

Cognitive Abilities, Mood Changes and Adaptive Functioning in Children with β Thalassaemia

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ABSTRACT

Background: In Egypt, Thalassaemia is considered the most common genetically determined haemolytic disease. Its high prevalence causes a significant burden on health resources. Few studies of children with thalassaemia have shown a heightened risk of developmental and behavioral problems. However, results vary from mild behavioral problems to frank psychiatric disorders. **Objective:** This study addresses psychiatric problems among Thalassaemia patients. It is hypothesized that these patients will have a higher burden of mental health problems that will be reflected on adaptive functioning. A case-control study was conducted at the Thalassaemia clinic, Abu El-Reesh Children Hospital; Cairo University, One Hundred children with transfusion-dependent thalassaemia were included in the study group by consecutive sampling and compared to 100 normal children matched for age and sex and of similar socioeconomic standard. Age ranged between 5 and 15 years. Cases and controls were assessed by the WISC-III to measure cognitive and intellectual abilities, the CDI to measure depressive symptoms, and the Vineland Adaptive Functioning Scale to measure a broad range of adaptive functions. **Results:** Patients with thalassaemia showed a significantly worse performance on all tests. Apart from two subtests that are usually not affected by intellectual deterioration, all WISC-III subtests were significantly lower in Thalassaemia patients. They also showed as much as three times higher levels of depressive symptoms and their adaptive functioning is impaired in all domains assessed. **Conclusion:** Thalassaemia major exerts a dramatic influence on the mental health of affected children. The mental health problems are broad in range and severity. They are mostly due to the impact of a chronic illness on the daily life of children. However, a direct influence on brain functioning during development cannot be excluded. An assessment questionnaire should be integrated in the regular follow up clinical assessment of thalassaemia major patients for the early detection and management of psychological disturbance.

Key word: β Thalassaemia, Cognitive abilities, Mood changes, Adaptive Functioning, Egypt.

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INTRODUCTION

β -Thalassaemia major is a severe hematologic disorder characterized by a complete or partial absence of the beta chain of blood hemoglobin¹. Thalassaemia

is a chronic disease which places a tremendous psychosocial burden on the patient and the family². β -thalassaemia is endemic in all countries of the Arab world,

probably due to the presence of malaria in the region³. In Egypt, it is considered the most common genetically determined haemolytic disease⁴. The carrier rate varies from 6 to 10 %, gene frequency is 0.03. It was estimated that 1000 per 1.5 million live births per year are born with thalassaemia. Patient numbers are steadily increasing reaching more than 2000 in the year 2003 at the largest hematology center in Cairo University. Sixty percent of the patients are less than 10 years old, 30% 10-18 years old and 10% >18 years old⁵.

This high prevalence causes a significant burden on health resources⁶. Modern treatments have greatly increased the life expectancy of patients with thalassaemia. The need to ameliorate the associated psychosocial burden thus becomes even more important. The scarcity of data on the psychosocial life aspects of thalassaemia patients limits the implementation of proper intervention strategies⁷.

Thalassaemia is a haemolytic anemia that attains the status of a chronic disease through multisystem involvement. When the abnormality is heterozygous, synthesis of hemoglobin is only mildly affected. When the patient is homozygous, synthesis is grossly impaired and severe anemia results⁸.

Children with thalassaemia may be labeled because of changes in facial characteristics; they may not be able to be fully active like other children because of the persistent anemia and hypoxia. They are also candidates for repeated blood transfusion, and iron chelating therapy, with all the psychological and medical problems that may occur⁹. A few studies of children with thalassaemia have shown heightened risk of developmental and behavioral problems.

Results vary from mild behavioral problems to frank psychiatric disorders¹⁰.

This study addresses the psychiatric problems of this group of patients. It is hypothesized that they suffer from depression, problems in adaptation and limited intellectual abilities due to persistent hypoxia.

SUBJECTS AND METHOD

The study was conducted at the Thalassaemia Clinic in Abu El-Reesh Children Hospital; Cairo University.

