Association of Pro-inflammatory Cytokines with the Psychological Problems in Children with Sickle Cell Disease

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Abstract

Background: Sickle cell disease (SCD) is a genetic disorder Characterized by chronic hemolysis accompanied by several complications which significantly affect the outcome. It occurs at variable frequencies in Middle Eastern Arab countries. Cytokines one of the most important factors plays a central role in pathogenesis of the disease and its complications. Children with SCD continue to face many challenges of living with a chronic condition that requires lifelong medical management that may place them at risk of psychiatric symptoms and disorders Psychological disorders are one of the most important complications faced by SCD and depression is the commonest one. IL- 6 one of pro- inflammatory cytokines related to certain psychiatric conditions like depression.

Aim: This study aimed to evaluate the association of IL- 6 with the behavioural disturbances in Children with Sickle Cell Disease (SCD) patients in steady state.

Methods: This study comprised 62 children diagnosed as having (SCD) in steady state. Another 62 healthy children served as control group. They were screened for their anthropometric measurements (height, weight, Body mass index (BMI) for- age Z- score), clinical parameters and laboratory assessment (serum IL- 6, LDH, plasma ferritin, reticulocytic count, CBC), psychological assessment using the Pediatric Symptom Checklist- 17 (PSCL- 17).

Results: The psychological parameters showed a significant higher 3 subscale of the test in patients than control, Positive correlation between IL6 and 3 subscale of the test. SCD patients taking hydroxyurea were not at increased risk of psychiatric disorders compared with patients not taking hydroxyurea.

Conclusion: It was concluded from this study that Children with SCD had several psychological problems which related to increase levels of pro- inflammatory cytokines (IL- 6).

Key Words: Sickle Cell Disease- Pro- inflammatory and Anti- inflammatory Cytokines- psychological problems

مدى ارتباط مستوى السيتوكينات الموالية للالتهاب بالحالة النفسية لاطفال مرضى فقر الدم المنجلي

مقدمة: ان مرض فقر الدم المنجلى يعتبرمن الامراض الوراثية ويتميز بالتكسير المزمن لخلايا الدم والمصاحب بمشاكل عديدة التى لها تأثير سئ على المدى البعيد. التوزيع الجينى لمرض فقر الدم المنجلى فى البلاد العربية فى الشرق الاوسط مختلفا. تلعب السيتوكينات فى هذا المرض دور محورى فى الية عمل المرض ومضاعفاته. ان مرضى فقر الدم المنجلى يتعرضون لعدة مخاطر ومن اهمها الاضطرابات النفسية نتيجة التعايش مع مرض مزمن يتطلب الرعاية الطبية مدى الحياة. الانترلوكين– ٦ واحد من السيتوكينات الموالية للالتهاب وثبت أنهم لهم صلة بالاضطرابات النفسية مثل الاكتئاب.

الهدف: ان هذة الدراسة تهدف الى اثبات انة توجد علاقة بين الانترلوكين ٦ والحالة السلوكية لاطفال مرض فقر الدم المنجلى فى الحالة المستقرة.

طرقة اجراء البحث: ضمت الدراسة ٦٢ طفل من المرضى الذين ثبت انهم يعانون من مرض فقر الدم المنجلى وهم فى الحالة المستقرة و٦٢ طفل من الأصحاء كمجموعة ضابطة من نفس العمر والجنس والحالة الاجتماعية والاقتصادية. وخضع كل طفل الى فحص اكلينيكى شامل وقياس القياسات الانثروبومترية واخذ عينة دم لعمل التحاليل الاتية: الانترلوكين٦، LDH، فيريتين البلازما، عدد الخلايا الشبكية، صورة دم كاملة. وتم عمل التقييم النفسى باستخدام قائمة فحص الاعراض النفسية للاطفال ١٧ (PSC- 17).

النتائج: اظهرت النتائج للقياسات النفسية ارتفاع معدل مستويات الاختبارالنفسي: مستوى فرعى داخلى، مستوى فرعى خارجي، مستوى فرعى انتباهى عند المقارنة بين الاطفال المرضى والاطفال الاصحاء. وجود علاقة ايجابية بين الانترلوكين٦ ومستوى الاختبار الفرعى الداخلى والخارجى والانتباهي. بالاضافة الى ان المرضى الذين يأخذون دواء الهيدروكسى يوريا ليسوا عرضة للاضطرابات النفسية بالمقارنة بالمرضى الذين لا يأخذون هذا الدواء.

الخلاصة: نستخلص من دراستنا ان الاطفال المصابين بمرض فقر الدم المنجلى يعانون من مشاكل نفسية والتى لها علاقة بزيادة مستوى السيتوكينات الموالية للالتهاب الانترلوكين ٦.

