CASE REPORT

Congenital Rubella Syndrome With Autistic Disorder

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Congenital rubella syndrome (CRS) consists of a group of abnormalities that develop in children as a result of maternal infection with rubella virus. CRS may lead to new physical symptoms during adolescence or adulthood, referred to as "late manifestations". Psychiatric disorders are often seen among CRS patients, with an incidence of 4.12–7.3% for autism. We report a case of adolescent CRS with autism. A 20-year-old man had received treatment with antipsychotics and antidepressants since the age of 12 years because of unstable moods, violence, and stereotypic behavior. During follow-up, he developed some insidious-onset physical problems, including hyperlipidemia, dyspnea, constipation, torticollis and a tilted trunk. Under careful survey and evaluation, some physical problems were recognized as side effects of psychotropics, which gradually subsided after adjustment of the medications, and some of the problems were considered partially as manifestations of CRS, such as progressive pulmonary artery stenosis-related dyspnea. We managed some of the patient's physical problems and then he received catheterization for pulmonary artery stenosis. His general physical condition improved and some further improvement in psychiatric status was noted thereafter. Because of a high comorbidity rate for patients with autistic disorder, the clinician should be aware of the possibility of CRS if the patient has multiple congenital physical abnormalities with a history of maternal rubella infection. If patients develop physical symptoms in adolescence, awareness of late manifestations of CRS and differentiation from the adverse effects of psychotropic medications are essential. In addition to psychiatric treatment, management of physical problems associated with CRS would be beneficial for the patients' psychiatric condition. [*J Chin Med Assoc* 2010;73(2):104–107]

Key Words: autistic disorder, congenital rubella syndrome, late manifestations

Introduction

Rubella, also known as German measles, was first described by 2 German physicians in the mid-18th century.[1] In early 1941, Sydney ophthalmologists, Gregg and Banatvala, identified a group of infants with congenital cataracts and other abnormalities, most of whose mothers reported having had rubella early in pregnancy.[2] Their suggestion about rubella's teratogenicity was subsequently confirmed by others.[3]

Congenital rubella syndrome (CRS) is used to describe the group of congenital abnormalities that occur in a child as a result of rubella infection of the mother during gestation. The clinical features of CRS can be classified as transient, self-limiting, or permanent, and some of them may not present until adolescence or adulthood. These are referred to as "late manifestations" or "delayed manifestations",[3] and include auditory and visual disorders, cardiac disorders, endocrinal disorders, esophageal and gastrointestinal problems, and urogenital problems.[4]

Psychiatric disorders are seen in up to half of all patients born with CRS.[5] The rate of mental retardation among children with CRS is as high as 42%,[5] and 4.12–7.3% of CRS patients show signs of autism.[6] Prenatal rubella-exposed subjects demonstrate a greater risk for nonaffective psychosis than those non-exposed, with a relative risk of 5.2.[7] A high rate of impulsivity and behavioral problems such as disruptive activity, tantrums and outbursts, self-injury, and aggression, has also been observed.[4]

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Case Report

Our patient, a 20-year-old male, was delivered full-term with a low birth weight of 2,000 g. Many congenital abnormalities, including hearing and visual impairments, iris hypoplasia, heart problems (patent ductus arteriosus, pulmonary artery stenosis, and aortic regurgitation), as well as inguinal hernia, were found immediately after birth. The diagnosis of CRS was made based on the fact that the patient's mother had rubella infection during gestation and his multiple congenital physical defects. The mother's history included a flu-like episode with fever and malaise, which was accompanied by a reddish skin rash at approximately 8 weeks of gestation. Although symptoms subsided spontaneously, "rubella infection" was diagnosed by both her physician and obstetrician, and termination of pregnancy was suggested. The mother was unable to recall whether her own or the patient's serum rubella immunoglobulin had been measured when rubella or CRS was diagnosed.