One Hundred children with transfusion-dependent thalassaemia major were included in the study group by consecutive sampling. Age range was 5-15 years. Patients on regular blood transfusion with no history of other medical illness were included in the study. A written informed consent form described the study and its purposes. Consent was taken from the parents, mostly the mother. One hundred normal control subjects were also included in the study and matched with the study group for age and socioeconomic status and absence of medical illness.

All patients' medical conditions were checked, they were all maintained on HB level not less than 7g%. The protocol used in Abu El-Reesh hospital for managing cases of thalassaemia major, Includes regular blood transfusion every 3-4 weeks. All patients were on chelation therapy, usually with the iron binding agent, desferrioxamine, which is needed to prevent death from organ injury. Patients with thalassaemia intermedia are not usually involved in the regular transfusion program. The latter is a rather ill-defined subgroup of patients who have less severe hemolysis and the physician believes that they can

function without frequent blood transfusion or without transfusion at all. Twelve patients with thalassaemia intermedia who all required blood transfusion were included in the study.

Psychometric assessment:

All children in the patient and control groups were subjected to psychometric testing as follows:

*The Children's Depression Inventory*¹¹ (CDI) has been chosen because its items cover nearly all the criteria required by both the ICD 10 and DSM IV for diagnosing depressive disorders (major depressive disorders and dysthymia) in children. It is also easily administered and understood by the children¹². It is a 27 item scale, each consists of three statements. The child chooses the statement that best describes his /her state during the past two weeks. Statements are scored from 0-2 according to severity. The total score varies from 0 to 45. Half of the items are written such that the first statement represents the severest form of the symptoms while the third statement represents the opposite. The CDI has been judged to be readable at third grade level. For children with reading difficulties, the test items are read to the patient. In this study the items were read to all patients regardless of level of education. Cut Off scores provided by the scale were used. These differ according to age and gender¹³⁻¹⁴.

*Vineland Adaptive Behavior Scale*¹⁵: The Vineland-II scale is designed to assess adaptive behavior of individuals from birth to age 90. Adaptive functioning implies personal and social sufficiency. The Vineland scale can be used when an assessment of an individual's daily

functioning is required. It covers the domains of communication (67 items), daily living skills (92 items), socialization, (66 items) and motor skills (36 items). Motor skills are particularly used for children below 6 years. The scale can be used in a variety of clinical, educational, and research settings. The parent/caregiver rating form which is used in this study is presented in checklist format and was translated to Arabic (16). The Vineland scale uses a semi-structured interview technique, and can be administered by a trained interviewer to a parent or caregiver. The items that guide the interviewer on the survey form are presented in developmental sequence. The interviewer begins with items that correspond to mental or chronological age and establishes a basal and ceiling score before concluding the interview. Each item is scored to reflect whether the individual performs the activity described: 2 = yes, the behavior is usually performed; 1=sometimes or partially; and 0=no, the behavior is never performed. Several types of age-based norms are available for adaptive behavior Composite (total score) and each domain. Standard scores (mean=100, SD=15) are provided and bands of error for three levels of confidence (85%, 90%, and 95%) are available for the standard scores. National percentile ranks are also provided. Broad ranges of standard scores may be described using the adaptive levels of high, moderately high, adequate, moderately low and low. Age equivalents are offered for each domain.

Wechsler Intelligence Scale for Children 3rd edition (WISC-III-R): This is the most widely used test for intelligence for school-age children and adolescents¹⁷. The Arabic version has been prepared and yields a verbal, performance, and a combined full-

scale IQ¹⁸. The verbal subtests consist of vocabulary, information, arithmetic; similarities, comprehension and digit span (supplements) categories. The performance subtests differ from the adult version of the scale and include block design, picture completion, picture arrangement, object assembly, coding, mazes (supplemental) and symbol search (supplemental) the scores of the supplemental categories are not included in the computation of IQ.

