

Psychiatric morbidity in patients with rheumatoid juvenile arthritis: a SPECT study

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Introduction

Children with chronic illness have increased rates of mental health problems and psychological difficulties. Juvenile rheumatoid arthritis (JRA) is one of the most common rheumatic diseases of children and is considered a major cause of chronic disability in children. Thirty-eight percent of patients with JRA showed some difficulties in mental flexibility.

Aim of this study

To detect psychiatric morbidity and cognitive deficit in a sample of children and adolescents with JRA, and to attempt to correlate the psychiatric and cognitive findings with concurrent cerebral perfusion abnormalities using the cerebral single photon emission computed tomography neuroimaging technique.

Method

Thirty children and adolescents with JRA included in this study were recruited from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. These patients were subjected to full physical and psychiatric clinical interview, along with thirty healthy children and adolescents as the control group with matched age and sex. Patients and control groups were assessed using General Health Questionnaire, Wechsler Intelligence Scale, Revised Behavioral Problem Checklist, Mini kid test, Benton Visual Retention Test, and single photon emission computed tomographic imaging.

Results

Significant difference in cerebral perfusion was observed in patients compared with the control group. Behavioral and cognitive function showed significant difference in patients compared with the control group. Patients with depression showed significant perfusion differences compared with the control group, as well as the anxiety group. Therapy duration and dose showed significant difference in different brain areas.

Conclusion

Patients with JRA experience psychiatric morbidity as well as behavioral and cognitive dysfunction. The patterns of cerebral perfusion deficit are similar to those seen in depression, anxiety, and cognitive disabilities of patients.

Keywords:

juvenile arthritis, psychiatric morbidity, single photon emission computed tomography

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Introduction

Juvenile rheumatoid arthritis (JRA) is one of the most common rheumatic diseases of children and is considered a major cause of chronic disability in children; it is characterized by an idiopathic synovitis of the joints associated with soft-tissue swelling and effusion [1]. Early epidemiologic studies showed that the prevalence of JRA ranges from 0.16 to 1.10/1000 and the incidence ranges from 0 to 9.2/100 1000 in the USA [2]. In Egypt, incidence of JRA is 9.3 cases per 100 1000 per year [3].

Oligoarthritis represents the most common onset type of juvenile idiopathic arthritis in both Europe and North America, accounting for 50–75% of all cases with a meta-analysis producing an overall 58% estimate within population-based studies [4].

Although systemic onset JRA accounts for only approximately 20% of most reported series, children with systemic onset JRA are often the most difficult to treat. Many children have marked physical and emotional disability as a result of both disease and treatment-related morbidities [5].

Children with chronic illness have increased rates of mental health problems and psychological difficulties [6]. There is a decline in social and physical activities. Psychological factors may play a more active role in debilitating pediatric patients with JRA [7]. The long duration of illness is often associated with higher proportion of cases with psychiatric disorders. The diagnoses in decreasing order are depressive disorder 15%, somatoform disorder 12.5%, adjustment disorder 5%,

and mixed anxiety and depression disorder 2.5% [8]. The strongest predictors of depression were high tension and low self-esteem, fatigue, passive coping, pain, and physical disability [9].

Previous research [10] detected some difficulties in mental flexibility in 38% of patients with JRA. These poor performances are related to hypoperfusion of the frontal and parietal lobes as detected by brain single photon emission computed tomography.

The aim of this study was to detect psychiatric morbidity and cognitive deficit in a sample of children and adolescents with JRA recruited from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. The study also aimed to attempt to correlate the psychiatric and cognitive findings with concurrent cerebral perfusion abnormalities using the cerebral single photon emission computed tomography neuroimaging technique.

Method

Patient enrollment

Thirty children and adolescents with JRA were included in the study. These patients were recruited from the Pediatric Allergy and Immunology Unit, Children's Hospital, Ain Shams University. The diagnosis of JRA was based on clinical, laboratory, and radiological findings. These patients were subjected to full physical and psychiatric clinical interview with documentation of type of arthritis, duration, and severity of the disease. Patients of both sexes enrolled in the study were aged between 8 and 16 years, and all cases had disease duration of more than 6 months to ensure chronic disease. In addition, 30 healthy children and adolescents with matched age and sex to patients with JRA were included in the study to serve as a control group. Written informed consent was obtained from parents or care givers of both groups before enrollment in the study.

