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Case Report: 6-Year-Old Male With Autism and Systemic Onset Juvenile Rheumatoid Arthritis

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Autism is a developmental disorder characterized by pervasive social and communication impairments and restricted range of interests and activities. Although the specific cause is unknown, proposed etiologies for autism have included autoimmune dysregulation of cellular or humoral components and maternal–fetal immunoregulation problems. Juvenile rheumatoid arthritis (JRA) constitutes several heterogeneous arthritides with onset in childhood. JRA is believed to be an autoimmune disorder whose pathogenesis is currently being elucidated. We present a case report of a 6-year-old male diagnosed with both autism and systemic onset JRA (SO-JRA). This co-occurrence has not previously been reported in the medical literature and raises the issue of a possible association between these 2 entities. Additional research to determine the frequency with which these 2 disorders coexist and to delineate potential immune mechanisms in autism could provide insights as to the etiology of both autism and SO-JRA and/or suggest a pathway to address treatment.

KEY WORDS: autism; juvenile rheumatoid arthritis; autoimmune disorders.

Autism is a developmental disorder characterized by pervasive social and communication impairments in conjunction with restricted range of interests and activities. Autism is a relatively common disability with prevalence of at least 1:1,000 and male to female predominance of 4:1 (Filipek *et al*., 1999). The neurobiologic basis of autism is well accepted despite the fact that a specific etiology has not been established. Features of autism which

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support a neurobiologic basis include mental retardation in the approximately 70% of affected individuals; increased frequency of seizures; associated sensorimotor deficits; and strong genetic component evidenced by a recurrence risk of 3–7% and twin studies indicating a high concordance rate for monozygotic twins (Bailey *et al*., 1996; Smalley *et al*., 1988). Other medical and/or genetic conditions have been associated with autism in approximately 10–15% of cases. These have included such diverse disorders as Fragile × Syndrome, Trisomy 21, tuberous sclerosis, phenylketonuria, Fetal Rubella syndrome, and congenital brain malformations (Barton and Volkmar, 1998). Many theories regarding etiology in autism have been proposed. Among these are immune hypotheses that link autism to prenatal viral infections, autoimmune dysregulation of either cellular or humoral components, or maternal–fetal immunoregulation problems (VanGent *et al*., 1997).

Juvenile rheumatoid arthritis (JRA) is the term used to describe several chronic heterogeneous arthritides with onset before age 16. Specific types of JRA are clinically determined based on disease presentation in the first 6 months and include systemic, polyarticular, oligoarticular, and psoriatic. Estimates of prevalence are 10–13 per 100,000 with female predominance in all but the systemic type (Woo and Wedderburn, 1998). Although the pathogenesis of JRA is not well understood, it is believed to be an autoimmune disorder resulting from a combination of genetic and environmental factors. We present a case report of a young child with both autism and JRA, an association not previously described in the medical literature.

CASE REPORT

BB is a 6-year-old Caucasian male diagnosed with autism at age 4 who was admitted to the hospital at age 5 years, 1 month with 11-day history of spiking fevers to 104, malaise, transient maculopapular rash, and vomiting. BB was the first child of parents who were then 23 years. Family history was significant for a maternal second cousin with Attention Deficit Hyperactivity Disorder, another maternal second cousin with cleft palate, distant maternal family members with diabetes mellitus and hypertension, and maternal grandmother and great-grandmother with hypothyroidism; paternal grandfather had coronary artery disease and paternal grandmother had unknown psychiatric illness. Pregnancy was complicated by breech presentation with several ultrasounds performed prior to Caesarean-section delivery. Apgar scores of 9 at 5 min and 9 at 10 min were assigned. Birth weight was 2.7 kg; length was 48.3 cm; OFC was 34.3 cm. BB had an unremarkable neonatal course. Past medical history was significant for frequent congestion, rhinorrhea, and ear infections. BB had previously normal audiologic evaluation.

BB was seen for multidisciplinary developmental team evaluation at age 4 secondary to a history of social and communication difficulties. Early motor milestones were within the normal range; however, BB regressed in communication abilities at 18 months after developing fairly typically. At the time of the developmental evaluation, he was saying only a few single words. He communicated by pulling his parents toward a desired object or bringing them objects. He ignored much of the language directed toward him. He rarely initiated interaction with other children and tended to play in isolation. He visually inspected toys and arranged them in order; he enjoyed playing with string-like objects. Psychological evaluation included the Autism Diagnostic Interview—Revised (ADI-R) and Developmental Profile II (DP-II); BB met *DSM-IV* criteria for autism. On the DP-II, his self-help age equivalent was 24 months and academic age equivalent was 22 months. Receptive and expressive language skills were at the 12- to 15-month level. Chromosome analysis, Fragile × DNA testing, thyroid stimulating hormone, and sleep-deprived electroencephalography (EEG) were all normal.