The patient was noted to have developmental delay, was walking at 2 years of age and was speaking at 3 years of age. He was brought to our psychiatric clinic in 2001 at 12 years of age, while in the 6th grade, because of poor adaptation to school, impulsive behavior, and a short temper when he was prohibited from doing things he wanted to do, or when he was criticized. Since his early childhood, his mother had observed that he did not understand the social situation and how to engage with other children in conversation or in play. He also displayed little eye contact and had difficulty in developing peer relationships. There was a lack of social and emotional reciprocity, idiosyncratic use of language, inflexible adherence to nonfunctional routine (such as refusing to eat rice because the rice looked disgusting to him, and refusing to flush the toilet out of a belief that the running water would not stop). An obsessive preoccupation with being dirty was also present, and the patient checked the door and windows compulsively. He also displayed a persistent interest in reading comic books that was limited to violent themes. He was diagnosed with high-functioning autistic disorder. An intelligence test had been administered twice—first when he was 12 years old and then when he was 17 years old—with the full-scale IQ/verbal IQ/performance IQ results of 87/78/101 and 80/76/89, respectively.

The patient was barely able to graduate from elementary school; he needed the assistance of his parents and teachers. His attendance was irregular from the 4th grade due to irritability, aggressive outbursts, argumentativeness and refusal to comply with teacher directions. The above symptoms worsened and caused him to be suspended from school in 7th grade and then to remain withdrawn at home. In recent years, he was frequently preoccupied and demanded that he be bought original VCDs/DVDs (about 2–3 disks every week), and would fly into a rage with temper tantrums and violence if his demands were refused.

Psychotropic drugs had been prescribed for the patient's severe symptoms of violence, irritability, inflexible thinking, impulsivity, and stereotypic behavior and motor tics starting from age 12. In October 2001, risperidone was initially administered, with a dosage of 1 mg/d, and then up-titrated to 4 mg/d according to his condition over the following 3 years. The patient had a relatively good response to risperidone treatment in the early stages, especially for treatment of impulsivity and rigid thinking. Fluvoxamine was combined with risperidone for compulsive buying behavior beginning at the age of 15 years (May 2004). However, neither of the medications appeared to effectively control his progressive violence later in 2004. In addition, with the higher dosage of risperidone, intolerable adverse effects of rigidity and tremor were observed. Olanzapine 10 mg/d was then used to replace risperidone starting in January 2005, and this resulted in less aggressive behavior, although his condition was variable depending on his drug adherence. However, 1.5 years later, in July 2006, he became overtly suspicious, with worsening violent and threatening behavior. This behavior was difficult to control in spite of olanzapine being adjusted up to 20 mg/d, accompanied by valproate sodium 1,000 mg/d and fluvoxamine 100 mg/d, and then he was first admitted to psychiatric hospital in 2006.

The patient had a short stature of 147 cm and central obesity, with a weight of 51 kg. Mild hearing loss in the left ear and mild optic atrophy associated with amblyopia of the left eye had been observed since very early childhood. However, there was an intermittent decline in vision, constipation and dysuria over the years.

The patient had 3 psychiatric hospitalizations; 2 at the age of 17 years (2006) and 1 at the age of 19 years (2008), all related to severe violence. During the last hospitalization, he was also distressed with physical discomfort including dyspnea, general weakness, abdominal distension, torticollis and a tilted trunk. Since he was a victim of autistic disorder with limited verbal ability, he could not describe his discomfort precisely. Degenerative retinopathy was found by the consulted ophthalmologist. Worsening pulmonary stenosis was suspected according to the cardiac examination. KUB (kidney-ureter-bladder) showed stool impaction, which was consistent with constipation. Laboratory findings showed normal blood sugar and thyroid function, elevated serum triglyceride levels (789 mg/dL), cholesterol levels (365 mg/dL), and uric acid levels (11.2 mg/dL).

Several physical problems were recognized as side effects of psychotropics and some were considered partially as manifestations of CRS. Retinopathy with a decline in vision was thought to be a late manifestation of CRS. The patient's torticollis and tilted trunk were recognized to be antipsychotic-related extrapyramidal symptoms and they improved after adjustment of psychotropics or combined use of anticholinergics. Constipation was considered to be related to the anticholinergic effects of the psychotropics and delayed manifestation of CRS; it was partially resolved after the giving of enemas and laxatives. The patient's dysuria was a long-term, progressive problem that emerged in his childhood. It was not a rare late manifestation of CRS, although it could become worse by psychotropics. Hyperlipidemia and hyperuricacidemia were thought to be partially due to sequelae of the antipsychotics. Fenofibrate 400 mg/d and benzbromarone 100 mg/d were prescribed in accordance with a metabolic physician's suggestion for the significant hyperlipidemia. We attempted either to switch to olanzapine to other antipsychotics with fewer metabolic side effects or to reduce the patient's olanzapine dosage. However, this treatment was discontinued under the request of the patient's mother because the patient's impulsivity worsened immediately or severe drug-related extrapyramidal symptoms emerged after a shift back to risperidone. After partially resolving physical and psychiatric problems, he was discharged.

