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Profile of Behavior and IQ in Anemic Children

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ABSTRACT

Objectives: Study the profile of behavior and intelligence of children with anemia and their possible association to the hematological parameters.

Methods: Fifty-eight children (42 anemic; 16 controls), matched by age, sex, and culture with the patients, were subjected to both behavioral and IQ testing using Revised Behavior Problem Checklist (RBPCL) and Wechsler intelligence scale for children-revised and hematological laboratory evaluation

Results: After controlling for age, sex and culture, the mean IQ was lower in the iron deficiency group than both thalassemic and control groups (P<.000). The mean scores of conduct disorder, socialized aggression, and anxiety withdrawal of RBPCL were higher in thalassemic group while the mean scores of motor excess and attention problems score were higher in the iron deficiency group. Regression analysis showed that hemoglobin concentration in gram/dl was the predictor of IQ in both anemic group and for attention problems in iron deficiency group while the mean corpuscular volume was the predictor of motor excess score in iron deficiency group. Other associations were not statistically significant.

Conclusion: Behavior problems and low intelligence were significantly high among anemic children. Their association with the

FOCUS POINTS

- The behavioral problems of anemic children are significantly higher compared with children of the same age, sex and culture.
- The main problems of iron deficiency anemia are, inattention, hyperactivity and low IQ.
- The main problems of thalassemic children are in conduct, socialized aggression and anxiety withdrawal.
- The hemoglobin concentration show significant predictive value for inattention and low IQ in iron deficiency anemia.
- The hematological parameters did not show significant predictive value in behavioral problems of thalassemic patients.

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hematological parameters varies according to the type of behavior and the type of anemia. These results cannot exclude the role of other factors in shaping the profile of behavior and IQ.

INTRODUCTION

Anemia is considered a worldwide problem, affecting all age groups and socioeconomic levels of society. Approximately 15% to 20% of the population of the United States <18 years of age is iron deficient.[1] Adolescents are susceptible to iron deficiency because of high requirements due to the growth spurt, dietary deficiencies, and menstrual blood loss. In several affluent countries, ~40% of adolescent girls and 15% of boys have serum ferritin levels <16% reflecting low bone marrow iron stores.[2] In the National Nutritional Survey conducted for the general population in Egypt in 1978 and 1980, the prevalence of anemia in the preschool age was 38% and 39%, respectively.[3] In spite of a large amount of information pointing to a severe retardation of physical growth in patients with thalassemia, very little has been said concerning mental development.[4] Since physical, mental, emotional, and social growth and development proceed simultaneously, physicians should realize that a threat to any of these areas could indicate a threat to others especially in the child with chronic disease or disability.[5]

Abnormalities in emotional response, character and behavior, such as anxiety, sense of inferiority, and oversensitivity, were reported in thalassemic patients. These manifestations are suggested to be due to the chronicity of the disease and its restrictive nature which interferes with successful achievement of those children.[6] Underachievement was reported in 10% of school children due to frequent and multiple absences from school.[4] There is now reason to believe that the degree of visibility of the lesion forces the child to recognize himself as "disabled" compared to non-visible disorders such as diabetes, this contribute to a great degree of psychological maladjustment.[7]

Our objectives is to study the profile of behavior and IQ in one group of children suffering from iron deficiency anemia and another group suffering from β-thalassemia major and comparing both groups with a group of healthy children matched to both by age, gender, and cultural background and to test for any possible relationship of the profile of behavior and IQ to the hematological parameters and consequently to anemia.

METHODS

The sample of this study was collected from children between 6–12 years of age attended an outpatient clinic of the Hematology Unit at the Tanta University Hospital in Egypt (Table 1). The objectives and procedures of the study were explained to the children and relatives and written consent was taken giving the child or the relative the right to stop during any step of the study. The sample was classified into three groups. Group A had 22 children with iron deficiency anemia according to the diagnostic criteria of iron defi-