Introduction:

Sickle cell disease (SCD) is a genetically inherited blood disorder as Red blood cells become misshapen and sticky, which restricts their flow through blood vessels and deprives organs of oxygen (Ciribassi and Patil, 2016).

The sickle cell (HbS) gene occurs at a variable frequency in the Middle Eastern Arab countries, (El- Hazmi et.al., 2011). In Egypt, along the Nile Valley, the HbS gene is almost nonexistent, but in the western desert near the Libyan border variable rates of 0.38 percent in the coastal areas to 9.0 per cent in the New Valley oases have been reported. HbS carrier rates vary from 9 to 22 percent in some regions (El- Beshlawy and Youssry, 2009).

Cytokines in SCD patients play a central role in the pathogenesis of the disease and its complications. The altered balance of proinflammatory and anti- inflammatory cytokines was believed to play an important role in the pathogenesis of painful crisis (Makis et.al., 2000).

Evidence of altered cytokine profile during vaso- occlusive crisis (VOCs) and the stimulation of an ongoing inflammatory response in SCD patients come from several studies (Duits et.al., 1998; Graido- Gonzalez et.al., 1998; Pathare et.al., 2004; Musa et.al., 2010).

Children with SCD continue to face many challenges of living with a chronic condition that requires lifelong medical management that may place them at risk of psychiatric symptoms and disorders (Benton et.al., 2011). Depression is a common co- occurring disorder in persons with sickle- cell disease (SCD) (Katz and Schatz, 2014).

Cytokines are considered a group of biological factors that may play an important role in co- occurring stress, SCD, and depression. Enhanced production of proinflammatory cytokines is supposed to be associated with the pathogenesis of depression (Katz and Schatz, 2014).

IL- 6 is involved in the regulation of several physiological processes (Levandovski et.al., 2013). Recent research shows that IL- 6 is increased in relation to psychosocial stressors and in certain psychiatric conditions like depression (Ai et.al., 2011).

Hypothesis:

This study hypothesizes that there is positive association between IL6 with the Behavioral disturbances in Children with Sickle Cell Disease.

Aim:

To evaluate the association of IL- 6 with the behavioural disturbances in Children with Sickle Cell Disease (SCD) patients in steady state.

Subjects:

The study population was including 62 patients that were confirmed sickle cell disease patients in steady state attending routine follow- up visits at the outpatient clinic of haematology, New Children's Hospital, Cairo University. They were 39 Male, 23 Female. These patients were compared with comparable number of apparently healthy children with matching age& sex and in the same socioeconomic state (as control). They were recruited from children follow up clinic, New Children's Hospital, Cairo University.

1. Inclusion Criteria:
   a. Males and females aged from (4- 11) years
   b. Established Diagnosis Of Sca.
   c. Steady State Disease.
2. Exclusion Criteria:
   a. Acute febrile illness within 72 hours prior to enrollment
   b. Acute vaso- occlusive event within 3 months prior to enrollment
   c. A Serious Concurrent Illness.

Ethical Aspects:

- Ethical approval from the ethical committees of national research center and Institute of Postgraduate Childhood Studies were taken.
- Care givers of children were informed of the nature and aims of the study, plain simple explanation of the procedures of the study was introduced.
- Written informed consent was obtained from care givers to in roll their children in the study.
- Assent was taken from children over 8 years and adolescents.

Methods:

All patients were subjected to:

1. Medical History Assessment: Thorough history taking with special stress on:
   a. Consanguinity or similar conditions in the family.
   b. The frequency and amount of transfusion therapy.
   c. The type of chelation therapy received.
   d. Drugs including hydroxyurea and antioxidants
   e. Whether or not splenectomy was performed.

   Medical history assessment included both patient interview and review of the hematology records of the hematology clinic.
2. Physical Examination: Thorough clinical examination with stress on: measuring the weight and height, abdominal and cardiac examination.
   a. Investigations:
      - Laboratory: Blood samples were taken from the children attending the outpatient clinic of hematology. New Children's hospital Cairo University.
        1. Complete blood picture with blood indices by Coulter Counter.
        2. Reticulocytic Count.
        3. Plasma ferritin was estimated by ELISA technique.
        4. Plasma lactate dehydrogenese (LDH) was assayed by spectrophotometric procudure.
        5. IL- 6 will be measured by commercially available ELISA kits in SCD patients in steady state compared with nonanemic age- and sex- matched normal controls.
      - Psychological Assesment: All studied cases and controls were subjected to psychological assessment using the Pediatric Symptom Checklist- 17 (PSCL- 17) parents and youth form.

The Pediatric Symptom Checklist- 17 (PSC-17) is a psychosocial screen designed to facilitate the recognition of cognitive, emotional and

behavioral problems, so that appropriate interventions can be initiated as early as possible.