The multiple breakdowns of the performance and verbal subscales of the WISC allow greater flexibility in identifying specific areas of deficit and scatter in intellectual abilities. Because a large part of intellectual testing measures abilities used in academic settings; the breakdown of the WISC-III-R can also be helpful in pointing out abilities in which a child is weak and may benefit from remedial education¹⁹.

Statistical analysis:

The data were coded, and entered on an IBM compatible computer using the statistical package for the Social Sciences SPSS version 16.

Results are presented as mean \pm SD and as percentages for nominal data. The significant differences in means for CDI, WISC III-R and Vineland Adaptive subsets between patients and controls were analyzed by unpaired student t-test.

Table (1) shows that both the patient and control groups are matched as regards age and sex. The mean age in cases is 9.5 ± 2.8 years and 9.8 ± 2.7 years in the control group. Both groups are from lower socioeconomic strata of population.

There is a statistically significant difference on levels of education between the patient

and control group; 55% of cases did not attend school compared to 12% of the control group, and 36% of the patient group are in primary education, compared to 70% of the control group.

Fig. (1) and tables (3 and 4) show the results of the WISC III R of both cases and controls. Mean scores of both groups fall in the borderline intelligence level. The mean score for total intelligence in cases was 74.1 compared to 81.5 for the control group. The mean score for performance intelligence is 79.9 in controls compared to 73.8 in cases. Mean verbal intelligence for the control group is 85.7 compared to 78.2 for cases with $p=0.001$. There was a statistically significant difference on raw scores of all the subscales of verbal intelligence except for vocabulary. Performance intelligence also showed statistically significant difference in all the subscales except for picture completion.

Fig. (2) and table (4) show that the mean score of Child Depression Inventory (CDI) in the study group was 24.1 ± 7.57 ; 11% had minimal depressive symptoms, 32% had mild depressive symptoms, 35% had moderate depressive symptoms, and 22% had severe depressive symptoms. On the other hand, the mean score of the CDI in the control group was 8.22 ± 3.96 ; 70% show no depressive symptoms, 21% minimal depressive symptoms, 9% had minimal depressive symptoms and non show moderate or severe depressive symptoms. The difference between both groups is highly significant.

The Vineland Adaptive behavior scale results within the two studied groups demonstrate that there is no statistically significant difference between the two groups in the adaptive behavior composite scores (table 5). Both of them were

considered moderately low. However for the cases, the standard deviation is very wide reflecting a wide score scatter.

Results of the subscales show a statistically significant difference in the domains of communication skills, daily activity skills and socialization skills. The scores of the control group were within moderately low degrees for communication skills, daily activity skills and socialization skills. The age equivalence for the communication skills is 8 years and one month, for the socialization skills is 8 years and 3 month and for the socialization skills it is equivalent to 6 years and 11 months.

The case scores in the subscales are considered within the low performance range. The age equivalence for both communication skills and daily activity skills is 7 years and 7 month, while for socialization skills; the age equivalence is 5 years and 9 month level of adaptive functioning.

RESULTS

Fig. 1 shows that the differences in overall verbal, performance, and total intelligence levels are highly significant; Verbal intelligence, $t=5.24$ $p<0.001$; Performance intelligence $t=4.66$, $P<0.001$, total intelligence $t=5.24$, $P<0.001$.

The difference in depressive manifestations between thalassaemia children and controls according to the Children Depression Inventory is highly significant (fig 2). The mean total score for depression in patients is almost three times that of controls ($t=18.66$, $P<0.001$, CI 14.3–17.6)

