

of exon 4 during mRNA splicing and undetectable p22phox protein expression (A220). Exon 4 skipping caused an in-frame deletion and a polypeptide shortened by 28 amino acids. It is possible that the IVS3-2A>G mutation we reported may result in the expression of such a truncated protein. We speculated that such heterozygous mutations combined with G24R mutation and splice mutation might lead to an extremely low level or total absence of p22phox protein expression based on a severe clinical phenotype in our patient.

The most prevalent sites for CGD are the lungs, skin or subcutis, lymph nodes, gastrointestinal tract, and liver. Data collected from 429 patients with CGD showed the most frequently isolated microorganisms per episode were *S. aureus*, *Aspergillus* spp, and *Salmonella* spp.¹¹ Data also showed a milder clinical course and a longer survival for patients with AR CGD than those with XL CGD. However, there are individual patients with AR CGD with an early and extremely severe expression of the disease. The severe clinical course and the poor respiratory burst activity in the DHR assay in our patient indicate a greater dysfunction of NADPH oxidase, similar to patients with XL CGD. In NADPH oxidase, the membrane-bound flavocytochrome b558, consisting of gp91phox and p22phox, is the enzymatic subunit. The protein p22phox is needed to stabilize the dimer,¹² and coexpression of gp91phox and p22phox were needed to support the generation of oxygen radicals.¹³ Absence of gp91phox protein in patients with AR CGD carrying G24R mutations (A22+)⁷ or splice mutation (A22⁰)¹⁰ have been reported.

IFN- γ is a macrophage-activating cytokine produced by T cells and NK cells.¹⁴ IFN- γ could improve splicing and generate a small amount of a normal gp91phox transcript. Ezekowitz et al¹⁵ showed that using IFN- γ in XL CGD patients increased cytochrome b expression from 0 to 10% to 50% of normal values and improved reactive oxygen species production and bactericidal activity of neutrophils and monocytes. IFN- γ may enhance respiratory burst function in patients with AR CGD, thus aiding in prophylaxis of AR CGD.⁹ However, the positive effect of IFN- γ on neutrophil biology or innate immunity in general is poorly understood. Besides, IFN- γ is costly, requires repeated injections, and has adverse effects (eg, fever, which our patient had initially). Marciano et al¹⁶ also showed a high rate of successful reinitiation of IFN- γ therapy and overall long-term tolerability. Follow-up on the patient's outcome is important, especially given the timing of hematopoietic stem cell transplantation, which is a curative therapy for CGD.

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SEVERE ANAPHYLAXIS TO HYMENOPTERA STINGS: DOES THE BASAL SERUM TRYPTASE CONCENTRATION REALLY MATTER?

A recent article by Ruëff and colleagues¹ addressed risk factors associated with severe reactions in Hymenoptera venom allergy. In contrast to earlier beliefs, they showed that not only is a basal serum tryptase concentration (BTC) greater than 11.4 $\mu\text{g/L}$ the dominating risk factor for predicting severe reactions but also that a much lower concentration is currently regarded as normal (cutoff value, 5.84 $\mu\text{g/L}$). Thus, they concluded that even minor increases in BTC are associated with more frequent severe systemic reactions after a field sting.

We support this notion by reporting the case of a 43-year-old apparently healthy male surgeon who had collapsed immediately after a vespid sting on the golf course. Professional cardiopulmonary resuscitation by a physician lasted for approximately 20 minutes

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before the patient arrived at the emergency department. Initial cerebral magnetic resonance imaging showed extensive global hypoxic brain damage and bilateral ischemic lesions in the territory supplied by the posterior cerebral artery (Fig. 1A, Left). The patient was diagnosed as having apallic syndrome and was transferred to the neurorehabilitation department. As expected, a follow-up cerebral magnetic resonance image revealed marked global atrophy (Fig. 1A, Right).

Dermatologic inspection revealed multiple hyperpigmented brown-red macules and papules distributed predominantly on the trunk and lower limbs. Histologic analysis of 1 papule showed mast cells with metachromatically staining granules infiltrating the papillary dermis and around the vessels (Fig. 1B), confirming the diagnosis of urticaria pigmentosa, a form of cutaneous mastocytosis. Owing to the patient's poor overall condition, a bone marrow biopsy was not performed. However, abdominal ultrasound and radiographs of the skull and femur did not show signs of mast cell infiltration. The patient's wife reported a history of unexplained attacks of urticaria after certain meals or when swimming in cold water, pointing to the typical "mediator release syndrome" in mast cell diseases. Tragically, these clear-cut clinical symptoms were ignored for many years, and the patient remained undiagnosed although being a physician himself.

