Research Article

Study of Reproductive & Thyroid Hormones in adolescent with Sickle Cell Disease

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Abstract

Introduction: Sickle cell anaemia patients have been reported to suffer from endocrine dysfunctions which often have an influence on growth, development, and metabolism. Delayed somatic and sexual developments have been well described in patients with homozygous sickle cell disease**.** The present study focuses plasma levels of seven different endocrine hormones in individuals aged between 10-18 years, with a diagnosis of homozygous sickle cell disease. **Material & methods:** All study subjects were undergone for estimation of follicular stimulating hormone (FSH), Leuteinizing Hormone (LH), Testosterone, T3, T4 & TSH measured and value were analyse statistically. **Observation:** Study Patients with sickle cell disease showed LH, FSH Testosterone and Estradiol are significantly reduced in individual with homozygous sickle cell disease (SS) in comparison with control group suggest that the sickle cell gene abnormality has an adverse effect on endocrine functions. **Conclusion**: Routine screening for endocrine dysfunctions are advocated in all adolescent sickle cell disease patient.

Keywords: Sickle Cell Disease, Reproductive Hormone, Follicular Stimulating Hormone, Leuteinizing Hormone, Testosterone.

Introduction

Sickle cell disease (SCD) is an autosomal, recessive hemoglobinopathy characterized by hemolytic anemia, intermittent occlusion of small vessels leading to acute and chronic tissue ischemia, and organ dysfunction. Anthropological Survey of India [1] established sickle cell trait frequencies up to 35% throughout much of central India, the highest frequencies occurring in Orissa, Madhya Pradesh, Maharashtra and Gujarat [2,3].

Chhattisgarh is a new state, formed in November 2000 from the south-eastern part of Madhya Pradesh, with a population of approximately 21 million of whom 32% are tribal in origin [4]**.** As per Balgir et al the highest prevalence of SCD in India has been recorded in the state of Orissa (1-44.4%), followed by Madhya Pradesh including Chhattisgarh (1-40.0%). The prevalence of SCD in the population of Chhattisgarh is about 10 to 15% of which about 1 to 1.27% are likely to be sufferers and the rest carriers. About 35 lacs of carriers and 2.5 lacs of sufferers are expected to exist in Chhattisgarh. Prevalence is more in certain communities of Chhattisgarh like Sahu, Kurmi, Nayak, Patel and some tribal populations [5,6,7].

Sickle cell anemia patients have been reported to suffer from endocrine dysfunctions which often have an influence on growth, development, and metabolism. Delayed somatic and sexual developments have been well described in patients with homozygous sickle cell disease [8-12]**.** The cause of hypogonadism and impaired infertility of homozygous sickle cell disease is yet unknown, but primary gonadal failure [12], hypothalamic dysfunction [13], pituitary infarction [14], and constitutional delay of puberty have been suggested

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as possible mechanisms. The variations in the extent of severity of endocrine abnormality may be related, at least in part, to the severity of the sickle cell disease. In addition to other contributory factors, such as tissue hypoxia secondary to red cell sickling and, hence tissue damage are mainly responsible for dysfunction.

Material & Methods

This prospective cross sectional study was conducted in department of paediatrics, Pt JNM medical college Raipur Chhattisgarh over a period of 2 year from November 2012 to September 2014 in children between 10 to 18 years of age group diagnosed as sickle cell disease by haemoglobin electrophoresis. Age and sex matched normal children attended paediatrics OPD for minor illnesses were used as control. Study was approved by ethical and scientific committee. Informed consent was obtained from all the guardian or caregivers regarding nature of study. All study subjects were undergone for estimation of follicular stimulating hormone (FSH), Leuteinizing Hormone (LH), Testosterone, T3, T4 & TSH measured by Electrochemiluninescence using COBAS E 411 analyzer by Roche.

The present study focuses on endocrine abnormalities as a cause for delay in puberty in such individuals. The plasma levels of seven different hormones were determined in individuals aged between 10-18 years, with a diagnosis of homozygous sickle cell disease.

The mean standard deviation and standard error of mean were calculated for both the group. The significance of the difference in the mean of the case and control were determined by student t test, p value of less than 0.05 was considered significant.

