Health and Population Development, and physicians in charge of muscle/neurology clinics at medical centres in all four provinces. Further information was disseminated by medical articles in local journals and through lectures, seminars and the presentation of papers at medical congresses. In addition, rural populations were screened at routine genetics clinics held in peripheral centres throughout South Africa.

DMD and BMD were differentiated on the basis of age of onset and wheelchair confinement, as described by Emery.² In all instances the clinical diagnosis was established by a paediatrician or physician and confirmed by appropriate ancillary investigations, including the findings of elevated

serum creatine kinase levels. In some instances, the diagnosis was established through histological studies assisted by electromyography. Minimum prevalences for the condition were calculated for the four major ethnic groups found in South Africa on the basis of the number of living affected males identified during the period 1987-1992 (Table I).

Blood specimens were collected from each patient, and the DNA isolated for molecular analysis, as described previously.⁵ The DNA was screened for intragenic deletions with probes from hotspot areas in the 5' and 3' region of the dystrophin gene.^{6,7} These investigations were supplemented by DNA amplification technology such as oligonucleotide primers which were specific for exons in the deletion-prone regions. The frequencies of deletions identified in the various ethnic groups are summarised in Table II.

Results

A total of 143 DMD and 20 BMD patients were investigated during 1987-1992. All the boys of Indian origin were referred from Natal, whereas the majority of patients of mixed ancestry (97%) were investigated in the Cape. About 40% of the black patients were examined in Cape Town; the remaining 60% were referred by clinicians from the other provinces. The white referrals came from all parts of the country. Of the 143 males with DMD, 66 had at least one affected relative while 77 were sporadic. Twelve of the 20 patients with BMD had affected kin and 8 cases had occurred sporadically.

Observed minimum prevalence for DMD varied for each ethnic group, the highest prevalence occurring among the Indian population and the lowest among the black. Only 2 BMD patients were seen in each of the black, Indian and mixed ancestry groups, whereas 14 affected white males were studied.

Table I. Minimum prevalences calculated for DMD in South Africans of different ethnic origins

Ethnic group	Male population x 10 ³	Affected DMD	Minimum prevalence of DMD x 10 ⁻³	Affected BMD	Minimum prevalence of BMD x 10 ⁻³
Black	CP	965	18		
	TVL	3 218	12		
	N	5 571	9		
	OFS	951	4		
		10 700	43	1:250	2
Indian	CP	1 332	0		
	TVL	72	0		
	N	373	33		
	OFS	0	0		
		465	33	1:14	2
Mixed ancestry	CP	1 332	32		
	TVL	150	0		
	N	53	3		
	OFS	35	1		
		1 570	13	1:45	2
White	CP	692	8		
	TVL	1 408	13		
	N	320	6		
	OFS	190	5		
		2 610	32	1:82	14
Total	15 092	143	1:100	20	1:755

Table II. The frequency and distribution of deletions in the dystrophin gene of South African DMD and BMD patients

Ethnic group	No. of unrelated patients	Deletions		5'		3'		5' - 3'	
		No.	%	No.	%	No.	%	No.	%
Black									
DMD	39	10	26	3	30	5	50	2	20
BMD	2	0	-	-	-	-	-	-	-
White									
DMD	23	13	57	4	31	9	68	0	-
BMD	9	3	44	2	-	1	-	-	-
Indian									
DMD	21	10	45	2	20	8	80	0	0
BMD	3	2	67	1	-	-	-	-	-
Mixed ancestry									
DMD	27	13	48	4	31	8	61	1	8
BMD	4	1	25	-	-	1	-	-	-
Total									
DMD	110	46	42	28	-	65	-	7	-
BMD	18	6	33	50	-	25	-	25	-

5' = 5' hotspot of DMD gene
3' = 3' hotspot of BMD gene

Deletion detection

Molecular investigations were undertaken in 110 males with DMD and 18 with BMD. Deletions were detected in 46 (42%) of the DMD patients and 6 (33%) of the BMD patients. More than 60% of the DMD deletions occurred in the 3' region of the dystrophin gene while the BMD deletions occurred predominantly in the 5' region of the gene. Forty-five percent to 60% of DMD patients from the white, Indian and mixed ancestry groups had detectable deletions. Only 10 (26%) of the black patients had detectable deletions.