TABLE 1.
Sociodemographic Backgrounds

		Iron Deficiency N=22	*Thalassemia* N=20	*Control* N=16	Statistics		
Age in years (Mean±SD)		8.00±1.60	7.75±1.51	8.06±0.92	df=2	F=0.26	*P*=.77
Gender (number)	Male	11	12	10	df=2	χ^2=0.71	*P*=.70
	Female	11	8	6			
Culture	Urban	11	9	8	df=2	χ^2=0.13	*P*=.94
	Rural	11	11	8			
Socioeconomic condition	Poor	2	2	2	df=4	χ^2=0.14	*P*=.99
	Average	11	10	8			
	Above Average	9	8	6			

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ciency anemia in children.[8] Group B had 20 children with β-thalassemia major.[9] Group C was the control group of 16 healthy children of matched age, gender, and cultural background to both thalassemic and iron deficient anemic groups (they were collected from the relatives and companions of the sick children).

All children (patients and control) were subjected to the Revised Behavior Problem Checklist (RBPCL)[10] which is composed of six scales which measures the following patterns of behavior. Scale I: conduct disorder (22 items). Scale II: socialized aggression (16 items). Scale III: attention problem-immaturity (16 items). Scale IV: anxiety-withdrawal (11 items). Scale V: psychotic behavior (6 items). Scale VI: motor excess (5 items). The Wechsler intelligence scale for children-revised[11] assessed the IQ of all the studied groups. Complete blood picture was tested using automatic blood cell counter K 1000, and hemoglobin electrophoresis. Serum iron was tested using iron without deproteinization test.[12] Total iron binding capacity was tested using test combination iron-binding capacity (Table 2).[13]

Statistical Analysis

The SPSS software package version 13 under Windows[14] was used for computer data analysis and graphs, cross-tabulation, and one-way analysis of variance (ANOVA) was used to compare multiple means using the post-hoc LSD component. To test the relationship between the studied biochemical parameters and both RBPCL and IQ results we

TABLE 2.
Results of Hematological Evaluation

							95% CI for		ANOVA		
	Case Type	*NO*	*Mean*	*SD*	*Min*	*Max*	*Lo*	*Up*	*Df**	*F*	*P*
Hemoglobin concentration (gm/dl)	Iron Deficiency	22	7.41	0.85	6.00	9.00	7.03	7.78	2; 55	213.59	0.000
	Thalassemia	20	6.50	1.17	4.30	8.30	5.95	7.04			
	Control	16	13.48	1.24	12.30	17.30	12.81	14.14			
Mean corpuscular hemoglobin concentration (%)	Iron Deficiency	22	20.05	2.32	17.00	24.00	19.02	21.07	2; 55	86.14	0.000
	Thalassemia	20	24.10	2.27	21.00	28.00	23.04	25.16			
	Control	16	28.67	0.81	27.50	30.00	28.24	29.10			
Mean corpuscular volume (fl)	Iron Deficiency	22	63.64	2.57	60.00	68.00	62.50	64.78	2; 55	453.95	0.000
	Thalassemia	20	68.10	1.86	66.00	72.00	67.23	68.97			
	Control	16	86.84	2.82	83.70	95.00	85.34	88.35			
Serum ferretin (ng/ml)	Iron Deficiency	22	8.27	1.78	6.00	12.00	7.48	9.06	2; 55	430.86	0.000
	Thalassemia	20	777.20	152.62	570.00	1000.00	705.77	848.63			
	Control	16	103.88	21.35	71.00	138.00	92.50	115.25			
Serum iron (ug/dl)	Iron Deficiency	22	37.32	10.52	25.00	57.00	32.66	41.98	2; 55	450.71	0.000
	Thalassemia	20	214.70	30.34	173.00	274.00	200.50	228.90			
	Control	16	89.50	8.33	70.00	101.00	85.06	93.94			
Total iron binding capacity (ug/dl)	Iron Deficiency	22	492.32	88.15	313.00	655.00	453.24	531.40	2; 55	93.81	0.000
	Thalassemia	20	239.30	25.69	199.00	281.00	227.28	251.32			
	Control	16	316.13	45.79	251.00	402.00	291.73	340.52			
Iron store	Iron Deficiency	22	7.50	2.02	6.61	8.39	4.10	10.00	2; 55	835.03	0.000
	Thalassemia	20	89.14	9.47	84.70	93.57	64.00	99.20			
	Control	16	27.04	6.59	23.52	30.55	13.70	37.90			

*df (between groups; within groups)

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used regression analysis with each component of the RBPCL and IQ as dependent variables and all hematological parameters together as independent variables after controlling for age and sex.

