Refractory kawasaki disease after dpt vaccination: A case report and literature review

Santoshi Subhadarsini[1], Vani Narayani[1], Saba anwar[1], Sudhir Baghel[2], Shivani Deswal[3], Vivek Dewan[4]

From [1]Senior Resident, [2]Junior Resident, [3]Associate Professor, [4]Professor & Incharge Paediatric Gastroenterohepatology Unit, Department of Paediatrics, Dr. RML Hospital & PGIMER, New Delhi, India.

Correspondence to: Dr. Santoshi Subhadarsini, Department of Paediatrics, Dr. RML Hospital & PGIMER, New Delhi – 110001, Delhi, India. E-mail: santropixie@gmail.com

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ABSTRACT

The etiology and pathogenesis of Kawasaki disease (KD) remain poorly understood. Among the diverse infectious and environmental factors examined to be triggers for, or be associated with, KD, are immunizations. We are reporting a case of refractory Kawasaki disease after DPT booster in a 5-year-old male child, who responded after two doses of IVIG and a course of IV Methylprednisolone. Prior published case reports and large epidemiological studies, which explore potential associations between immunization and KD, are also comprehensively reviewed.

Keywords: *DPT, IV Methylprednisolone, Strawberry tongue, Vasculitis.*

Kawasaki disease (KD) is an acute, multisystem vasculitis, characterized by a combination of symptoms, including fever for > 5days, rash, conjunctival injection with limbal sparing, unilateral cervical lymphadenopathy of more than or equal to 1.5 cm, oral mucosal changes and characteristic extremity changes. The etiology of KD is not clear but certain epidemiologic and clinical features support an infectious origin. These features include the young age group, self-limited nature of acute febrile illness and the clinical features of fever, rash, exanthem, conjunctival injection and cervical lymphadenopathy. However, there are features that are not consistent with an infectious origin such as multiple members within the same family being affected at the same time. Furthermore, no single infectious etiologic agent has been successfully identified despite a comprehensive search [1].

In addition, data indicate that host genetics underlie the disease's pathogenesis. Few cases of occurrence of KD after vaccination have been reported but no causal relationship has been established [2,3]. Histologically, coronary arteritis begins 6-8 days after the onset of KD, and leads immediately to inflammation of all layers of the artery. The inflammation spreads completely around the artery; as a result, structural components of the artery undergo intense damage; the artery then begins to dilate. Inflammatory cell infiltration continues until about the 25th day of the disease, after which the inflammatory cells gradually decrease in number.

KD arteritis is characterized by granulomatous inflammation that consists of a severe accumulation of monocytes/macrophages. Aberrant activation of monocytes/macrophages is thought to be involved in the formation of vascular lesions. The lesions in all the arteries are relatively synchronous as they evolve from acute to chronic injury [4]. We herein report the case of a 5-year-old male child, who developed KD two days after receiving Diphtheria, Pertussis, and Tetanus (DPT) booster and was managed with two courses of Intravenous immunoglobulin (IVIg) and a course of intravenous (IV) methylprednisolone.

CASE REPORT

A 5-year-old male child presented with complaints of fever, headache, pain in the neck and vomiting for two days. He was vaccinated for DPT booster two days ago. There was no history of cough, cold, loose stools, urinary complaints or rashes. Past and family history was also not significant.

On examination, he was febrile, sick looking and vitals were stable. Multiple right cervical lymph nodes were tender, palpable and were measuring 2cmx2cm. Cardiovascular, neurological and respiratory system examinations were normal. On abdominal examination, mild distension, 1.5 cm soft liver with a smooth surface and the regular margin was palpable below the right costal margin. There was no splenomegaly, no free fluid and bowel sounds were normal.

Investigations revealed erythrocyte sedimentation rate (ESR)-29 mm, C-reactive protein (CRP) - 10 mg/dl, total leucocyte count (TLC) - 16600/mm^3 with 85% neutrophils, and 13% lymphocytes. Platelet count was 340,000/mm^3, and there was mild transaminitis (Serum glutamic oxaloacetic transaminase (SGOT) - 117U/dl, Serum glutamic pyruvic transaminase (SGPT) -120 U/dl) and hyponatremia (126 mg/dl).

A provisional diagnosis of acute febrile illness was kept and the child was started on IV antibiotics in view of neutrophilia and

raised CRP. On day 5 of fever, red strawberry tongue, conjunctival redness and a maculopapular rash over the back were noticed. Diagnosis of Kawasaki disease was considered and IVIG was given at a dose of 2 g/kg over two days. Aspirin was started at a dose of 80mg/kg/day in four divided doses.

Echocardiography done at this stage was normal. Reports of blood culture, urine culture, typhi dot, dengue serology, chikungunya serology, leptospira serology, Weil-Felix reaction and tubercular work-up were negative. Antibiotics were stopped. Ultrasonography (USG) neck revealed multiple necrotic lymph nodes. Fine needle aspiration cytology (FNAC) of the right cervical lymph node revealed reactive lymphoid cells with occasional plasma cells and histiocytes. Magnetic resonance imaging (MRI) brain revealed a hyperintense signal with restricted diffusion in the splenium of corpus callosum suggestive of post-vaccination encephalitis or post-infective ischemic changes. However, there were no clinical signs suggestive of encephalitis.