When BB presented to the hospital in January 2000, his family reported a brief illness with vomiting and diarrhea shared by other family members 15 days prior to admission. Fever and transient rash began 11 days prior to admission after the patient received his OPV, diphtheria–tetanus–pertussis (DTP), varicella, and measles–mumps–rubella (MMR) vaccines. Spiking fevers persisted with increased malaise and elevated white blood count (maximum of 21,000) and erythrocyte sedimentation rate (maximum of 93) for a period of 8 weeks. Workup in the hospital, guided by an Infectious Disease Consultant, included chest X-ray (normal), computed tomography of sinuses (normal), blood and urine cultures (normal), abdominal ultrasound (normal), purified protein derivative (negative), Epstein–Barr virus serology (negative), antinuclear antibodies and rheumatoid factors (negative), cat scratch fever titers (negative), and fungal serology (negative). No infection-mediated source of a spiking fever was found. Rheumatology consultation was obtained and diagnosis of systemic onset JRA (SO-JRA) was made after the patient developed a dactylitis of the right middle finger in the 7th week of his illness and a tender right knee effusion 3 weeks later. He was subsequently started on prednisolone and naproxen with marked improvement in symptoms. He continues to be followed through the Pediatric Rheumatology Clinic.

DISCUSSION

Immune hypotheses regarding the etiology of autism have generally taken two forms (VanGent *et al.*, 1997). The first proposes that autism occurs as the result of prenatal viral infections. Indeed, case reports have described

autism in association with fetal rubella, cytomegalovirus, varicella zoster, syphilis, and toxoplasmosis infections. However, Deykin and MacMahon (1979) found no significant positive association between autism and maternal viral infections and efforts to detect specific viral agents in serum or cerebrospinal fluid have generally been unsuccessful. The second is an autoimmune hypothesis that focuses on a breakdown of self-recognition mechanisms characterized by either cellular or humoral immunologic reactions against components of the self or maternal–fetal immunodysregulation. In fact, various studies have identified abnormalities in the immune systems of children with autism. These abnormalities have included decreased subsets of T lymphocytes (CD4 cells), reduced levels of natural killer-cell cytotoxicity, serum antibodies to neuro-axon filament proteins and cerebellar neurofilaments, serum antibodies against serotonin (5-HT) receptors, and elevated maternal-complement-dependent cytotoxic reactions to their children's lymphocytes (VanGent *et al*., 1997). However, immune studies in autism have been plagued by methodologic issues and poor replicability, making it difficult to draw definitive conclusions. Research into the pathogenesis of JRA, although not definitive, appears to be more systematic with current interest focused on the role of Th1/Th2 pathways and the production and balance of proinflammatory cytokines such as interleukins and tumor necrosis factors (Gallagher and Bernstein, 1999; Moore, 1999; Onel, 2000).

Despite lack of compelling evidence that autoimmune abnormalities are related to the pathogenesis of autism, intravenous gammaglobulin (IVIG) has been proposed as a treatment for autism. IVIG is a serum antibody preparation used to treat a variety of immunodeficiencies. An initial report by Gupta *et al*., (1996) noted significant behavioral improvement in 5 of 10 children with autism treated with IVIG over a 6-month period. However, this study was not controlled and behavioral measures of improvement were highly subjective. A recent study by Plioplys (1998) administered four infusions of IVIG over a 6-month period to 10 children with autism and found no clinical improvement in 5 children, mild improvement in attention and hyperactivity reported by parents in 4 children, and significant improvement globally in 1 child. Again, no controls were used and behavioral measures were unspecified. Plioplys (1998) concluded that use of IVIG for autism should be undertaken only with great caution and only within a research format.

