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Endocrine function and haemoglobinopathies: biochemical assessment of thyroid function in children with sickle-cell disease

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Summary

Thyroid function was assessed in ninety children with homozygous sickle-cell disease (haemoglobin genotype SS) in forty-five children with heterozygous sickle-cell trait (AS) and in 162 control children with haemoglobin genotype AA. Serum levels of thyroxine, the *in vitro* triiodothyronine resin uptake and the calculated index of 'free thyroxine' were not significantly different in the three groups. The distribution of individual thyrotropin (TSH) values showed that only 11% of the HbSS subjects had values below the 95% confidence limits for the HbAA controls. However, the mean level of TSH was significantly lower in the HbSS than the other two groups of children.

Résumé

Une évaluation du fonctionnement thyroïde était faite chez quatre-vingt dix enfants avec la maladie homozygote de 'sickle cells' (HbSS), quarante-cinq avec des traits heterozygotes de 'sickle-cells' (HbAS) et 162 enfants de contrôle avec hémoglobine de génotype AA. Les niveaux de sérum de thyroxine, le *in vitro* triiodothyronie de résine prise et l'index calculé de 'thyroxine libre' n'étaient pas significativement différents dans les trois groupes. La distribution des valeurs de thyrotropin (TSH) individuel a révélé que 11% des sujets de HbSS seulement avaient des valeurs basses. Ces valeurs-ci se trouvent au-dessous de la limite de 95% de confiance pour les contrôles de HbAA.

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Pourtant le niveau moyen de TSH était remarquablement en bas dans le groupe de HbSS par rapport aux deux autres groupes d'enfants.

Introduction

Homozygous sickle-cell disease is usually associated with clinical complications arising from abnormal functions of organs such as the liver, kidney and the endocrine system (Luzzato, 1981). Studies on endocrinopathies in particular have reported hypopituitarism as resulting from intravascular thrombosis and pituitary infarction (Wintrobe, 1967; Adadevoh, 1968). There are indications also that the impairment of gonadal and adrenal function in this disease may be related to hypopituitary function (Olamiwonnu, Penny & Frasier, 1975; Abbasi *et al.*, 1976; Dada & Nduka, 1980; Rosenbloom, Odell & Tanaka, 1980). A study of the endocrine function of the pancreas among adult males with sickle-cell disease in this environment however revealed no gross derangement (Okafor & Osamo, 1981).

Application of the technique of microcalorimetry to the study of erythrocyte metabolism *in vitro* by Boyo & Ikomi-Kumm (1972) revealed an increased metabolic heat production by HbSS compared to normal HbAA erythrocytes. The possibility that such elevated heat production in erythrocytes may be related to an impairment of thyroid function or reflect an increase in basal metabolic rate (BMR) in sickle-cell disease has not been fully investigated.

We report here the results of biochemical

investigations of the pituitary-thyroidal axis in children with homozygous sickle-cell disease as compared to children with other haemoglobin genotypes (HbAA, HbAS).

Materials and methods

The patients consisted of ninety children aged between 1-15 years, with a diagnosis of homozygous sickle-cell disease attending the children's outpatient anaemia clinic at the University College Hospital, Ibadan. They were all in a steady, crises-free state at the time of the study. All were on routine folic acid and darapim and none had received a blood transfusion in the preceding 3 months. Their haematocrit (PCV) ranged between 17 and 31%. The controls were 181 apparently healthy children (eighty-five girls, ninety-five boys) from neighbourhood schools and twenty-six other children (thirteen girls, thirteen boys) attending the children's outpatient general clinic, but presenting with minor complaints, such as the common cold and cough. The control subjects were aged 1-15 years and had their genotype confirmed through haemoglobin electrophoresis. 162 of these had haemoglobin genotype AA while the remaining forty-five had HbAS. Blood was collected from each subject by venepuncture and the sera were stored at -20°C until analysed. The thyroid function tests included (i) the assay of serum thyrotropin (TSH), (ii) *in vitro* triiodothyronine resin uptake (T3RU) (iii) serum thyroxine (T_4).

(i) TSH was assayed using the radioimmunoassay kit of Amersham International Ltd. The standards were in the range 0-50 mU/l of the reference preparation MRC 68/36. The sensitivity of the assay was 0.4 mU/l and within and between assay coefficients of variation were 7.1% and 7.2% respectively.

(ii) T3RU assay utilized the macro albumin aggregates (MAA) kits of Amersham International. The within- and between-assay coefficient of variation were 4.0 and 4.2% respectively.

(iii) Estimation of total serum T_4 utilized the Amerlex T_4 radioimmunoassay kit of Amersham International. Standards were in the range 0-325 nmol/l. The within- and between-assay coefficient of variation were 5.2 and 7.2% respectively.

(iv) The free thyroxine index (FTI) was calculated for each subject from the results of the T_3 resin uptake test and the total serum T_4 by the equation:

$$\text{FTI} = \frac{\text{T3RU}}{100} \times T_4 \text{ value (Osorio et al., 1962).}$$

The determination of radioactivity in each case was performed on the Packard Auto-gamma spectrometer model 5530. Statistical evaluation of the results was by the Student's *t*-test.