RESULTS

Our results showed that the mean IQ of iron deficiency group was lower than both thalassemic and control groups ($P<.001$). No significant difference was found between thalassemic group and control group. In RBPCL mean scores; with the exception of psychotic behavior; all the mean test scores showed significant difference among the three studied groups (Table 3). Post-hoc multiple comparison analysis (Table 4) showed that; conduct disorder mean score was highest among thalassemic children compared with those with iron deficiency ($P<.005$) and control ($P<.001$), the mean score of children with iron deficiency anemia was still higher than the control ($P<.001$). Socialized aggression mean score was higher in children with thalassemia than both children with iron deficiency anemia ($P<.001$) and control cases ($P<.01$) but without significant difference between children with iron deficiency anemia and control cases ($P>.05$). Motor excess mean score was higher in children with iron deficiency anemia than thalassemia and control ($P<.001$), thalassemic children mean score was lower than control ($P<.000$). Attention problems mean score was higher in both type of anemic children than control ($P<.001$). However, the mean score of iron deficiency anemia group was still higher than thalassemic ($P<.001$). Anxiety withdrawal mean score was higher in thalassemic children than both iron

TABLE 3.
The Results of RBPCL and IQ Tests Among the Three Studied Groups

						95% CI for				
RBPCL Scores	***Case Type***	***N***	***Mean***	***SD***	***SE***	***Lo***	***Up***	***Df***	***F***	***Sig.***
Conduct disorder	Iron Deficiency	22	19.91	4.93	1.05	17.73	22.09	2	29.22	0.000
	Thalassemia	20	25.90	7.97	1.78	22.17	29.63			
	Control	16	10.19	4.92	1.23	7.57	12.81			
Socialized aggression	Iron Deficiency	22	0.68	1.32	0.28	0.10	1.27	2	7.78	0.001
	Thalassemia	20	2.75	2.47	0.55	1.60	3.91			
	Control	16	1.00	1.27	0.32	0.33	1.67			
Attention problems	Iron Deficiency	22	24.919	4.30	0.92	23.00	26.81	2	88.84	0.000
	Thalassemia	20	17.15	5.79	1.29	14.44	19.86			
	Control	16	4.75	3.09	0.77	3.11	6.40			
Anxiety withdrawal	Iron Deficiency	22	5.89	3.75	0.80	4.16	7.48	2	51.15	0.000
	Thalassemia	20	15.55	3.15	0.71	14.07	17.03			
	Control	16	5.50	3.67	0.92	3.55	7.46			
Psychotic behavior	Iron Deficiency	22	0.17	0.35	0.08	-0.02	0.29	2	2.00	0.145
	Thalassemia	20	0.40	0.82	0.18	0.02	0.78			
	Control	16	0.06	0.25	0.06	-0.07	0.20			
Motor excess	Iron Deficiency	22	6.86	1.81	0.39	6.06	7.67	2	68.80	0.000
	Thalassemia	20	0.35	0.67	0.15	0.07	0.66			
	Control	16	4.062	2.60	0.65	2.68	5.45			
Intelligence quotient (WISC-R)	Iron Deficiency	22	78.23	4.85	1.04	76.08	80.38	2	18.81	0.000
	Thalassemia	20	89.50	4.26	0.95	87.51	91.49			
	Control	16	95.44	15.24	3.81	87.32	103.56			

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deficiency group and control. On the other hand, there was no significant difference between iron deficiency group and control. Psychotic behavior mean score was not significant among the three groups children ($P>.05$).