The PSC-17 consists of 17 items that are rated as (Never, Sometimes or Often) present and scored (0, 1 and 2) respectively. The total score is calculated by adding together the score for each of the 17 items. Items that are left blank are simply ignored (i.e., score equals 0). If four or more items are left blank, the questionnaire is considered invalid. A PSC-17 score of 15 or higher suggests the presence of significant behavioral or emotional problems. It consists of 3 subscales: internalizing subscale, where cutoff point is 5, externalizing subscale, its cutoff point is 7 and attention subscale, its cutoff point is 7.

Results:

The study was conducted on 62 patients age range (4- 11) years and age and sex matched with controls.

Table (1) Comparison of psychiatric assessment data in case and control group.

	Group	Mean	Std. Deviation	T- Test	P
Internalizing Symptoms	Patients	5.15	2.04	9.409	0.000*
	Control	1.58	2.18		
Externalizing Symptoms	Patients	5.02	1.86	5.818	0.000*
	Control	2.48	2.88		
Attention Symptoms	Patients	5.50	2.51	7.080	0.000*
	Control	2.08	2.86		
Pediatric Symptoms Check List	Patients	15.66	5.35	10.522	0.000*
	Control	6.15	4.70		

P< 0.05 is significant

In table (1) The mean internalizing symptoms, externalizing symptoms, attention symptoms, pediatric symptoms check list of the patients were significantly higher than that of control.

Table (2) Association between Hydroxyurea intake and internalizing symptoms

			Internalizing Catigory		Total
			At Cut Off	Under Cut Off	
Hydroxyurea Intake	Yes	Count	29	15	44
		% Within Hydroxyurea Intake	65.9%	34.1%	100.0%
	No	Count	11	7	18
		% Within Hydroxyurea Intake	61.1%	38.9%	100.0%

OR= 1.23 95% CI0.396- 3.825 p= 0.720, P <0.05 is significant

Table (3) Association between Hydroxyurea intake and externalizing symptoms

			Externalizing Catigory		Total
			At Cut Off	Under Cut Off	
Hydroxyurea Intake	Yes	Count	12	32	44
		% Within Hydroxyurea Intake	27.3%	72.7%	100.0%
	No	Count	2	16	18
		% Within Hydroxyurea Intake	11.1%	88.9%	100.0%

OR= 3.000 95% CI0.598- 15.050 p= 0.182, P <0.05 is significant

Table (4) Association between Hydroxyurea intake and attention deficit symptoms

			Attention Catigory		Total
			At Cut Off	Under Cut Off	
Hydroxyurea Intake	Yes	Count	16	28	44
		% Within Hydroxyurea Intake	36.4%	63.6%	100.0%
	No	Count	6	12	18
		% Within Hydroxyurea Intake	33.3%	66.7%	100.0%

OR= 1.143 95% CI0.360- 3.633 p= 0.821, P <0.05 is significant

Table (5) Association between Hydroxyurea intake and pediatric symptoms check list

			Pediatric Symptoms Check List Catigory		Total
			At Cut Off	Under Cut Off	
Hydroxyurea Intake	Yes	Count	27	17	44
		%Within Hydroxyurea Intake	61.4%	38.6%	100.0%
	No	Count	9	9	18
		%Within Hydroxyurea Intake	50.0%	50.0%	100.0%

OR= 1.588 95% CI0.526- 4.797 p= 0.412, P <0.05 is significant

In tables from (2- 5) SCD patients taking hydroxyurea were not at increased risk of psychiatric disorders compared with patients not taking hydroxyurea (p >0.05).

Table (6) Correlations of IL6 with psychiatric assessment data in patients group:

	IL6	
	r	p
Internalizing Symptoms	0.726**	0.000*
Externalizing Symptoms	0.511**	0.000*
Attention Symptoms	0.512**	0.000*
Pediatric symptoms check list With psychiatric problems	0.695**	0.000*

