

TETRAHYDROBIOPTERIN METABOLISM IN DOWN'S SYNDROME AND IN NON-DOWN'S SYNDROME MENTAL RETARDATION

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INTRODUCTION

Tetrahydrobiopterin is the rate limiting factor in catecholamine synthesis (Leeming, Pheasant & Blair, 1981) and deficient tetrahydrobiopterin metabolism may cause reduced neurotransmitter production and hence disease of the central nervous system. Serum dihydrobiopterin levels are significantly lowered in malignant hyperphenylalaninaemia due to reduced tetrahydrobiopterin synthesis (Leeming, Blair & Rey, 1976; Rey, 1977), tuberose sclerosis (unpublished data), non-specific mental retardation in males (Leeming & Blair, 1980), Hartnup disease (Leeming & Blair, 1980), and senile dementia (Leeming & Blair, 1979, 1980; unpublished data). They are elevated in malignant hyperphenylalaninaemia caused by dihydropteridine reductase deficiency (Rey *et al.*, 1977) and untreated phenylketonuria (Leeming *et al.*, 1976). This paper records the measurement of serum dihydrobiopterin in patients with Down's syndrome and in a control group of mentally retarded patients without Down's syndrome.

METHODS OF INVESTIGATION

Down's syndrome patients

They totalled 56 cases: 31 females and 25 males with ages ranging from 20 to 61 years. All suffered from severe mental retardation. All had had chromosomal studies to establish their diagnosis. One patient suffered from diabetes mellitus, and another had psoriasis. Otherwise none had any clinical or biochemical evidence for systemic disease. Nineteen patients were on one or more of the following medications: haloperidol, maprotiline hydrochloride, a phenothiazine, and contraceptive pills.

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Control patients

They totalled 54 patients: 25 females, and 29 males. Their ages ranged from 20 to 80 years. All were mentally retarded. The causes of their mental retardation were due to birth injury, unknown constitutional factors, and in two cases to congenital syphilis. Besides mental retardation, 16 patients had epilepsy, 13 spastic paraplegia, five diabetes mellitus, and one suffered from congestive cardiac failure. Thirty-six of the control patients were on one or more of the following medications: sodium valproate, phenytoin, carbamazepine, chlorpropamide, a phenothiazine, digoxin, and diazepam.

The Down's syndrome patients and the control group of mentally retarded patients were all adult long-stay residents of St Lawrence's Hospital for the Mentally Handicapped, Caterham. Serum samples were obtained from blood samples taken in the course of a routine yearly medical check-up. The patients were not prepared in any special way prior to sampling.

The serum samples were frozen and samples from each group were assayed within a week. The standard bioassay technique as described previously (Leeming & Blair, 1980) was used to assess concentration of serum dihydrobiopterin. The mean and standard error of the mean of serum dihydrobiopterin concentrations were calculated for each group of patients separately, as a whole group, according to sex and according to the following inclusive age intervals: 20-39, 30-39, 40-49 and above 50 years (Table 1).

Table 1. Concentration of serum dihydrobiopterin in Down's syndrome and mentally-retarded control groups

Age group (yr)	Down's syndrome mean \pm s.e.m. (μ g/l)*	Control group mean \pm s.e.m. (μ g/l)*	Significance by Student's <i>t</i> test
20-29	1.88 \pm 0.09 (6)	1.25 \pm 0.24 (4)	NS < 0.05
30-39	2.00 \pm 0.07 (21)	1.00 \pm 0.05 (17)	< 0.001
40-49	1.88 \pm 0.08 (21)	1.04 \pm 0.07 (12)	< 0.001
50+	1.90 \pm 0.15 (8)	1.27 \pm 0.09 (21)	< 0.01
Total	1.93 \pm 0.05 (56)	1.13 \pm 0.05 (54)	< 0.001
Female	1.94 \pm 0.07 (31)	1.32 \pm 0.08 (25)	< 0.001
Male	1.93 \pm 0.06 (25)	0.97 \pm 0.04 (29)	< 0.001

NS = not significant. *Numbers of subjects in each group are given in parentheses.

Student's *t* test was used to compare results of relevant groups.

RESULTS

Serum dihydrobiopterin concentrations in the whole group of Down's syndrome patients (1.93 \pm 0.05 μ g/l) are significantly higher ($P < 0.001$) than the mean concentration (1.13 \pm 0.05 μ g/l) of the whole group of mentally handicapped controls. Serum dihydrobiopterin concentrations in female (1.94 \pm 0.07 μ g/l) and male (1.93 \pm 0.06 μ g/l) Down's syndrome cases are also significantly higher ($P < 0.001$) than the mean value of the mentally retarded control females (1.32 \pm 0.08 μ g/l) and males (0.97 \pm 0.04 μ g/l) (Table 1). The mean serum dihydrobiopterin level of the Down's syndrome patients are

Table 2. Serum dihydrobiopterin concentration in Down's syndrome patients and normal population