In order to test if the hematological parameters have direct relationship to IQ and RBPCL scores we carried out regression analyses with all the seven hematological parameters (hemoglobin concentration, mean corpuscular hemoglobin concentration percentage, mean corpuscular volume, serum ferretin, total iron binding capacity, serum iron, iron store) as independent variables with IQ and each score of RBPCL as dependent variable. Age, gender, and cultural background were controlled in the model. This model tests if any of these hematological parameters could predict the changes in RBPCL scores. The result of this analysis showed that in the iron deficiency group hemoglobin concentration in gram/l was the predictor of IQ (df=7, 14; F=11.94; $P=.000$, $\beta=0.61$; t=2.19; $P=.046$) (Figure 1) and attention problem score of the RBPCL (df=7, 14; F=10.55; $P=.000$, $\beta=-1.12$; t=–3.84; $P=.002$) ie, negative correlation (Figure 2). The mean corpuscular volume was predictor of motor excess score (df=7,14; F=3.56; $P=.021$ $\beta=0.55$; t=2.24 ; $P=.042$). No significant association between the other RBPCL scores and hematological parameters.

In the thalassemia group, hemoglobin concentration in gram/l was the predictor of IQ that was predicted by l (df=7, 13; F=9.617; $P=.000$ $\beta=0.185$; t=4.75; $P<.05$). The blood parameters could not predict any of the RBPCL sub items in thalassemia patients. The control cases showed no correlation between these factors and either IQ or RBPCL mean score.

TABLE 4.
Post Hoc Multiple Comparisons Among the Three Studied Groups

	Score	(I) Case Type	(J) Case Type	Mean Difference (I-J)	SE	Sig.	Lo	Up
RBPCL	Conduct disorder	Iron Deficiency	Control	9.72	2.02	.000	5.67	13.77
		Thalassemia	Iron Deficiency	5.99	1.99	.003	2.19	9.80
		Thalassemia	Control	15.71	2.06	.000	11.58	19.84
	Socialized aggression	Thalassemia	Iron Deficiency	2.07	0.55	.000	0.96	3.18
		Thalassemia	Control	1.75	0.60	.005	0.55	2.95
		Control	Iron Deficiency	0.328	0.59	.591	-0.86	1.50
	Attention problems	Iron Deficiency	Thalassemia	7.76	1.42	.000	4.91	10.61
		Iron Deficiency	Control	20.16	1.51	.000	17.13	23.19
		Thalassemia	Control	12.40	1.55	.000	9.30	15.50
	Anxiety withdrawal	Iron Deficiency	Control	.318	1.16	.785	-2.01	2.64
		Thalassemia	Iron Deficiency	9.73	1.09	.000	7.55	11.92
		Thalassemia	Control	10.05	1.19	.000	7.68	12.42
	Psychotic behavior	Iron Deficiency	Control	0.074	0.18	.682	-0.29	0.43
		Thalassemia	Iron Deficiency	0.26	0.17	.123	-0.07	0.60
		Thalassemia	Control	0.34	0.18	0.07	-0.03	0.70
	Motor mxcess	Iron deficiency	Thalassemia	6.51	0.56	.000	5.40	7.63
		Iron deficiency	Control	2.80	0.59	.000	1.62	3.99
		Control	Thalassemia	3.71	0.60	.000	2.50	4.92
	IQ	Thalassemia	Iron deficiency	11.27	2.74	.000	5.79	16.76
		Control	Iron deficiency	17.21	2.91	.000	11.37	23.05
		Control	Thalassemia	5.94	2.97	.051	-0.02	11.90

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DISCUSSION

The results of RBPCL showed that anemic children have more behavioral problems (except psychotic behavior [*P*>.05]) than the control group. The association between iron deficiency anemia and cognitive function is reported in previous studies.[17]

Our study showed that the mean IQ was lower among iron deficiency children than both thalassemic and control groups (*P*<.001). The IQ in thalassemic children was not significantly lower than the control group (*P*=.051). This non-significant difference between the thalassemic and control groups could be explained by the notion that the low intelligence in thalassemic children is attributed more to indirect effects related to social or environmental disadvantages (eg, decreased learning opportunities, increased physical limitations from chronic illness).[18,19] These factors do not usually lead to severe mental retardation in the same way that the biological factors do.[20] The significant difference in IQ between the control and the iron deficiency anemia children can be attributed to the of biological effects of anemia as a cause of the behavioral and cognitive impairment. This attribution is well supported in the literature.[21-25] An interesting observation on the IQ of both patient groups is the narrow standard deviation than the control group, a possible explanation of this is that no child could escape the effect of the illness on IQ. This anecdotal explanation needs support by future studies on a large samples.

