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Alterations in plasma dipeptidyl peptidase IV in autism: A pilot study

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ABSTRACT

Immune factors such as autoimmunity have been implicated in the genesis of autism.

This study aimed to investigate the role of dipeptidyl peptidase (DPP) IV serum levels, which were measured by ELISA method, in 62 (mean age 7.02 ± 2.03 years) autistic children in comparison to 16 (mean age 7.25 ± 2.14 years) healthy-matched children. The Childhood Autism Rating Scale (CARS) was used for the assessment of autistic severity.

The DPP IV level was significantly lower ($p = 0.05$) in autistic subjects than normal controls, although there were no significant relationships between the plasma DPP IV level and the CARS score, age or gender.

Therefore, we concluded that alterations in the plasma level of DPP IV play a role in the pathophysiology of autism. However, this is an initial report that warrants further research to determine the pathogenic role of DPP IV and its possible link to neuroinflammation in autism.

1. Introduction

Autism is a neurodevelopmental disorder characterized by impairments in communication, language and reciprocal social interaction and unusual patterns of restricted and repetitive interests or behaviors, as defined by the Diagnostic and Statistical Manual of the American Psychiatric Association – 4th ed. (DSM-IV).[1] The etiology and pathogenesis of 70–90% of autism cases[2,3] remain unexplained despite the fact that autism is one of the most extensively studied disorders in child psychiatry.[4]

Antigens from infectious agents may stimulate lymphocyte receptors with digestive functions in the gastrointestinal tract.[5] One such receptor protein with this inherent enzymatic activity is dipeptidyl peptidase IV (DPP IV), or CD26.[5] DPP IV has been detected in various tissues and cell types, including cells of the immune system.[6]

A soluble form of this peptidase exists in the serum/plasma,[7] and significantly reduced levels of serum DPP IV have been observed in transplant patients receiving cyclosporin A for immunosuppression[8] as well as patients with inflammatory disorders.[9] In addition, altered DPP IV activity has been observed in patients with immune and liver disorders, such as autoimmune disorders, lymphosarcoma, Hodgkin's disease, acute lymphatic leukemia and hepatobiliary disorders.[9] Furthermore, in rheumatoid arthritis, a significant inverse relationship was found between plasma DPP IV activity and illness severity.[5,10] DPP IV is also involved in lymphocyte activation, differentiation and proliferation through its effects

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on interleukin-2 (IL-2).[10] Finally, DPP-IV also has a role in the metabolism of immunologically responsive molecules, and IL-1 has been proposed as a potential substrate for DPP IV.[9,10] Studies have also shown that lower DPP IV levels in patients with major depression and schizophrenia reflect the immune-mediated inflammatory response and that reductions in DPP IV activity may particularly affect IL-1-related immune responses[11–14] and disorders of peptide metabolizing enzymes.[15]

However, no research has examined whether alterations in DPP IV activity occur in autism. Therefore, the aim of this study was to examine (i) plasma DPP IV activity in patients with autism spectrum disorder (ASD) versus normal controls and (ii) the relationship between DPP IV activity and the Childhood Autism Rating Scale (CARS) as measures of social and cognitive impairments in patients with autism was screened among the measured parameters.

2. Materials and methods

2.1. Subjects

This cross-sectional study was conducted on 62 children who had ASD, recruited from the Autism Research and Treatment Center, Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia. Their ages ranged between 3 and 12 years (mean SD = (mean age 7.02 ± 2.03 years)). The control group comprised 16 age and sex-matched apparently healthy children with mean age 7.2 ± 2.14 years. The patients met the diagnostic criteria of ASD according to the 4th edition of the Diagnostic and Statistical Manual of Mental Disorders.[1] The controls were normally developing, healthy children, unrelated to the autistic subjects and without any of the exclusion criteria. These children were the healthy older siblings of healthy infants who were attending the Well Baby Clinic at King Khalid University Hospital for routine check-up of their growth parameters. They had no clinical indications of infectious disease or neuropsychiatric disorders. The local Ethical Committee of the Faculty of Medicine, King Saud University, Riyadh, Saudi Arabia, approved this study. In addition, an informed written consent of participation in the study was signed by the parents or the legal guardians of the investigated subjects according to the Helsinki principles.