Patients and control groups were assessed using the following tests:

- (1) General Health Questionnaire: this was developed as a first screening instrument for psychiatric illness to identify potential cases [11]. The version used in this study was the Arabic version of the short 28-item scale [12].
- (2) Wechsler Intelligence Scale: this is the most commonly used test for children to assess intelligence quotient [13].
- (3) Revised Behavioral Problem Checklist: this is a family self-rated instrument that surveys a broad range of difficulties encountered in children from preschool age through adolescence [14].
- (4) Mini kid Test: this is a clinical psychiatric interview for children to detect any type of psychiatric morbidity, developed jointly for *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition and *International Statistical Classification of Diseases and*

Related Health Problems, 10th revision psychiatric disorders [15].

- (5) Benton Visual Retention Test: this is used for assessing visual perception, visual memory, and visuo-constructive abilities [16].
- (6) Single photon emission computed tomographic imaging: a dose of technetium-99m-labeled-hexamethyl propylene amine oxime is calculated according to body weight by the equation $\text{body weight} \times \text{adult dose (20 mCi)}$ and injected intravenously. A gamma camera single head was used to evaluate perfusion pattern of the brain [17].

Data obtained were tabulated and processed in a personal computer. All statistical analyses were carried out using Statistical Package of Social Science version 10 (Chicago, Illinois, USA). Independent student's *t*-test was used to evaluate the statistical differences in regional cerebral blood flow between patients and controls. We used Pearson's correlation coefficient for the bivariate correlation procedure.

Results

Demographic data

In this study, the patients' age ranged from 8 to 16 years, whereas that of the control group was from 8 to 15.8 years, thereby showing no significant difference between both groups. Of patients with JRA, 14 were boys (46.67%) and 16 were girls (53.33%), whereas eight were boys (26.67%) and 22 were girls (73.33%) in the control group. Duration of illness was 6 months–12 years (mean $\pm$ standard deviation, 3.997 ± 3.039 in years).

Family history of juvenile rheumatoid arthritis

The family history was positive in 13 patients (43.33%) and negative in 17 patients (56.67%).

Rheumatoid factor of patients with juvenile rheumatoid arthritis

Seven patients (23.33%) were positive for rheumatoid factor and 23 patients were negative (76.67%) during the study.

Disease status

Twenty-two patients were in remission (73%), whereas the remaining eight patients (27%) were in relapse.

Type of arthritis

Two patients (7%) were pauciarticular rheumatoid arthritis (RA), five (17%) were systemic RA, whereas the remaining 23 patients (76%) were polyarticular RA.

Behavioral and cognitive difference in patients and control groups

Comparing behavior of patients with the control showed a significant increase in attention problem ($P = 0.000^*$), anxiety withdrawal ($P = 0.000^*$), and conduct behavior ($P = 0.000^*$), whereas cognitive functions showed a significant decrease in visual memory ($P = 0.003^*$ and $P = 0.002$) as well as total intelligence quotient ($P = 0.001^*$).

Table 1 shows a majority of patients (93%) with depressive symptoms, whereas specific phobia was 20%, social phobia and oppositional defiant disorder were 16% each, major depression, obsessive-compulsive disorder (OCD), and conduct disorder were 3% each. As a result of sample size, in further analysis, dysthymic and depression patients were included as the depression group, and specific phobia, social phobia, and OCD were included in the anxiety group.

Patient's characteristics in relation to brain perfusion

Cerebral perfusion findings in relation to juvenile rheumatoid arthritis status

Unlike the disease activity, which showed a significant decrease in left frontal lobe perfusion in patient's group ($P = 0.024^*$), the type of JRA did not have any significant correlation with brain perfusion findings.

Brain perfusion study

Perfusion studies showed a decrease with statistical difference between patients and control in right frontal ($P = < 0.001^*$) and right parietal lobes ($P = < 0.001^*$) and a statistically significant increase in left parietal ($P = < 0.001^*$) and left occipital lobes ($P = 0.003^*$).

Behavioral and cognitive function in relation to brain perfusion study

Correlating behavioral checklist items with cerebral perfusion indicated statistical differences between patients and controls in term of psychotic behavior, which showed significant difference with direct relation to left parietal perfusion ($P = 0.023$) and right occipital lobe ($P = 0.04$) brain perfusion. Although motor excess was significantly related with inverse relation to left frontal brain perfusion ($P = 0.041$), visual memory, and visual perception were significantly correlated with inverse relation to right frontal lobe brain perfusion ($P = 0.007$, $P = 0.04$, respectively).

