

Mercury Promotes Catecholamines Which Potentiate Mercurial Autoimmunity and Vasodilation: Implications for Inositol 1,4,5-Triphosphate 3-Kinase C Susceptibility in Kawasaki Syndrome

Deniz Yeter, MD¹, Richard Deth, PhD², and Ho-Chang Kuo, MD³

¹Shawnee, KS,

²Department of Pharmaceutical Sciences, Northeastern University, Boston, MA, USA

³Division of Allergy, Immunology and Rheumatology, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, Kaohsiung, Taiwan

Previously, we reviewed biological evidence that mercury could induce autoimmunity and coronary arterial wall relaxation as observed in Kawasaki syndrome (KS) through its effects on calcium signaling, and that inositol 1,4,5-triphosphate 3-kinase C (ITPKC) susceptibility in KS would predispose patients to mercury by increasing Ca^{2+} release. Hg^{2+} sensitizes inositol 1,4,5-triphosphate (IP_3) receptors at low doses, which release Ca^{2+} from intracellular stores in the sarcoplasmic reticulum, resulting in delayed, repetitive calcium influx. ITPKC prevents IP_3 from triggering IP_3 receptors to release calcium by converting IP_3 to inositol 1,3,4,5-tetrakisphosphate. Defective IP_3 phosphorylation resulting from reduced genetic expressions of ITPKC in KS would promote IP_3 , which increases Ca^{2+} release. Hg^{2+} increases catecholamine levels through the inhibition of S-adenosylmethionine and subsequently catechol-O-methyltransferase (COMT), while a single nucleotide polymorphism of the COMT gene (rs769224) was recently found to be significantly associated with the development of coronary artery lesions in KS. Accumulation of norepinephrine or epinephrine would potentiate Hg^{2+} -induced calcium influx by increasing IP_3 production and increasing the permeability of cardiac sarcolemma to Ca^{2+} . Norepinephrine and epinephrine also promote the secretion of atrial natriuretic peptide, a potent vasodilator that suppresses the release of vasoconstrictors. Elevated catecholamine levels can induce hypertension and tachycardia, while increased arterial pressure and a rapid heart rate would promote arterial vasodilation and subsequent fatal thromboses, particularly in tandem. Genetic risk factors may explain why only a susceptible subset of children develops KS although mercury exposure from methylmercury in fish or thimerosal in pediatric vaccines is nearly ubiquitous. During the infantile acrodermatitis epidemic, only 1 in 500 children developed acrodermatitis whereas mercury exposure was very common due to the use of teething powders. This hypothesis mirrors the leading theory for KS in which a widespread infection only induces KS in susceptible children. Acrodermatitis can mimic the clinical picture of KS, leading to its inclusion in the differential diagnosis for KS. Catecholamine levels are often elevated in acrodermatitis and may also play a role in KS. We conclude that KS may be the acute febrile form of acrodermatitis. (Korean Circ J 2013;43:581-591)

KEY WORDS: Kawasaki syndrome; Catecholamines; Mercury; Autoimmunity.

Introduction

Kawasaki syndrome (KS) is an acute febrile illness which predominantly occurs in young children under 5 years of age (75-80%) while it is exceptional in adults (<1%). The clinical picture consists of a persistent, erratically spiking-high fever ranging from 38° to 40°C

(101° to 104°F) which is resistant to antipyretics and antibiotics. In addition to the fever, four out of five of the following principle features are required for diagnosis: 1) a polymorphous rash; 2) conjunctival injection; 3) bright red, swollen extremities with subsequent desquamation typically during the second or third week; 4) oral changes which include bright red fissured lips, oropharyngitis, st-

Correspondence: Ho-Chang Kuo, MD, Department of Pediatrics, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University College of Medicine, No. 123, Dapei Road, Niasong District, Kaohsiung City, Taiwan
Tel: 886-77317123 ext. 8802, Fax: 886-77338009, E-mail: erickuo48@yahoo.com.tw

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