As previously mentioned, autism has been linked causally in a minority of cases with a variety of medical and/or genetic conditions impacting central nervous system development. These have included chromosomal abnormalities (Trisomy 21), genetic disorders (Fragile × Syndrome, tuberous sclerosis, phenylketonuria), structural brain abnormalities (congenital hydrocephalus), infectious diseases (Fetal Rubella syndrome), and teratogen exposures (Fetal Valproate syndrome, thalidomide exposures). In our case,

the association between autism and SO-JRA would not appear to be causally related given the timing of the diagnoses. Yet the combination of SO-JRA and autism raises the question of a common immune pathway or abnormality leading to both. Warren *et al*. (1992) reported an increased frequency of a major histocompatibility complex subtype (B44-SC30-DR4) in autism. Zimmerman (2000) noted that this subtype is also common in rheumatoid arthritis. However, there are virtually no reports of autism in individuals affected with common autoimmune disorders. Indeed, Zimmerman observed in a recent commentary that rheumatoid arthritis and autism do not seem to occur together in the same patients. He suggested that major histocompatibility complex mechanisms may exist which predispose to rheumatioid arthritis or autism, but not both. Comi *et al*. (1999) hypothesized that different paths to rheumatoid arthritis or autism may be the result of such factors as modifying genes, trigger injuries, or environmental factors. Although SO-JRA and rheumatoid arthritis are distinct entities mediated through different autoimmune mechanisms (SO-JRA is likely IL-6 regulated; Fishman *et al*., 1998), this hypothesis raises intriguing questions about protective mechanisms limiting the concordance of autism and autoimmune disorders. In autistic individuals, Gupta *et al*. (1998) found no difference in IL-6+ CD4+ or IL-6+ CD8+ T cells as compared to controls, but found an increase in IL-4+ CD4+ and CD8+ T cells. This suggests that anti-inflammatory cytokines may be upregulated in autism, as compared to SO-JRA in which proinflammatory cytokines predominate.

One recent study that looked at family members of autistic individuals indicated increased incidence of autoimmune disorders in families of individuals with autism as compared to healthy controls; 46% of participants had two or more family members with autoimmune disorders (Comi *et al*., 1999). The most common autoimmune disorders for both participants and controls were Type 1 diabetes mellitus, systemic lupus erythematosus, adult rheumatoid arthritis, and hypothyroidism. Mothers and first degree relatives of autistic children had more autoimmune disorders (16 and 21%, respectively) than controls (2 and 4%, respectively). Interpretation of study results included the possibility that immune dysfunction could interact with various environmental factors to play a role in autism pathogenesis in some families. Noteworthy in our specific case was the occurrence of hypothyroidism and diabetes mellitus in distant maternal family members, although no cases of rheumatoid arthritis were reported in the family.

Also of passing interest is the timing of this child's fever immediately following vaccination. The possibility of a link between the MMR vaccine and autism has been highly controversial since Wakefield *et al*. (1998) initially reported on 8 of 12 children with "autistic regression" and ileolymphoid nodular hyperplasia whose parents attributed their regression to the MMR

vaccine. Subsequent large-scale studies by Taylor *et al*. (1999) and Peltola *et al*. (1998) failed to find any causal association between the vaccine and autism. Yet in view of Wakefield's hypothesis that the combined mumps and measles vaccine given at an early age creates an increased risk for inflammatory bowel disease and autism, parents have expressed concern that the vaccine may act as a trigger for an unknown sequence of events resulting in the autism behavioral phenotype. In the same vein, a recent article by Shoenfeld and Aron-Maor (2000) reviewed numerous anecdotal reports of vaccinations (tetatus, mumps, rubella, Hepatitis B, etc.) being linked temporally with onset of autoimmune disorders such as Guillain–Barre syndrome, multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus. The authors point out that the benefits and safety of vaccination for the general population are obvious and that irrevocable proof is lacking for a causal association between vaccines and autoimmune disease. However, research is needed to determine whether vaccines could play a role in the development of autoimmune disorders for a small subset of individuals.

Our case report raises the question of an association between autism and JRA. Data is not currently available to allow a determination of whether autism occurs in conjunction with SO-JRA more frequently, less frequently, or with the expected frequency given the prevalence of the two disorders. If SO-JRA occurs more frequently in individuals with autism, then this might suggest a common autoimmune mechanism. If SO-JRA occurs less frequently in individuals with autism as might be inferred from the lack of previous cases of co-occurrence, perhaps one disorder protects against the other. Registries of developmental disabilities and connective tissue disorders would provide a means for accessing and analyzing such information. It is hoped that this case study will stimulate an interest in looking further at this issue, in hopes of gaining an insight into the pathogenesis of either or both diseases. Systematic research is also needed to delineate possible immune abnormalities in autism. Such research has the potential for providing insights into the etiology and treatment of autism.

REFERENCES

Bailey, A., Phillips, W., and Rutter, M. (1996). Autism: Towards an integration of clinical, genetic, neuropsychological perspectives. *J. Child Psychol. Psychiatr*. 37: 89–126.