Brain perfusion study in relation to disorder

Patients in the depressed group showed a significant decrease in right frontal ($P = 0.000^*$) and left parietal brain perfusion ($P = 0.000^*$), and a significant increase in right parietal ($P = 0.000^*$) and left occipital lobe ($P = 0.079^*$), compared with the control group. Meanwhile, the anxiety group showed a significant increase in right frontal lobe ($P = 0.000^*$) and a significant decrease

in both parietal lobe ($P = 0.000^*$) cerebral perfusion compared with the control group.

Brain perfusion study in relation to therapy

Duration of therapy showed a significant difference with inverse relation to brain perfusion between corticosteroid and right parietal lobe ($P = 0.02$), and methotrexate and left parietal lobe ($P = 0.01$). Meanwhile, dose of therapy showed a significant difference with inverse relation between methotrexate and both right temporal ($P = 0.02$) and left temporal ($P = 0.04$) lobes. In addition, NSAID dose of therapy showed a significant difference with inverse relation in right temporal brain perfusion ($P = 0.04$).

Discussion

Several studies have found a direct relationship between stress (negative life events, daily hassles, and interpersonal stressors) and adjustment problems (depressed mood and behavior problems) [18]. A variety of internalizing problems and deficiencies in the social activities [7], social isolation, and sexual anxieties [19,20] have also been reported among youth with arthritis. These manifestations were evident in our patients who showed anxiety withdrawal, conduct behavior, and attention problem compared with the control group, indicating that children suffering from chronic diseases such as JRA are in need for psychiatric follow-up and therapy.

As the majority of children with arthritis were girls in previous studies, these factors may have contributed toward the higher rate of internalizing problems in their population. It has been postulated that RA shares the characteristics of being more common with depression in girls and have the diurnal variability with worsening of symptoms in the morning [21].

Previous research [22] on cognitive impairment in systemic onset JRA found that cognitive performance and social adjustment of young patients were not affected by the activity and/or duration of the disease. These findings are different from our study in terms of the study sample in which our cases were mainly polyarticular RA (76%) in whom cognitive deficit (the intelligence quotient) was a significant finding as compared with the controls. This could be explained by different sensory stimulating upbringing, the use of different cognitive assessment tool, difference in sample selection, as well as central nervous system involvement in the course of RA, which is considered to be an infrequent event. In fact, there are few surveys with conflicting results regarding the occurrence of cognitive or behavioral abnormalities [23,24].

The prevalence of psychiatric morbidity among patients with JRA was 35%, depressive disorder was 15%, somatoform disorder was 12.5%, adjustment disorder was 5%, and mixed anxiety and depressive disorder was 2.5% [8]. Another study [25] reported depressive disorder in 58–60%, anxiety disorder in 45–52%, and adjustment disorder in 28–36% of patients with JRA. In our sample,

Table 1 Psychiatric morbidity in patients group

Psychiatric morbidity	Patients group
	N (%)
Dysthymic disorder	28 (93.33)
Specific phobia	6 (20)
Social phobia	5 (16.67)
ODD	5 (16.67)
Major depression	1 (3.33)
OCD	1 (3.33)
Conduct disorder	1 (3.33)

N, number; OCD, obsessive-compulsive disorder; ODD, oppositional defiant disorder.

psychiatric morbidity did not differ regarding the type or the prevalence. They were as follows in decreasing order: dysthymic disorder in 93%, specific phobia in 20%, social phobia and oppositional defiant disorder each in 16%, and finally major depression, OCD, and conduct disorder each in 3%. These findings are matching with internalizing symptoms of patients with chronic medical illness such as JRA [25].

As central nervous system involvement is infrequent but evident in RA [26], in this study we attempted to evaluate cerebral perfusion to determine whether the observed psychiatric manifestations were due to immune vacuities that may alter cerebral perfusion. Our results showed a significant decrease in right frontal and right parietal lobes, and a significant increase in left parietal and left occipital lobes in patients compared with the control group. Interestingly, these regions are known to be involved in mood regulation, anxiety, and attention span. A recent study [27] reported that depressed adolescents have abnormal hyperactivity of amygdale compared with control. Another study [28] correlated severity of depression to brain perfusion. These findings were evident in our study as the decreased perfusion of the right frontal and right parietal lobes were seen more in patients with depression compared with healthy control.

Anxiety affects amygdale perfusion [29] and another study [30] suggested that youth with generalized anxiety disorder shows hyperresonance amygdale in the absence of a compensatory increase of ventrolateral prefrontal modulation. Our results support these suggestions as the anxiety group showed increased right frontal and decreased parietal perfusion compared with the controls, which all reflects the dysfunctional brain circuit of anxiety patients.