In order to test the direct (biological) or indirect (psychosocial) impact of the disease process on the difference in behavior and IQ, we selected the control sample to be matched for age, sex, cultural background, and economic status. The data from a meta-analysis on cognitive deficits of sickle cell anemia[26] indicate that studies using demographically matched peers as a control group showed approximately a 2-point greater IQ discrepancy than studies that used a sibling control group. The difference has a little effect and did not reach statistical significance with a large number of cases and controls. In their analysis; the authors found no evidence that the choice of control groups poses a meaningful bias in outcomes for general cognitive functioning and either siblings or nonsibling peers are appropriate choices. We acknowledge the limitation of the small number of our control sample compared with the patients groups but the non significant difference was based on nonparametric statistical analysis that considers such types of discrepancies in sampling.

Studying the role of changes of the studied hematological parameters on the behavior and IQ in the two types of anemia we found different associations.

In thalassemia cases, regression analysis showed non-significant predictive value of the studied hematological parameter for the mean score of RBPC which supports the likelihood that the behavioral changes are associated more to social and psychological problems than the

FIGURE 1.
Profile of behavior and IQ in anemic children

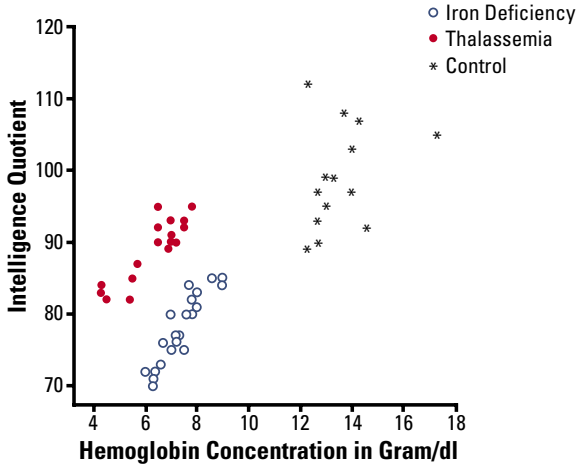

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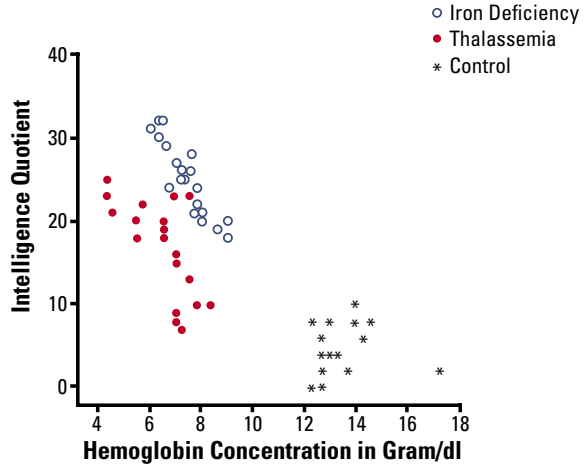
FIGURE 2.
Relationship between attention problems and hemoglobin concentration



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hematological changes of the disease. The chronic disabling illness causes more stress due to both actual and anticipated disability caused by more hospitalization, more time in blood transfusion and multiple school absences with consequent academic and social backwardedness.[27,28] Another source of stress on the child and family is the cost of treatment and loss of working days of the caregivers (parents) that creates a more stressful family environment.[29-32] Our findings do not rule out the effect of other disease related biological changes such as focal cerebral infarcts that could happen in some cases.[33-35]