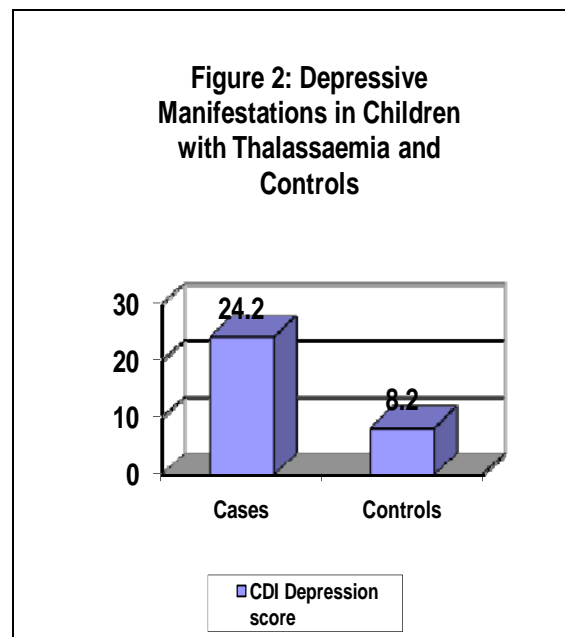
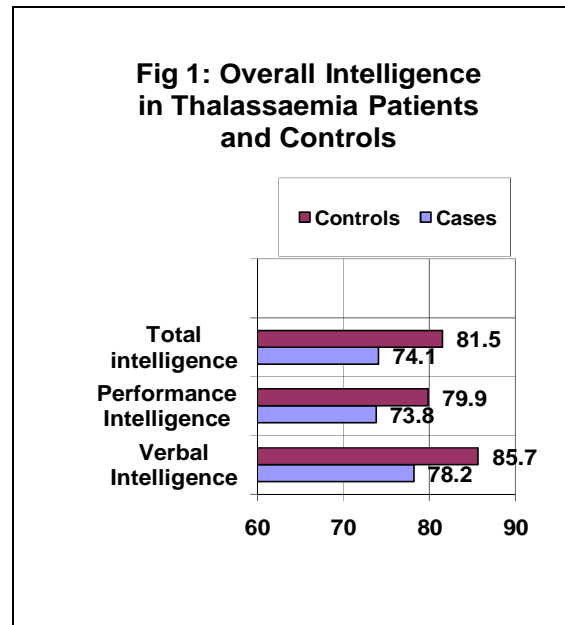


Table 1: Demographic Characteristics of Cases and Controls

		Cases		Controls		Test	P
Age	(mean + SD)	9.5 ± 2.8		9.8 ± 2.7		t= .765	0.44
Sex	Male	54/100	54%	53/100	53%	X ² = .02	0.88
	Female	46/100	46%	47/100	47%		
Education	Primary	36/100	36%	70/100	70%	44.9	0.0001
	Preparatory	9/100	9%	12/100	12%		
	Nursery	0/100	0%	6/100	6%		
	No schooling	55/100	55%	12/100	12%		

Table (2) Verbal Intelligence scores in Thalassaemia Patients and Controls

WISC subscale	Cases	Controls	t =	P
Comprehension	7.5 ± 2.7	8.5 ± 1.7	-3.01	<.003
Arithmetic	4.9 ± 2.5	7.2 ± 1.7	-7.47	<0.001
Similarities	6.2 ± 1.8	7.4 ± 1.4	-5.3	<0.001
Vocabulary	9.7 ± 1.8	9.7 ± 1.8	-0.39	< 0.97
Digit span	4.5 ± 1.7	5.9 ± 1.4	-6.26	<0.001
Total Verbal	32.7 ± 7.4	38.3 ± 7.7	-5.24	<0.001

Table (3): Performance Intelligence in Thalassaemia Patients and Controls

WISC Subscale	Cases	Controls	t =	P<
Picture Completion	7.9 ± 2.5	7.8 ± 1.7	.46	<0.64
Picture Arrangement	5.6 ± 1.8	6.5 ± 1.5	-3.9	<0.001
Block Design	5.1 ± 2.1	6.5 ± 1.4	-5.57	<0.001
Object Assembly	5.2 ± 1.6	6.6 ± 1.3	-6.88	<0.001
Coding	7.8 ± 1.9	8.4 ± 1.8	-2.31	<0.022
Total Performance	31.6 ± 6.6	35.9 ± 6.4	-4.66	<0.001