Fever was persistent although with decreased spikes (up to 101.6^0 F) on day11 of illness. CRP (6.4 mg/dl), ESR (40 mm) and platelet count (520,000/mm^3) were still raised even after 36 hours of initial IVIG infusion. A repeat dose of IVIG (2g/kg) was administered over two days. The child responded to the second dose of IVIG as fever resolved but CRP (2.2 mg/dl) and ESR (18 mm) were still raised and platelet count (634,000/mm^3) was on increasing trend after another 48 hours. However, there was a repeat fever spike, so IV Methylprednisolone was given at a dose of 30 mg/kg/day for three days followed by oral prednisolone at a dose of 1 mg/kg/day for one week and then tapered over the next week to prevent a recurrence. Aspirin was reduced to 3mg/kg/day and was given for 8 weeks.

Coronary findings were normal throughout the course. Inflammatory markers (CRP 0.8 mg/dl, ESR 6 mm, platelet count 360,000/mm^3) normalized within 48 hours after IV methylprednisolone infusion and repeat echocardiography at two weeks was also normal. Follow-up echocardiography and inflammatory markers (CRP 0.5 mg/dl, ESR 4 mm, platelet count 300,000/mm^3) at six weeks and three months were also normal. This entire event following DPT vaccination was reported to the adverse drug reaction (ADR) system.

DISCUSSION

Incidence of KD in Japan, Taiwan and Germany are 264.8/lakh, 55.9/lakh and 7.2/lakh respectively. Incidence of IVIG resistance in Japan, Taiwan and Germany is 17%, 12.5% and 26.8%, respectively [5]. Although we do not have any countrywide epidemiologic data for India reports strongly suggest that the incidence of KD is showing an upward trend. For instance, extrapolations from the hospital-based registry at Chandigarh showed that the incidence of KD had increased from 0.51 to 4.54/100,000 children aged below 15 years during the period 1994- 2007 [6].

Common side effects following DPT vaccination are local pain, swelling and fever [7]. Cases of KD are reported after rotavirus and pentavalent (DTaP-IPV-HiB) and pneumococcal (PCV 13) vaccination [3]. Ece I et al [3] described a case of KD in a 2-month-old infant who developed KD 1 day after receiving his first dose of conjugate vaccine (DTaP-IPV-Hib) and PCV13. Yin Set al. [8] described a 20-month-old child who developed KD after receiving her second dose of Lanzhou lamb rotavirus vaccine (LLR) and her first dose of freeze-dried live attenuated hepatitis A vaccine. Shaikh S et al [9], Talebian A et al [10], and Leonardi S et al [11] have described the cases of refractory KD post-vaccination, who responded after 2 doses of IVIG and IV methylprednisolone.

Central nervous system (CNS) lesions may occur and despite their severity, as shown in a number of case reports in the literature [12], they are mostly self-limited findings, whose clearing could take months, but could also leave sequelae, such as brain atrophy, ischemic lesions, including cognitive and behavioral conditions [13]. Meningoencephalitides, subdural effusions, hypoperfused brain, and ischemia, cerebral and cerebellar infarction are CNS changes also being frequently detected from better KD recognition and from a more extended follow-up in these patients. CNS lesions should always be considered in KD, mainly in severe cases with high and extended inflammatory activity and the presence of a coronary impairment with or without neurological manifestations.

This was a 5-year-old male child who developed fever two days after DPT vaccination and other features of KD by 5^{th} day of fever. To the best of our knowledge, no such case of KD has been reported after DPT vaccination alone in the literature till now. In our case, in the absence of any infectious etiology and presence of persistent fever, rash, conjunctivitis, strawberry tongue, cervical lymphadenopathy and increased levels of acute-phase reactants (ESR, CRP and platelets) clinched the diagnosis of KD. The child responded partially to the first dose of IVIG, so repeat dose of IVIG was given. In view of persistently elevated acute phase reactants and recurrence of fever, IV Methylprednisolone was given followed by oral steroids for 2 weeks.

According to a study, in cases of KD unresponsive to an additional infusion of IVIG, IV methylprednisolone therapy-induced prompt defervescence and subsequent treatment with oral prednisolone suppressed recurrent fever [14]. Follow-up protocol of Kawasaki disease includes ECHO at diagnosis, at 2 weeks and 6 - 8 weeks later. Repeat echocardiogram beyond 8 weeks in patients with previously normal findings is considered optional. Cardiological risk assessment and counseling is advised every 5 years. For patients with coronary abnormalities, the frequency of cardiology follow-up visits is more. Overall DPT vaccination is very safe. KD may be a rare side effect of vaccination. Kawasaki disease (KD) is one of the most common vasculitides of childhood. Previous investigations into vasculitis and KD have reported them as side effects of various vaccinations [15-16].

CONCLUSION

Our case highlights the possible association of KD with DPT and the fact that there is a chance of no response to IVIG even after

36 hours of therapy; thus mandating a second dose of IVIG and IV methylprednisolone. Refractory cases of KD have never been reported post-DPT vaccines.

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