Result

In this study total cases were 70 and controls were 25. Maximum cases were in 12-12.9 year age group. Among cases 41(58.6%) were males and 29 (41.4%) were females. Male female ratio was 1.41%. Among the control group, 14(56%) were males and total number of females were 11(44%). Male female ratio was 1.27%.

Table 1a & 1b showed Among SCD SS male cases (n=41) and females (n=29), mean values of LH (mIU/ml) were found to be higher in males, values were as follows - MEAN ± SD - 2.36± 2.5 vs 2.6± 2.28 (p=0.602); not significant. FSH (mIU/ml) - 3.18± 2.42 vs 3.24± 2.28 (p=0.914) not significant. Testosterone (ng/ml) - 0.7± 0.99 vs 0.24± 0.48 (p=0.01); statistically significant. Estradiol (pg/ml)- 15.76± 9.62 vs 20.64± 12.85 (p=0.08); not statistically significant.

Table 1a comparison of mean values of serum LH, FSH , Testosterone, Estradiol & Thyroid Hormone between cases and controls

		LH	FSH	TESTOSTERONE	ESTRADIOL	T3	T4	TSH
Cases (70)	Mean	2.49	3.20	0.51	17.78	1.53	8.88	3.36
	SEM	0.29	0.28	0.10	1.34	0.04	0.17	0.15
	SD	2.40	2.34	0.85	11.24	0.31	1.40	1.25
Controls (25)	Mean	4.32	3.68	1.22	35.18	1.79	9.92	5.75
	SEM	0.51	0.38	0.32	3.08	0.04	0.28	0.16
	SD	2.53	1.89	1.62	15.41	0.19	1.41	0.78
Z value		3.22	1.80	2.09	11.80		3.70	3.37
p value			0.0017	0.307	0.036	<0.001	<0.001	0.0015

Among SCD SS male cases (n=41) and females (n=29); mean values of Triiodothyronine (ng/ml) were found to be as follows- 1.48± 0.34 vs 1.59± 0.26 (p=0.125). Thyroxine (microgm/dl)-8.73± 1.5 vs 9.1± 1.25 (p=0.26). TSH (mIU/L) - 3.41± 1.2 vs 3.29± 1.34 (p=0.701). No statistically significant difference was seen between male and female cases.

Table 1b comparison of mean values of LH, FSH, Testosterone, Estradiol & Thyroid Hormones between males and females in cases								
Cases (70)		**LH**	**FSH**	**Testosterone**	**Estradiol**	**T3**	**T4**	**TSH**
Females (29)	Mean	2.66	3.24	0.24	20.64	1.59	9.10	3.29
	SEM	0.42	0.42	0.09	2.39	0.05	0.23	0.25
	SD	2.28	2.28	0.48	12.85	0.26	1.25	1.34
Male (41)	Mean	2.36	3.18	0.70	15.76	1.48	8.73	3.41
	SEM	0.39	0.38	0.15	1.50	0.05	0.23	0.19
	SD	2.50	2.42	0.99	9.62	0.34	1.50	1.20
z value		0.52	0.11	2.50	1.74	1.53	1.12	0.38
P value		0.602	0.914	0.01	0.083	0.125	0.26	0.701

Table 2 Comparison of mean values of LH,FSH, Testosterone and Estradiol & thyroid hormones between male /female cases and male/ female controls								
		LH	**FSH**	**Testosterone**	**Estradiol**	**T3**	**T4**	**TSH**
Male Cases (n=41)	Mean	2.36	3.18	0.70	15.76	1.48	8.73	3.41
	SEM	0.39	0.38	0.15	1.50	0.05	0.23	0.19
	SD	2.50	2.42	0.99	9.62	0.34	1.50	1.20
Male controls (n=14)	Mean	3.26	2.95	2.05	24.78	1.82	10.01	5.74
	SEM	0.52	0.38	0.47	1.26	0.04	0.43	0.22
	SD	1.95	1.42	1.77	4.73	0.16	1.59	0.80
z value		1.38	0.429	2.71	4.59	4.98	2.63	8.15
p value		0.166	0.667	0.0067	<0.001	<0.001	0.0083	<0.001
Female Cases (29)	Mean	2.66	3.24	0.24	20.64	1.59	9.10	3.29
	SEM	0.42	0.42	0.09	2.39	0.05	0.23	0.25
	SD	2.28	2.28	0.48	12.85	0.26	1.25	1.34
Female controls (11)	Mean	5.67	4.62	0.15	48.42	1.76	9.80	5.77
	SEM	0.79	0.62	0.03	4.22	0.07	0.36	0.24
	SD	2.62	2.05	0.11	14.01	0.24	1.20	0.79
Z value		3.35	1.84	0.94	5.72	1.95	1.62	7.19
p value		0.008	0.065	0.344	<0.001	0.057	0.103	<0.001