The observed psychiatric changes in our series were influenced by the duration of intake rather than the dose of immunosuppressive drugs. These drugs are commonly used to control JRA disease activity. Of note, most cases (73%) were studied during disease remission, denoting that the observed cerebral perfusion changes were not due to disease activity and active vasculitis. These patients were maintained on very low doses of corticosteroids (0.1–0.3 mg/kg/day). However, a significant inverse relationship was found between the right parietal perfusion and the duration of steroid intake. A similar relationship was also found between the left parietal lobe perfusion and the duration of methotrexate intake. These findings suggest that the long duration of intake of corticosteroids and other medications may alter cerebral perfusion leading to the development of depressive symptoms. Indeed, depression was reported to be more common with corticosteroid than mania during long-term therapy, as well as with a decline in working memory [31].

To conclude, this study shows that patients with JRA experience psychiatric morbidity as well as cognitive deficit. The patterns of cerebral perfusion deficit are similar to that observed in patients diagnosed with depression, anxiety, and cognitive disabilities. It is

suggested that psychiatric changes observed in our patients were due to therapy duration rather than the drug dosage.

References

- 1 Miller ML, Cassidy JT. Juvenile rheumatoid arthritis. In: Behrman RE, Kliegman RM, Jenson HB, editors. *Nelson textbook of pediatrics*. 16th ed. Philadelphia: Saunders; 2000. pp. 704–709.
- 2 Schneider R, Passo MH. Juvenile rheumatoid arthritis. *Rheum Dis Clin North Am* 2002; 28:503–530.
- 3 El Gamal Y, Mokhtar GM, Omar OH, El Sayed ZA, Mostafa GA. Bone metabolism in juvenile rheumatoid arthritis. *Egypt Rheumatol Rehab* 1999; 26:153–166.
- 4 Borchers AT, Selmi C, Cheema G, Keen CL, Shoenfeld Y, Gershwin ME. Juvenile idiopathic arthritis. *Autoimmun Rev* 2006; 5:279–298.
- 5 Adams A, Lehman TJ. Update on the pathogenesis and treatment of systemic onset juvenile rheumatoid arthritis. *Curr Opin Rheumatol* 2005; 17: 612–616.
- 6 Glazebrook C, Hollis C, Heussler H, Goodman R, Coates L. Detecting emotional and behavioural problems in paediatric clinics. *Child Care Health Dev* 2003; 29:141–149.
- 7 Carter BD, Kronenberger WG, Edwards JF, Marshall GS, Schikler KN, Causey DL. Psychological symptoms in chronic fatigue and juvenile rheumatoid arthritis. *Pediatrics* 1999; 103 (5 Pt 1):975–979.
- 8 Mullick MS, Nahar JS, Haq SA. Psychiatric morbidity, stressors, impact and burden in juvenile idiopathic arthritis. *J Health Popul Nutr* 2005; 23: 142–149.
- 9 Covic T, Tyson G, Spencer D, Howe G. Depression in rheumatoid arthritis patients: demographic, clinical and psychological predictors. *J Psychosom Res* 2006; 60:469–476.
- 10 Bartolini M, Candela M, Brugni M, Catena L, Mari F, Pomponio G, et al. Are behaviour and motor performances of rheumatoid arthritis patients influenced by subclinical cognitive impairments? A clinical and neuroimaging study. *Clin Exp Rheumatol* 2002; 20:491–497.
- 11 Goldberg DP. *The detection of psychiatric illness by questionnaire*. London: Oxford University Press; 1974.
- 12 Okasha A, Kamel M, Fares R, Abdel Hakiem R. An epidemiological study of depressive symptoms in rural and urban population in Egypt. *Egypt J Psychiatry* 1988; 11:167–181.
- 13 Wechsler D. *WAIS-R Manual*. New York: Psychological corporation; 1981.
- 14 Achenbach TM. *Manual for the Child Behavior Checklist/4-18 and 1991 profile*. Burlington VT: Department of psychiatry, University of Vermont; 1991.
- 15 Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, et al. The mini-international neuropsychiatric interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatry* 1998; 59 (Suppl 20):22–33. quiz:34–57.
- 16 Benton H. A visual renetion test for clinical use. *Arch Neurol Psychiatry* 1945; 54:212–216.
- 17 Van den Abbeele AD, Donohoe KJ. *Teaching atlas of nuclear medicine*. New York: Thieme Medical Publishers; 2000.
- 18 Sandstrom MJ, Schanberg LE. Peer rejection, social behavior and psychological adjustment in children with juvenile rheumatic disease. *J Pediatr Psychol* 2004; 29:29–29:34.
- 19 Ennett ST, DeVellis BM, Earp JA, Kredich D, Warren RW, Wilhelm CL. Disease experience and psychosocial adjustment in children with juvenile rheumatoid arthritis: children's versus mothers' reports. *J Pediatr Psychol* 1991; 16:557–568.
- 20 Wilkinson VA. Juvenile chronic arthritis in adolescence: facing the reality. *Int Rehabil Med* 1981; 3:11–17.
- 21 Chikanza IC. Neuroendocrine immune features of pediatric inflammatory rheumatic diseases. *Ann N Y Acad Sci* 1999; 876:71–80. discussion: 80–82.
- 22 Feldmann R, Weglage J, Roth J, Foell D, Frosch M. Systemic juvenile rheumatoid arthritis: cognitive function and social adjustment. *Ann Neurol* 2005; 58:605–609.
- 23 Genet F, Lapeyre E, Schnitzler A, Hausseguy A, D'Apolito AC, Lafaye de Michaux R, et al. Psychobehavioural assessment for chronic low back pain. *Ann Readapt Med Phys* 2006; 49:226–233.
- 24 Cavalcanti A, Hilário MOE, Dos Santos FH, Bolognani SAP, Bueno OFA, Len CA. Subtle cognitive deficits in adults with a previous history of sydenham's chorea during childhood. *Arthritis Care Res* 2010; 62:1065–1071.
- 25 LeBovidge JS, Lavigne JV, Donenberg GR, Miller ML. Psychological adjustment of children and adolescents with chronic arthritis: a meta-analytic review. *J Pediatr Psychol* 2003; 28:29–39.
- 26 Carbotte RM, Denburg SD, Denburg JA. Cognitive deficit associated with rheumatic diseases: neuropsychological perspectives. *Arthritis Rheum* 1995; 38:1363–1374.