Discussion

Minimum prevalence

The determination of DMD and BMD prevalences in South Africa is necessarily incomplete for several reasons. Firstly, because a significant proportion of the South African population resides in rural areas, it is unlikely for logistic reasons, that all those affected have been identified. Estimates of population size based on census figures are also probably an underrepresentation of the true situation in South Africa. Also, some individuals had no knowledge of their family history. It is also possible that some sporadic DMD patients may be misdiagnosed instances of the rare but phenotypically similar autosomal recessive form of muscular dystrophy.^{8,9}

Minimum prevalence of DMD

Minimum prevalence estimates in the South African population reveal a higher DMD frequency in Indians (1/14 000) compared with other ethnic populations (1/45 000 - 1/250 000). A possible explanation might be an increased occurrence of the AR form of DMD in Indians. If this were so, however, one would expect also to encounter a significant proportion of affected females, which is not the case. Interestingly, a high frequency of DMD in the Indian population of the West Midlands region of the UK was recently reported.¹⁰ It is therefore possible that there is a genuine increased frequency of classic X-linked DMD in this

group. The frequency of DMD among patients of mixed ancestry is less than that among Indians, but greater than that of whites. The latter phenomenon possibly reflects genetic admixture.

Since the black male population of South Africa is much larger than that of any of the other ethnic groups (10,7 million v. 4,65 million for all others combined), the observed number of black males affected was unexpectedly low. Indeed, despite the urbanised black group served by good hospital facilities (e.g. Red Cross Children's Hospital in Cape Town, King Edward VIII Hospital in Durban and Medunsa in Pretoria), DMD patient numbers remained low. In this context, it is noteworthy that adverse socio-economic circumstances have not prevented black mothers from having their children investigated for other muscular disorders, e.g. spinal muscular atrophy is 15 times more prevalent than DMD in the South African black population (A. Moosa — personal communication). The latter evidence suggests that a black mother usually seeks professional help for any child with a progressive physical handicap such as DMD. The observed decreased frequency of DMD may therefore reflect a true underrepresentation of the disorder in the indigenous black population of South Africa.

Minimum prevalence of BMD

The overall BMD prevalence observed in this study (and in other parts of the world) is much lower (1/755 000) compared with recently published figures from the UK.¹¹ This apparent underrepresentation of BMD is probably caused by incomplete ascertainment as a result of lack of recognition of the milder disorders. In this regard, analysis of the protein product, dystrophin, allows BMD to be accurately distinguished from clinically similar muscle disorders such as spinal muscular atrophy and limb girdle dystrophy.

Interestingly, the range of clinical manifestations observed in patients with BMD is now extensive, e.g. a condition known as 'myalgia with cramps' has been identified by means of molecular studies as a mild form of BMD.¹¹ Accurate BMD prevalence estimations therefore require dystrophin analysis in all patients with suggestive clinical signs.

Molecular findings

A total of 46 (42%) deletions were identified in 110 unrelated South African DMD patients. This deletion frequency is consistent with published values of 40 - 60% in other populations, where a similar methodology was used.¹²⁻¹⁵ Of the 46 deletions detected in the present study, 65% had a breakpoint in the 3' mutation 'hotspot' whereas only 28% were detected in the 5' 'hotspot'. This distribution corroborates previous reports.^{16,17} However, although the deletion frequency and distribution in South African patients are similar to those in patients reported elsewhere, considerable inter-ethnic variation is apparent. The low rate of deletions in black patients (less than 30%) might be due to other intragenic mutations lying outside the known deletion hotspots. The phenotype in those black patients in whom deletions were not detected is identical to that in other groups and non-allelic heterogeneity seems unlikely. It would therefore appear that intragenic deletions for DMD/BMD among blacks occur less frequently and may differ from those previously described in whites.

The low prevalence of DMD and BMD observed in black South Africans remains an enigma but is in keeping with findings elsewhere. It is probable, given the wide but mild spectrum of clinical manifestations of BMD, that many patients do not seek medical appraisal. Previously underscribed point mutations and deletions are likely to be discovered in some affected black patients. Studies to elucidate these anomalies at the molecular level are currently underway.

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Aspects of Roaccutane prescription in South Africa

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A nationwide postmarketing surveillance study on the use and outcomes of use of isotretinoin has been conducted in South Africa. A representative sample of prescribers of the drug was identified from drug utilisation data and the overall doctor response rate was 90,1%. A total of 766 patients was enrolled in the study, of which 728 were analysable for safety and efficacy. More than half the patients prescribed isotretinoin were women, of whom only 48,25% were practising some form of contraception. The mean overall dosage prescribed was 0,64 mg/kg/day and the mean overall duration of therapy prescribed was 15,5 weeks. The mean dose and duration of therapy prescribed by dermatologists was significantly higher than that prescribed by general practitioners. Potentially dangerous drug interactions involving the concomitant use of isotretinoin with tetracyclines, vitamin A and oral contraceptives together with antibiotics were noted. Mucocutaneous drying effects were the most common adverse events and the incidence of these effects decreased with continuation of therapy. The known effectiveness of the drug was confirmed by the results of the study.

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