Age group (yr)	Down's syndrome patients mean \pm s.e.m. (μ g/l)		Normal population \ddagger mean \pm s.e.m. (μ g/l)		Significance by Student's <i>t</i> test $\dagger P_1$ $\ddagger P_2$
	Male \S	Female \S	Male \S	Female \S	
20-29	2.00 \pm 0.30 (2)	1.82 \pm 0.06 (4)	1.73 \pm 0.07 (45)	1.43 \pm 0.05 (68)	NS 0.05
30-39	2.06 \pm 0.10 (7)	1.99 \pm 0.10 (14)	1.65 \pm 0.12 (8)	1.70 \pm 0.08 (24)	0.05 0.05
40-49	1.86 \pm 0.08 (15)	1.93 \pm 0.24 (6)	1.86 \pm 0.31 (5)	1.94 \pm 0.11 (25)	NS NS
50+	1.90 \pm 0.00 (1)	1.90 \pm 0.17 (7)	2.54 \pm 0.30 (5)	1.84 \pm 0.15 (8)	NS NS
Total	1.93 \pm 0.06 (25)	1.94 \pm 0.07 (31)	1.79 \pm 0.03 (63)	1.61 \pm 0.04 (125)	0.05 <0.001
Total (male & female)	1.93 \pm 0.05 (56)		1.67 \pm 0.03 (188)		<0.001

* P_1 for comparing male patients. $\dagger P_2$ for comparing female patients. NS = not significant. \ddagger Leeming & Blair (1980). \S Numbers of subjects in each group are given in parentheses.

Table 3. Serum dihydrobiopterin concentration in non-Down's syndrome mentally retarded patients and normal population

Age group (yr)	Non-Down's syndrome, mentally retarded patients mean \pm s.e.m. (μ g/l)		Normal population \ddagger mean \pm s.e.m. (μ g/l)		Significance by Student's <i>t</i> test $\dagger P_1$ $\ddagger P_2$
	Male \S	Female \S	Male \S	Female \S	
20-29	0.90 \pm 0.14 (2)	1.60 \pm 0.30 (2)	1.73 \pm 0.07 (45)	1.43 \pm 0.05 (68)	<0.05 NS
30-39	0.92 \pm 0.05 (12)	1.20 \pm 0.11 (5)	1.65 \pm 0.12 (8)	1.70 \pm 0.08 (24)	<0.001 <0.02
40-49	0.96 \pm 0.05 (8)	1.20 \pm 0.15 (4)	1.86 \pm 0.31 (5)	1.94 \pm 0.11 (25)	<0.05 <0.02
Over 50	1.07 \pm 0.10 (7)	1.36 \pm 0.12 (14)	2.54 \pm 0.30 (5)	1.84 \pm 0.15 (8)	<0.01 <0.05
Total	0.97 \pm 0.04 (29)	1.32 \pm 0.08 (25)	1.79 \pm 0.03 (63)	1.61 \pm 0.04 (125)	0.001 <0.01
Total (male & female)	1.13 \pm 0.046 (54)		1.67 \pm 0.03 (188)		<0.001

* P_1 Comparing male group. $\dagger P_2$ Comparing female group. NS = not significant. \ddagger Leeming & Blair (1980). \S Numbers of subjects in groups are given in parentheses.

significantly higher than the normal population ($P < 0.01$ for the whole group, $P < 0.001$ for female group, $P < 0.05$ for male patients) (Table 2). The serum dihydrobiopterin levels from the mentally retarded non-Down's syndrome cases are significantly lower ($P < 0.001$ for whole group; $P < 0.001$ for males; $P < 0.01$ for females) than normal values (Table 3).

DISCUSSION

Serum dihydrobiopterin results from the intracellular breakdown of tetrahydrobiopterin and is normally maintained within a very narrow range (Leeming & Blair, 1980).

Our results show a significant increase in serum dihydrobiopterin levels in Down's syndrome cases compared to normal (Tables 1 & 2). Any exogenous influence from the peculiarity of the patients' environment should have had similar effect on the mentally retarded non-Down's syndrome cases and this is clearly not the case (Table 1). The increased serum dihydrobiopterin levels in Down's syndrome may therefore be due to the increased oxidation of cell tetrahydrobiopterin by accelerated oxidative processes (Blair & Pearson, 1974; Sinet, Lejeune & Jerome, 1979).

By analogy with malignant hyperphenylalaninaemia this would lead to lowered cell tetrahydrobiopterin levels and reduced neurotransmitter formation (Leeming, Pheasant & Blair, 1981). We suggest that this defect in tetrahydrobiopterin metabolism may be responsible for the lack of mental development in the patients and it may be a factor in predisposing these patients to develop the degenerative brain lesions characteristic of Alzheimer disease later in life (Yates *et al.*, 1980; Mann *et al.*, 1980).

The decreased serum dihydrobiopterin levels in the non-Down's syndrome mentally retarded group compared to normal subjects (Tables 1 & 3) may be due to reduced tetrahydrobiopterin levels in the cell arising from defective synthesis (Leeming, Pheasant & Blair, 1981). If so again by analogy with malignant hyperphenylalaninaemia this may be the cause of their mental retardation (Leeming, Pheasant & Blair, 1981). An alternative possibility that the low levels of serum dihydrobiopterin may be due to lack of functioning tissue seems less likely because the urinary neopterin (a precursor of tetrahydrobiopterin; Leeming, Pheasant & Blair, 1981) levels are the same or higher in these subjects as in normals (unpublished data).

SUMMARY

Tetrahydrobiopterin levels are reduced in Down's syndrome patients and in non-Down's syndrome mentally retarded patients. This may be the cause of the mental retardation in both groups.

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