Because of persistent dyspnea, which was thought to be related to the patient's cardiac problems, a cardiac catheterization for pulmonary stenosis was performed after psychiatric discharge, and both dyspnea and general weakness markedly decreased postoperatively. As the patient's physical condition improved, the psychiatric symptoms, irritability and violent behavior, also improved. Psychotropic drugs were able to be titrated down gradually with olanzapine 10 mg/d and valproate sodium 1,000 mg/d. Fluvoxamine was replaced by escitalopram 30 mg/d. The possible adverse effects of psychotropic drugs of constipation, torticollis and a tilted trunk also improved later. With fenofibrate and benzbromarone treatment, triglyceride and cholesterol levels were all decreased (308 mg/dL and 214 mg/dL, respectively) 4 months later.

Discussion

The exact way in which rubella continues to affect an individual with CRS has yet to be determined. Most experts believe that new problems are either due to a persistent infection of the rubella virus in the affected organ, or to the old infection, which causes an autoimmune response.[8,9] Although efforts to eradicate the disease have been in place for some time, it still affects many persons worldwide. Because of the progressive nature of CRS, it is important to monitor the wellbeing of the victims regularly. However, while most people are able to identify changes in their own health and seek treatment, many CRS patients cannot communicate their underlying symptoms, especially those with autistic disorders or hearing impairments.

Among the late manifestations of CRS, the development of diabetes mellitus is common, with a rate of approximately 20% by the third decade.[10] In our case, the blood sugar was normal, but hyperlipidemia and hyperuricacidemia were present. Olanzapine was prescribed for many years, which was thought to have a metabolic effect. Our patient's stereotypic dietary habits may have been another contributing factor. Additionally, the possibility of late manifestations of CRS cannot be ignored. Our patient showed a good response to fenofibrate and benzbromarone. Further close follow-up should be arranged.

Esophageal and gastrointestinal problems are also frequent complaints of CRS, with 24% of CRS patients having problems with swallowing, gagging or vomiting. Urogenital problems, especially dysuria, are not rare late manifestations for these patients.[11] Our patient has suffered from such physical problems for a long time, which may have been neglected because of poor communication abilities.

Cardiovascular anomalies include proliferation and damage of the integral lining of blood vessels, causing obstructive lesions of medium-sized and larger arteries in the systemic and pulmonary circulatory systems.[12] Because of progressive pulmonary stenosis, our patient gradually developed dyspnea and general weakness, which had once been mistaken as behavioral problems by his parents.

New onset of CRS is now rare in Taiwan, which has had rubella vaccination programs in place since 1986. However, there were 3 major rubella epidemics in 1958–1959, 1968, and 1977, and then rubella became endemically transmitted during the early-middle 1980s.[13,14] It is estimated that newborns with CRS account for approximately 0.4–3% of all newborns alive during epidemics.[15] Therefore, there should be some CRS victims in Taiwan mostly in their 20s to

40s. Since there is a comorbidity rate of psychiatric illness among those born with CRS that is as high as 50%,[5] including mental retardation (42%), autism (4.12–7.3%),[6] nonaffective psychosis (relative risk of 5.2 times those non-exposed),[7] and a high rate of impulsivity and behavioral problems,[4] it may not be uncommon to see patients with CRS at psychiatric clinics; this is especially true for those patients with autism and mental retardation. Among patients with autism, CRS should be suspected if a patient has multiple congenital physical abnormalities with rubella infection history in the mother. If physical symptoms develop in adolescence, awareness of late manifestations of CRS and differentiation from the adverse effects of psychotropic medications are essential. In addition to psychiatric treatment, management of CRS physical problems would also be beneficial for these patients' psychiatric condition.

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