Barton, M., and Volkmar, F. (1998). How commonly are known medical conditions associated with autism? *J. Autism Dev. Disord*. 28(4): 273–278.

Comi, A. M., Zimmerman, A. W., Frye, V. H., Law, P. A., and Peeden, J. N. (1999). Familial clustering of autoimmune disorders and evaluation of medical risk factors in autism. *J. Child Neurol*. 14(6): 388–394.

Deykin, E. Y., and MacMahon, B. (1979). Viral exposure and autism. *Am. J. Epidemiol*. 109: 628–638.

Filipek, P. A., Accardo, P. J., Baranek, G. T., Cook, E. H., Dawson, G., Gordon, B., Gravel, J. S., Johnson, C. P., Kallen, R. J., Levy, S. E., Minshew, N. J., Prizant, B. M., Rapin, I., Rogers, S. J., Stone, W. L., Teplin, S., Tuckman, R. F., and Volkmar, F. R. (1999). The screening and diagnosis of autistic spectrum disorders. *J. Autism Dev. Disord*. 29(6): 439–484.

Fishman, D., Faulds, G., Jeffery, R., Mohamed-Ali, V., Yudkin, J. S., Humphries, S., and Woo, P. (1998). The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels and an association with systemic juvenile chronic arthritis. *J. Chem. Invest*. 102: 1369–1376.

Gallagher, K. T., and Bernstein, B. (1999). Juvenile rheumatoid arthritis. *Curr. Opin. Rheumatol*. 11: 372–376.

Gupta, S., Aggarwal, S., and Heads, C. (1996). Brief report: Dysregulated immune system in children with autism: Beneficial effects of intravenous immune globulin on autistic characteristics. *J. Autism Dev. Disord*. 26(4): 439–452.

Gupta, S., Aggarwal, S., Rashanravan, B., and Lee, T. (1998). TH-1 and TH-2-like cytokines in CD4+ and CD8+ T cells in autism. *J. Neuroimmunol*. 85(1): 106–109.

Moore, T. L. (1999). Immunopathogenesis of juvenile rheumatoid arthritis. *Curr. Opin. Rheumatol*. 11: 377–388.

Onel, K. B. (2000). Advances in the medical treatment of juvenile rheumatoid arthritis. *Curr. Opin. Pediatr*. 12(1): 72–75.

Peltola, H., Patja, A., Leinikki, P., Valle, M., Davidkin, I., and Paunio, M. (1998). No evidence for measles, mumps and rubella vaccine associated in inflammatory bowel disease or autism in a 14 year prospective study. *Lancet* 351(9112): 1327–1328.

Plioplys, A. V. (1998). Intravenous immunogloglobulin treatment of children with autism. *J. Child Neurol*. 13(2): 79–82.

Shoenfeld, A., and Aron-Maor, A. (2000). Vaccination and autoimmunity—Vaccinosis: A dangerous liaison? *J. Autoimmun*. 14: 1–10.

Smalley, S. L., Asarnon, R. F., and Spencer, A. M. (1988). Autism and genetics. *Arch. Genl. Psychiatry* 45: 953–961.

Taylor, B., Miller, E., Farrington, C. P., Petropoulos, M. C., Fayvot-Mayaud, I., Li, J., and Waight, P. A. (1999). Autism and measles, mumps, and rubella vaccine: No epidemiological evidence for a causal assessment. *Lancet* 353: 2026–2029.

VanGent, J., Heijnen, C. J., and Treffers, P. D. A. (1997). Autism and the immune system. *J. Child Psychol. Psychiatr*. 38(3): 337–349.

Wakefield, A. J., Murch, S. H., Anthony, A., Linnell, J., Casson, D. M., Malik, M., Berelowitz, M., Dhillon, A. P., Thomson, M. A., Harvey, P., Valentine, A., Davies, S. E., and Walker-Smith, J. A. (1998). Ileal lymphoid nodular hyperplasia, nonspecific colitis, and pervasive developmental disorder in children. *Lancet* 351(1): 637–641.

Warren, R. P., Singh, V. K., Cole, P., Odell, J. D., Pingree, C. B., Warren, W. L., DeWitt, C. N., and McCullough, M. (1992). Possible association of the extended MHC haplotype B44-SC30-DR4 with autism. *Immunogenetics* 36: 203–207.

Woo, P., and Wedderburn, L. R. (1998). Juvenile rheumatoid arthritis. *Lancet* 351(9107): 969–973.

Zimmerman, A. W. (2000). Commentary: Immunological treatments for autism: In search of reasons for promising approaches. *J. Autism Dev. Disord*. 30: 481–484.