Among SCD SS male cases (n=41) and controls (n=14), there was statistically significant difference between triiodothyronine, thyroxine and TSH level were noted.

Among SCD SS female cases (n=29) and controls (n=11), the values were as follows-MEAN± SD- Triiodothyronine(ng/ml)-1.59± 0.26 vs 1.76± 0.24; Thyroxine (microgm/dl)- 9.1± 1.25 vs 9.8± 1.2 ; TSH (mIU/L)- 3.29± 1.34 vs 5.77± 0.79. There was no significant difference between values of T3 and T4; although significant difference was found between values of TSH (p <0.001).

Among the cases, the values of LH were found to be below normal range in total 18 patients (25.7%), of which 10 were male and 8 were female patients. In contrast among the control group, only 1 patient (4%) was found to have abnormal value of LH lying below the normal reference range. Only 2 male patients were seen to have LH values above the normal reference range. Rest 50 patients (71.4%) had values that were within the normal reference range, but the mean (2.48± 2.4mIU/ml) was significantly lower than those seen among control groups (4.32± 2.53mIU/ml).

21 SCD patients (30%) had depressed serum FSH values below normal range; in contrast to control group where only 2 (8%) patients had below normal values. The mean concentration of FSH among cases was 3.2± 2.34mIU/ml as compared

to that of 3.68± 1.89mIU.ml among controls, although the difference was not found to be statistically significant, (p=0.307).

Among the cases, 34 patients (48.5%) had serum values of testosterone that were found to be below normal range, of which 22 were male and 12 were female cases. This was significantly in contrast to control group where only 3 (12%) patients were seen to have depressed values of testosterone. The mean concentration of serum testosterone for Hb AA controls of 1.22± 1.62ng/ml was significantly higher than mean of 0.51± 0.85ng/ml obtained from Hb SS patients (p=0.036).

Table 3 25 patients (35.7%) among cases were found to have levels that were below the reference range in contrast to controls where none had value falling below normal reference range. The mean concentration of estradiol among cases was 17.78± 11.24pg/ml which was significantly lower than those of controls 35.18± 15.41 with a p value of <0.001.

Regarding T3, among the cases, only 3 patients (4.28%) had values lower than the normal reference range while 4 patients (5.7%) had values above normal reference range of which 1 was male and 3 were female. None of the controls had values lying outside the normal range. Although the mean concentrations of serum T3 for Hb SS cases was 1.53± 0.3 ng/ml which was found to be significantly lower than compared to Hb AA controls (1.79± 0.19 ng/ml) , (p<0.001). None of the cases or controls had values of thyroxine falling outside the normal reference range. 1 of the female patient (1.4%) among cases had abnormal value of TSH lying above the normal range while 1 male and 2 female (12%) had higher TSH values among controls.

Table 3: Distribution of LH, FSH, Testosterone and Estradiol ,T3,T4,TSH among cases and controls as per normal Reference Range

	LH		FSH		Testosterone		Estradiol		T3		T4		TSH	
	C	Ctrl	C	Ctrl	C	Ctrl	C	Ctrl	C	Ctrl	C	Ctrl	C	Ctrl
Within ref range	50(71.4%)	24(96%)	49(70%)	23(92%)	31(44.2%)	19(76%)	42(60%)	24(96%)	63(90%)	25(100%)	70(100%)	25(100%)	-	23(92%)
Below ref range	18(25.7%)	1(4%)	21(30%)	2(8%)	34(48.5%)	3(12%)	25(35.7%)	-	3(4.28%)	-	-		-	-
Above ref range	2(2.85%)	-	-	-	5(7.14%)	3(12%)	3(4.28%)	1(4%)	4(5.7%)	-	-		2(2.85%)	2(8%)

Table 3 showed Among SCD SS male cases (n=41) and male controls (n=14). There was statistically significant difference (p value is less than 0.05) in mean values of testosterone and estradiol between male cases and male controls. Among SCD SS female cases (n=29) and female controls (n=11). There was statistically significant difference between LH and Estradiol between female cases and female controls.