The CARS score was completed as a further measurement of the severity of disease. CARS rates the child on a scale from one to four in each of 15 areas (relating to people; emotional response; imitation; body use; object use; listening response; fear or nervousness; verbal communication; non-verbal communication; activity level; level and reliability of intellectual response; adaptation to change; visual response; taste, smell and touch response; and general impressions). According to the scale, children who have scored 30–36 have mild to moderate autism ($n = 28$), while those with scores ranging between 37 and 60 points have severe autism ($n = 34$).[16]

2.2. Assessment of plasma dipeptidyl peptidase (DPP) IV

The serum level of DPP IV was evaluated using an ELISA kit (R&D Systems, Inc., 614 McKinley Place NE, Minneapolis, MN 55413, USA) designed to measure human DPP IV in the serum. All samples were assayed in duplicate and in a double-blind manner. The assay reproducibility generally ranged from 5 to 10% error.

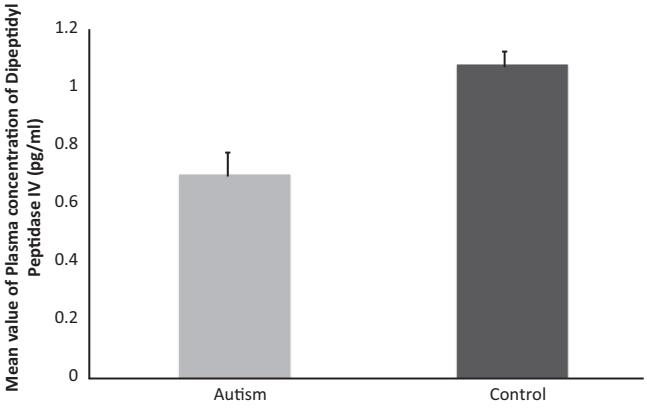

Fig. 1 – Serum level of dipeptidyl peptidase (DPP IV) in autistic patients and healthy children. The mean value for each group is shown with a horizontal bar. Student's *t*-tests revealed that the mean DPP IV levels were lower in patients (mean ± S.E. = 0.69 ± 0.08 pg/ml) than controls (mean ± S.E. = 1.07 ± 0.05 pg/ml) ($p = 0.05$, normal range 0.53–0.86 pg/ml).

2.3. Statistical analysis

The results were analyzed by the commercially available software package (Statview, Abacus Concepts, Inc., Berkley, CA, USA). The parametric data were presented as mean and standard deviation (SD). In addition, non-parametric data were presented as median and interquartile range (IQR), which is the difference between the 75th and 25th percentiles. Student's *t*-test was used for comparison of parametric data, while Mann–Whitney *U*-test was used for comparison of non-parametric data. Chi-square test was used for comparison between qualitative variables of the studied groups. Spearman's rho correlation coefficient ``r'' was used to determine the relationship between different variables (Fig. 1).

3. Results

Table 1 shows the demographic data of the 78 subjects in this study. There were no significant differences in the male/female ratio or age between the two study groups. Table 1 shows the measurements of DPP IV in the two study groups. The Student's *t*-tests revealed that the mean serum DPP IV level in patients (0.69 ± 0.08 pg/ml) was lower than that in the control group (1.07 ± 0.05 pg/ml) ($p = 0.05$, normal range 0.53–0.86 pg/ml).

There was a significant difference in DPP IV level between children with mild to moderate autism and severe autism ($p = 0.05$, Fig. 2).

However, the serum levels of DPP IV in autistic patients demonstrated no significant correlations with the CARS score