Table (4): CDI Scores in Thalassaemia and control according to level of depression

CDI Scores		Cases	Controls	Total
No depression	Count	0	70	70
	% within group	0%	70%	70%
Minimal	Count	11	21	32
	% within group	11%	21%	16 %
Mild	Count	32	9	41
	% within group	32%	9%	20.5%
Moderate	Count	35	0	35
	% within group	35%	0%	17.5%
Severe	Count	22	0	22
	% within group	22%	0%	11%
Total	Count	100	100	100
	% within group	100%	100%	100%

Pearson Chi square = 143.027 p>0.001

Table (5): Vineland Adaptive Behavior Scale Scores in Thalassaemia and normal controls

	Cases	Controls	T	P<
Communication	64.7 ± 24.8	70.9 ± 18.8	-2.00	<0.047
Daily activity skills	66.6 ± 23.2	72.9 ± 19.7	-2.09	<0.039
Socialization	64.5 ± 18.4	73.1 ± 19.8	-3.17	<0.003
Adaptive	75.8 ± 73.8	72.3 ± 19.2	0.46	<0.64

DISCUSSION

This study demonstrated significant and large differences between children with Thalassaemia and normal children on all aspects of mental health studied. Thalassaemic children have 3 times as much depressive manifestation, perform significantly poorly on measures of cognitive and intellectual functioning, and are more poorly adjusted in the social, occupational, and communication domains.

One important caveat of the study is that all thalassaemic children included were transfusion dependent which indicates a significant burden from physical illness. The chronic need for transfusion may explain some of the differences in depression scores and impaired adaptive functioning between cases and controls, but cannot in itself explain the cognitive and intellectual deficits.

Approaches to identify factors and processes associated with variability in adjustment to chronic illnesses include three broad parameters: illness parameters, including type, duration and severity; child parameters, including age, gender and coping methods and socio ecological parameters including socio-economic status., parental adjustment and family functioning²⁰. Comprehensive studies should be directed to cover all the domains

and correlate them together. This study addresses the child parameters and the impact of illness on cognitive, emotional and adaptive abilities.

The selected sample and controls are matched as regards age, and sex and both groups have a comparable social standard. There is however, a statistically significant difference as regards education between cases and the control group with almost 50% of patients not attending school. In this study, questions to explain reasons for irregularity in school were not included. Similarly in the UK, among 27 thalassaemic subjects, 90% had to take time off from school because of their medical condition²¹. Also, thalassaemia affected the scholastic performance of 70% of Indian adolescents adversely⁷. This includes that they had to take 1-3 days off from school every month to get their regular red cell transfusions, and complained that their academic performance was average or less because of their disease and its related problems. Over two thirds of adolescents in the Indian study were unable to engage in outdoor play at the same level as their peers, because of physical weakness related to their illness.

Such findings may be considered reasons for irregularity in school, but do not explain

lack of school entrance and having no education detected in this study. Egyptian parenting styles of over protectiveness to children especially when ill could be a cultural explanation of low education levels among cases. The low-moderate socio economic standard may also affect the value of education and adherence of the child to the education system in the whole sample. More studies are therefore needed among thalassaemic children to find out whether social class is the more basic influence on the marked psychiatric and social disabilities detected in this study. Economic under privilege may be a strong reason for excluding children from school. Further research is also needed to explore parenting styles and related dynamics between thalassaemic children and their parents.

Statistically significant differences were found between cases and the control group as regards total intelligence and its verbal and performance components. Results indicate that the mean IQ of controls is within the low average range, while that of cases is within the borderline range. The scatter of the performance through different subscales of intellectual abilities shows near uniform poor performance among the cases except for vocabulary and picture completion. The latter are subtests which are known to be less liable to deterioration with illness. It is therefore proposed that the lower intellectual performance is at least partly a consequence of thalassaemia and is not an innate difference between patients and controls. The disease process could influence indirectly intellectual performance through diminished opportunities for education and stimulation. A direct effect on brain functioning cannot be however excluded⁷.