Discussion

The mean values of LH, FSH, testosterone and Estradiol among cases was found to be lower than those in control group; although the difference in values of FSH was not found to be significant. There was statistically significant difference between LH and Estradiol between female cases and female controls. There was statistically significant difference in mean values of testosterone and Estradiol between male cases and male controls. No significant difference in the mean concentration of FSH between SS males and control subjects whereas in female level were significantly increased above that of control subjects.

Our results were similar to El Hazmi M et al (1992[15], and Dada OA, Nduka EU et al who found that the level of LH, FSH, and testosterone was significantly lower when compared to the control group. In contrast, Olambiwonnu NO, Penny R et al found that the mean serum concentration of LH in the cases including both male and females was found to be higher than controls although difference was not statistically significant. The findings indicated gonadal hypofunction in the sickle cell patients.

Abbasi AA, Prasad AO, et al and Modebe O, Ezeh UO, et al [16] found that the values of the mean basal serum testosterone values were significantly lower than controls matching to our study Whereas Belinda M, Soares-Wynter, et al [17] found testosterone levels were significantly lower in the SCD group whereas

serum FSH and LH values were significantly higher in the SCD group in comparison to controls.

The mean values of T3, T4, and TSH were all found to be significantly lower than those among the control

Lukambi F, Adeyokunnu A[18], Osifo B, Boodeoku J, Dada OA et al reported that mean levels of thyroxine T3 resin uptake or thyroid binding capacity in the SS subjects were not significantly different from those of the control subjects. Mean level of TSH was

Osegbe D N[19], Akinyanju O O et al found that 8 out of 33 SCD patients studied had high or severely elevated serum FSH. In contrast none of the control subjects had a raised FSH. Half of the patients (12%) with raised FSH had significantly raised LH and this was associated with low testosterone. Four SCD patients (12%) had low serum testosterone levels. In all, no single patient had depressed values of FSH and LH.

Abudu K, Akanmu A, et al [20] and Modebe O, Ezeh UO, et al found that Most of the Hb SS patients, had serum testosterone concentrations below the normal range when compared with control. The serum concentrations of FSH and LH were within the normal range in all patients and control subjects. A Taddessea, I. L[21]. Woldieb, et al reported that serum testosterone levels, FSH and LH levels were either low or inappropriately normal in all the one fourth patient with low testosterone, which indicates central hypogonadism.

When T3, T4 and TSH among cases and controls Were Compared With normal reference range then we found that T3 among the cases, only 4.28% had values lower than the normal reference range while 4 5.7% had values above normal reference range. None of the controls had values lying outside the normal range. Few of the cases or controls had values of thyroxin & TSH falling outside the normal reference range.

Conclusion

According this study Patients with sickle cell disease showed LH, FSH Testosterone and Estradiol are significantly reduced in individual with homozygous sickle cell disease (SS) in comparison with control group suggest that the sickle cell gene abnormality has an adverse effect on endocrine functions indicating a central etiology. The low levels of these hormones may reflect hypogonadal function secondary to hypopituitary group. Whereas no significant difference seen between male and female. The values of T3, T4 and TSH were significantly low among male cases than male controls; while significant relation was found only for TSH between female cases and controls.
significantly lower in the Hb SS than control. In contrast to our study, El Hazmi M,Bahakin HM, Al Farwaz I et al studied 80 male and female patients with SCD SS the difference in the mean was not statistically significant.

function.The low levels of T3, T4 and TSH in presence of low levels of LH, FSH, Testosterone and Estradiol are also consistent with hypopituitarism. Therefore routine screening for endocrine dysfunctions are advocated in all adolescent sickle cell disease patient.

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