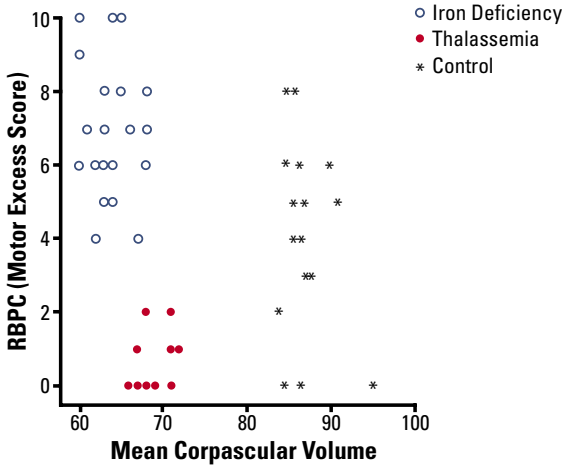
Steen and colleagues[36] found an association between focal brain injury and cognitive impairment, suggesting that diffuse brain injury may also contribute to impairment. However their result only showed a significant relationship $P<.02$) between abnormal brain magnetic resonance imaging and verbal IQ. The other components of WISC including full IQ scale showed non significant association. The significant association was detected with hematocrete value <27. Our results did not find such an association. This could be due to methodological difference with the fore mentioned study. For this reason a need of future studies with large samples and the inclusion of different variables including both brain and hematology and control for psychosocial factors may contribute to clarification of this controversy.

In iron deficiency anemia children our study showed that low hemoglobin concentration predicted the mean score of attention problems and low IQ while mean corpuscular volume predicted the mean motor excess score. Many studies support the relationship between iron deficiency anemia and attention deficit or motor excess or restless leg syndrome.[37-39] However, the explanations of this relationship were different from one study to another. One of these studies[40] found an association between the intellectual and behavioral deficits of the iron-deficient children and the changes of some urinary catecholamine metabolite and suggested that the dependence of monoamine oxidase on adequate iron stores could be a contributing factor in these deficits. The relationship between iron deficiency and monoamines was supported by a recent studies on rats.[41,42] Significantly lower serum ferritin levels have been observed in children with attention deficit hyperactivity disorder than in controls,[37] the authors reported 84% of attention-deficit/hyperactivity disorder (ADHD) children had serum ferritin levels of <30 ng/mL, compared with 18% of controls ($P<.001$). Although we found significant lower level of serum ferritin in iron deficient children than in controls, regression analysis of all the hematological parameters as independent variables and scores of behavior and intelligence as dependent variables showed no predictive value of ferritin.

In a recent study,[43] iron supplementation (80 mg/day) appeared to improve ADHD symptoms in children with low serum ferritin levels but the authors of this study suggested a need for future investigations with larger controlled trials to confirm their findings.

Another study[44] demonstrated that iron deficiency with or without anemia could affect the social-emotional behavior of infants. The relationship of the attention and IQ to the hemoglobin concentration and the motor excess to the main corpuscular volume could be explained by the decrease oxygen binding capacity which resulted from anemia. This explanation does not exclude by any means the changes in serum ferritin in these changes and needs confirmation by future studies because most of the studies that studied the role of ferritin were done on infants and preschool children.

FIGURE 3.
Relationship between motor excess score and the mean corpuscular volume



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CONCLUSION

From the results of our study we can conclude that: the children with iron deficiency anemia are

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more prone to having low attention and being hyperactive while thalassemic children tend to be more prone conduct problems. IQ is low in both groups, but iron deficiency anemia children are more affected than thalassemic. The controversy about the factors contributing to behavioral problems still needs more work to be clarified. Our findings give some evidence that changes in some hematological parameters, particularly the hemoglobin concentration and mean corpuscular volume, could contribute to attention problems, motor behavior and IQ changes in iron deficiency anemia. The absence of any biological correlate to the mean score of RBPCL in the thalassemic group could give indirect support for the role of psychosocial factors in the emergence of behavioral problems in thalassemic children, although not excluding the role of other biological factors.

There is a correlation between medical illness and behavioral changes, this makes psychiatrists who deal with behavioral problems screen carefully for medical illness especially in children. This also opens the door for pediatricians and primary care physicians to be insightful for the behavior changes that their patients have due to the medical illness.

We have to acknowledge the limitations of our study which are mainly the small sample size and also the lack of multicultural comparisons to evaluate the behavioral norms and the degree of social support for this group of children. For this reason we recommend a large scale study that considers, in addition to the hematological, other biological parameter, the impact of differences in social support among different cultures in shaping these behavioral changes particularly in thalassemic children. ***CNS***

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