- 27 Yang TT, Simmons AN, Matthews SC, Tapert SF, Frank GK, Max JE, et al. Adolescents with major depression demonstrate increased amygdala activation. *J Am Acad Child Adolesc Psychiatry* 2010; 49:42–51.
- 28 Perico CA, Skaf CR, Yamada A, Duran F, Buchpiguel CA, Castro CC, et al. Relationship between regional cerebral blood flow and separate symptom clusters of major depression: a single photon emission computed tomography study using statistical parametric mapping. *Neurosci Lett* 2005; 384:265–270.
- 29 Guyer AE, Lau JYF, McClure Tone EB, Parrish J, Shiffrin ND, Reynolds RC, et al. Amygdala and ventrolateral prefrontal cortex function during anticipated peer evaluation in pediatric social anxiety. *Arch Gen Psychiatry* 2008; 65:1303–1312.
- 30 Monk CS, Telzer EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. *Arch Gen Psychiatry* 2008; 65:568–576.
- 31 Brown ES. Effects of glucocorticoids on mood, memory and the hippocampus: treatment and preventive therapy. *Ann N Y Acad Sci* 2009; 1179:41–55.

الملخص العربي

الأمراض النفسية المصاحبة لمرض الروماتويد عند الأطفال

دراسة باستخدام الفوتونات المشعة لتصوير المخ

يعتبر مرض التهاب المفاصل الروماتويد الصغار من الأمراض المزمنة المنتشرة في الأطفال والتي تحدث إعاقات نفسية وحركية للأطفال. وثبتت بالدراسات السابقة أن حوالي 30% من الأطفال المصابين بالتهاب المفاصل الروماتويدي يعانون من أعراض نفسية تصل إلى حد تشخيص مرض نفسي. في هذه الدراسة ثم منظره 30 حالة التهاب مفاصل روماتويدي من الأطفال والكشف عن الإعاقات النفسية والمعرفية عن طريق استخدام الاختبارات النفسية والمعرفية اللازمة. وتم إخضاع هؤلاء الأطفال إلى فحص بالأشعة المقطعية أحادية الفوتون علي المخ ولقد وجد فارق احصائي بين المرض والإصحاء في معامل الذكاء واختبار الذاكرة البصريه — كما أن المرض يعانون من نقص في الدورة الدموية بالمخ بوجه عام مقارنة بالإصحاء وأن بعض المناطق التي تعاني من نقص في الدورة الدموية هي الأماكن المسؤولة عن ظهور الأعراض النفسية — خاصة وأنه وجد علاقة احصائية بين درجة تدفق الدم وفتره المرض — والعلاج بينما لم توجد هذه العلاقة مع جرعته العلاج