Results

Table 1 summarizes the results of the thyroid function tests in the children with sickle-cell disease (SS) and in age-matched controls with haemoglobin genotype AA and AS. The mean levels of thyroxine (113.8 ± 2.9 , 117.8 ± 2.6 and 120.0 ± 3.6 nmol/l respectively, T_3 resin uptake (30.0 ± 0.3 , 29.5 ± 0.2 and $29.1 \pm 0.4\%$ respectively) and hence the derived values of the FTI (34.6 ± 1.0 , 34.7 ± 0.8 and 34.7 ± 1.0 respectively) in the SS subjects were not significantly different from those of the control subjects. However the mean TSH level in the SS subjects (2.4 ± 0.2 mU/l) is significantly lower than in both AA (4.8 ± 0.2 mU/l) and AS subjects (4.8 ± 0.3 mU/l, $P < 0.01$) while the levels in the latter two groups show no statistical difference. The distribution of individual TSH values in all the subjects studied are shown in Fig. 1. Ten of the ninety children (11%) with sickle-cell disease had TSH values less than 1.0 mU/l.

In Table 2, mean TSH values for these children are compared in matched age groups with control HbAA subjects. No significant trends are observed between ages in either the HbAA or HbSS children, whereas at each age group, mean TSH values are significantly lower in the HbSS compared to HbAA children ($P < 0.01$) in each case.

Discussion

The present study shows that the blood levels of thyroxine, the thyroxine-binding capacity as assessed by T_3 resin uptake and hence the free thyroxine index were not significantly different

Table 1. Serum *in vitro* T₃ resin uptake (T₃U) and levels of thyroxine (T₄), the free thyroxine index (FTI) and thyrotropin (TSH) in children with homozygous sickle-cell disease (haemoglobin genotype SS) sickle-cell trait (AS) and age-matched controls with haemoglobin genotype AA

	Haemoglobin genotype		
	AA	AS	SS
No. of subjects:	162	45	90
T ₃ U (%)	29.5 ± 0.2 (23.9 - 35.7)	29.1 ± 0.4	30.0 ± 0.3
T ₄ (μmol/l)	117.8 ± 2.6 (62.7 - 172.8)	120.0 ± 3.6	113.8 ± 2.8
FTI	34.7 ± 0.8 (16.8 - 53.7)	34.7 ± 1.0	34.6 ± 1.0
TSH (mu/l)	4.6 ± 0.2 (1.0 - 6.8)	4.8 ± 0.3	2.4 ± 0.2*

*Significantly lower than for AA and AS subjects ($P < 0.01$ *t*-test).

Results are expressed as mean ± s.e. Values in parenthesis represent the 95% of confidence limits of AA control subjects.

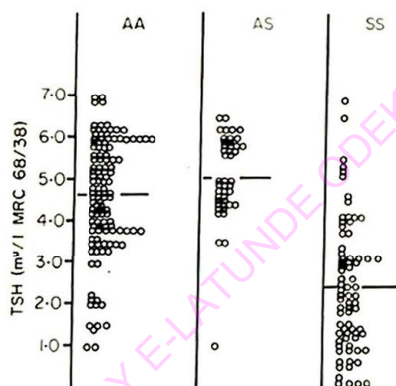


Fig. 1. Distribution of thyrotropin (TSH) values in children with haemoglobin genotype SS, AS and AA controls. The horizontal bars represent the mean of each group. Further details are given in Table 1.

in the three groups of children with haemoglobin genotypes AA, AS and SS. Thus the present results indicate that the reported increase in metabolic heat production by erythrocytes in sickle-cell disease is not directly associated with any changes in circulating thyroxine levels, in such individuals.

Table 2. Distribution of TSH values by age groups in ninety children with haemoglobin genotype SS and 207 control children with genotype AA and AS

Age (years)	Controls		SS	
	<i>n</i>	TSH (mu/l)	<i>n</i>	TSH (mu/l)
1-5	31	4.6 ± 0.2	33	2.3 ± 0.1*
5-9	92	4.4 ± 0.2	27	2.2 ± 0.3*
9-12	39	4.3 ± 0.3	15	2.3 ± 0.3*
12-15	45	4.8 ± 0.1	10	2.8 ± 0.2*

*Significantly lower than values for control group ($P < 0.01$, *t*-test).

Results are expressed as mean ± s.e. *n* represents the number of children in each group.

From the distribution of individual TSH values shown in Fig. 1, it is apparent that ten of the HbSS children (11%) have TSH values below 0.1 mU/l i.e., lower than the 95% confidence limit for the control subjects (Table 1). Overall, the mean serum TSH level was significantly lower in the SS than in control children with haemoglobin genotypes AA and AS. The significance of this observation of low serum levels of thyrotropin in the presence of

normal thyroxine levels in sickle-cell disease is not clear at present. The finding is not fully consistent with hypopituitarism but rather is suggestive of an impairment of the regulatory processes of the thyroid-pituitary axis, reflecting either an increased sensitivity of the thyrotropes to circulating thyroid hormones or peripherally, higher circulating blood levels of triiodothyronine (T_3). Indeed, alterations in peripheral events, such as the rate of cellular uptake or the intracellular degradation of T_4 to T_3 and reverse T_3 (3, 3', 5'-triiodothyronine) are not unlikely in sickle-cell disease. Previous results from this laboratory (Sogbesan, Dada & Adadevoh, 1974) showed that the peripheral metabolism of another hormone, testosterone, is altered in G6PD-normal, HbSS erythrocytes. This possibility of altered peripheral metabolism of the thyroid hormones in sickle-cell disease deserve further investigations.

In adults with sickle-cell disease, previous reports by Wintrobe (1967), Adadevoh (1968) and Rosenbloom *et al.* (1980) have implicated the occurrence of repeated episodes of intravascular thrombosis and pituitary infarction with subsequent pituitary dysfunction. In this regard, it is tempting to speculate as to whether hypofunction of the pituitary-thyroidal axis would present in HbSS subjects in adulthood. However, these results (Table 2) indicated no age-related effects on circulating blood levels of TSH in HbSS subjects. The assessment of pituitary secretory function, by the administration of thyrotropin-releasing hormone would help to further elucidate this problem.

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