In another study of 138 patients with thalassaemia, the intelligence quotient of all the thalassaemic children was within normal range²². However, the sample in this study may differ from that of the Logitihis et al. study in being of a more disabled patient group²².

The Vineland Adaptive behavior scale measures the effects of the relation between intellectual performance, and social context of the individual. This is the third dimension of Sternberg's Triarchic Theory of Intelligence¹⁶. Sternberg proposes that there are three types of intelligence: analytic, creative and practical intelligence means. Vineland adaptive behavior scale concentrate on the practical intelligence, which is commonly seen in those who have low intellectual abilities, but quickly grasps real- life problems. Practical intelligence includes the ability to get out of trouble and a knack for getting along with people. Sternberg describes practical intelligence as all of the important information about getting along the world that is not taught in school²³. Results showed no statistical difference between normal controls and cases in total score. However the wide standard deviation of cases limits the usefulness of this finding and indicates that it might be more valid to consider the results of the subscales. One of the important aspects of the Vineland scale is what the child actually does, not what he/she is able to do. In this sample it is evident that there are difficulties in communication, social interaction and daily activity in children with thalassaemia. This means that these children are low even in the practical aspects of intelligence which adds more to their handicap and difficulties to cope with different life situations.

The mean score of depressive manifestations in the patient group is three times that of the control group. No thalassaemia patient was found to be free from depressive manifestation compared to 70% of controls. At the opposite end of the spectrum, 22% of cases suffer from severe depressive manifestations (which can be diagnosed as major depression) and 35% of the cases suffered from moderate depressive symptoms, while the control group has neither severe nor moderate depressive manifestations. Dysphoric moods and low self-esteem were described in the majority of thalassaemic children²⁴. Woo et al. reported that 2/3rd of the patients were worried about pain, death and the unknown in a sample of 22 children with thalassaemia²⁵. This conclusion was also supported by Khurana et al. who stated that chronic illnesses like thalassaemia bring along feelings of being different and inferior with consequent loss of self-esteem and increased dependence⁷. Facial characteristics in thalassaemia occur as a consequence of the expansion of bones particularly the skull and jaw bones. Anemia and iron overload in these patients often leads to short stature and delayed puberty. They are likely to suffer from reduced self-esteem, feelings of difference, poor self-image, being dependent and anxiety over issues such as pain and death.

Thalassaemia challenges the individual at the physical, emotional, cognitive levels and disrupts the quality of life⁹. Its frequent and complex treatment might also lead to financial burden for the individual and his/her family which reduces further the adaptive and coping ability of affected children.

Although the results of the study support the hypothesis behind, several notes of

caution are important. First, the design of the study does not address the variables measured in the pediatric child report. It does not correlate with degree of handicap and with actual multisystem affection, number of blood transfusions, and visits to hospital among other effects of a chronic illness. Correlation between severity of the illness and the degree of intellectual impairment, and adaptive function should be addressed and studied carefully. Also the biological effects of the disease process on brain development, and its relation to the abnormalities detected in this study have not been addressed by the study design. Second, the sample may not be representative of the broader population of children with thalassaemia β especially those with higher socioeconomic standards which might reduce the effects of the disease process on educational, cognitive, psychological and adaptive adjustment. Third, the used instruments precluded assessment of other mental health aspects and behavioral presentations that might be present in this age group of patients such as aggression, conduct disorder, and attention deficit hyperactivity disorders.

It can be concluded that the high prevalence thalassaemia β and the fact that it hinders psychosocial adjustment in affected children markedly is alarming. This dictates the importance of integrating a multidimensional psychosocial battery in the regular follow up and clinical assessment of thalassaemia major patients in order to detect and manage any psychological disturbances in the early stages. Adopting the biopsychosocial approach in managing such lifelong medical conditions may add considerably to compliance and quality of life of these patients and their families. It also may help

in reducing the cognitive handicap and hence the social and economic burden.

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