* p <0.05 is statistically significant

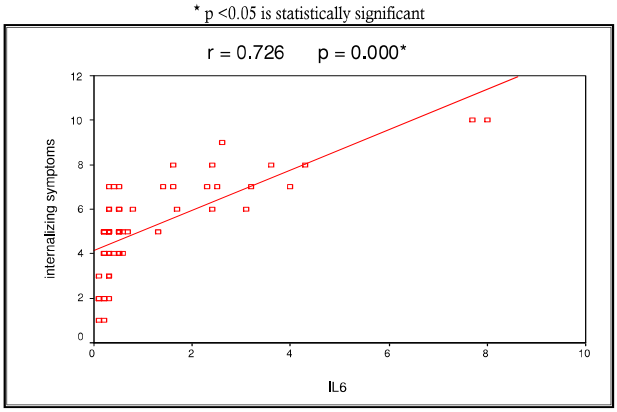

Figure (1) Correlation between IL 6 and internalizing symptoms in patients group

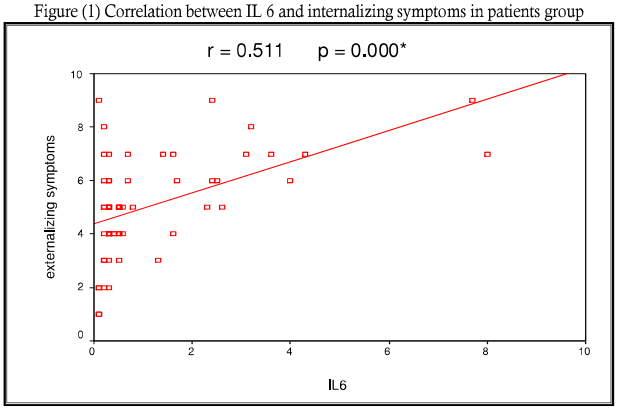

Figure (2) Correlation between IL 6 and externalizing symptoms in patients group

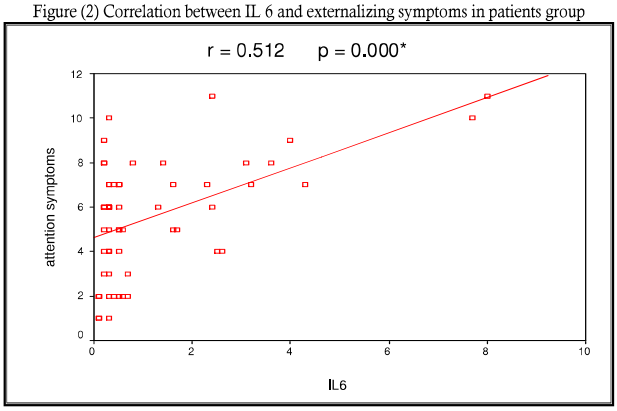

Figure (3) Correlation between IL 6 and attention symptoms in patients group

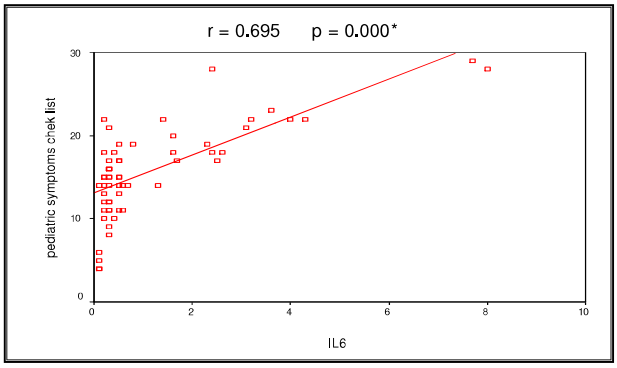

Figure (4) Correlation between IL 6 pediatric symptoms check list in patients group

Table (6) and Figures (1- 4) showed positive correlations between IL6 and internalizing symptoms, externalizing symptoms, attention symptoms pediatric symptoms check list with psychiatric problems.

Discussion:

Our patients have psychological problems when applying pediatric symptoms check list. Internalizing symptoms, externalizing symptoms, attention symptoms, pediatric symptoms check list were significantly higher than that of control. This was in agreement with Hasan et.al. (2003) who found that the prevalence of depression is higher in sickle cell patients than healthy peers. Also Belgrave and Molock (2003) in a study of 46 adult patients with sickle cell disease found that 56.5% of the sample was identified as being mildly to severely depressed.

Our SCD patients taking hydroxyurea were not at increased risk of psychiatric disorders compared with patients not taking hydroxyurea ($p > 0.05$). But Hasan et.al. (2003) observed that Hydroxyurea users were more likely to be depressed than those patients who didn't use hydroxyurea.

We found significant positive correlations between IL6 and internalizing symptoms, externalizing symptoms, attention symptoms pediatric symptoms check list with psychiatric problems. One meta-analysis reported significantly higher concentrations of TNF- a and IL- 6 in depressed patients (Dowlati et.al., 2010). It has been suggested that the pro- inflammatory cytokines IL- 6 and TNF- a are involved in the stimulation of corticotropin- releasing hormone activating the HPA axis and increasing the cortisol levels (Cowen, 2002). Dysregulation of the HPA axis is an important finding associated with depressive behavior (Dantzer, O'Connor, 2008). Another work (Howren et.al., 2009) determined that CRP, IL- 6, IL- 1, and soluble IL- 1 receptor levels are increased in depressed patients. On the other hand, other works suggest that the inhibition of anti- inflammatory cytokines promotes an increase in intensity and duration in sickness behavior (Dantzer, O'Connor, 2008).

Conclusion:

It was concluded from this study that Children with SCD had several psychological problems which related to increase levels of pro-inflammatory cytokines (IL- 6).

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