Allergologic workup revealed specific IgE levels of 0.37 kU/L to yellow jacket venom and less than 0.35 kU/L to honeybee venom,

with a low normal total IgE level of 5.6 kU/L demonstrating evidence of venom specific IgE that was previously unknown to the patient. The initial serum tryptase concentration determined a few hours after the sting was in the upper normal range (10.4 $\mu\text{g/L}$) (ImmunoCAP Tryptase; Phadia AB, Uppsala, Sweden) and returned to the patient's very low basal level of 3.1 $\mu\text{g/L}$ 4 days later.

Despite intensive neurorehabilitative measures, the patient remained in an apallic state for 8 months. He died of respiratory failure caused by pneumonia approximately 2 years after the vespid sting.

Current practice guidelines recommend specific venom immunotherapy in individuals with severe reactions after Hymenoptera stings.^{2,3} Measurement of BTCs might be helpful to identify those who simultaneously have mastocytosis or a monoclonal mast cell activation syndrome.³ Currently, the accepted upper limit for an apparently normal tryptase concentration is 11.4 $\mu\text{g/L}$. Ruëff et al¹ suggested an even lower cutoff value of 5.0 $\mu\text{g/L}$. In the present patient, with cutaneous mastocytosis and undiagnosed Hymenoptera venom allergy, the BTC of 3.1 $\mu\text{g/L}$ was even below this newly proposed cutoff value. Despite the very low BTC, the patient had an episodic, clinically severe systemic mast cell-mediated mediator release syndrome. Apart from the urticaria pigmentosa, 2 further cofactors might have worsened the shock: the physical exercise while playing golf and the fact that vespid venom allergy is reported to be associated with more severe reactions than is allergy to honeybee venom.¹ The elevated BTC a few hours after the shock

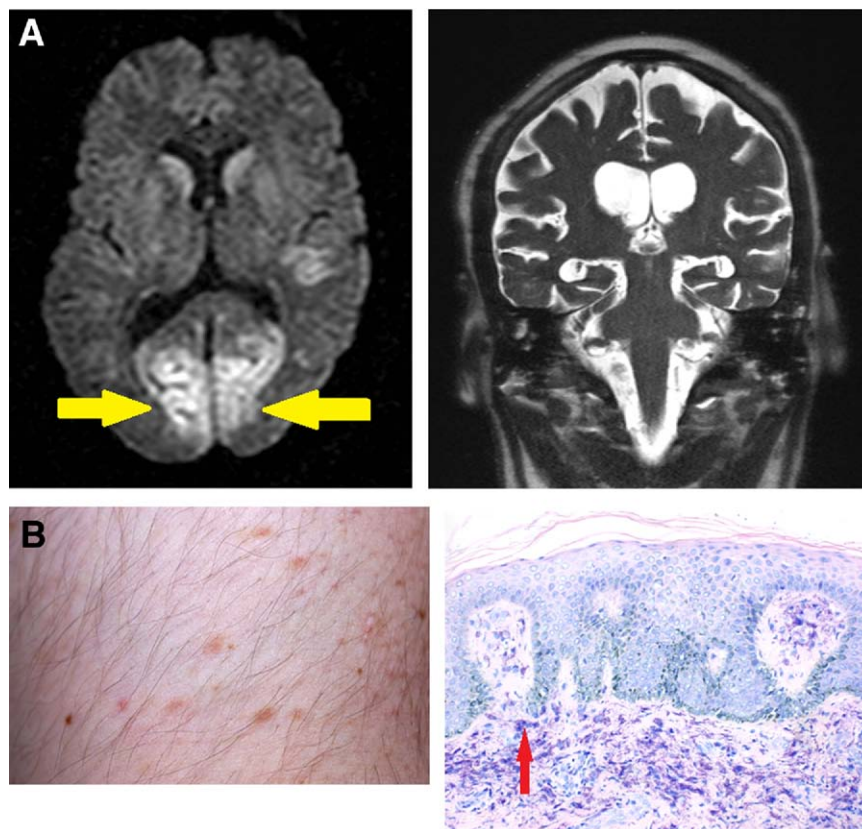


Figure 1. A, Brain atrophy after hypoxic damage. Left, Axial magnetic resonance image 6 days after the anaphylactic shock. Arrows indicate the ischemic lesions in the occipital lobes. Right, Coronal magnetic resonance image of the patient's brain 3 months after the anaphylactic shock. Note the marked global brain atrophy. B, Cutaneous mastocytosis. Left, The patient's urticaria pigmentosa. Right, Histologic image (Giemsa staining) of one of the cutaneous lesions seen in the left panel. The arrow indicates mast cells with metachromatically staining granules.

might have been caused by the activation of the mast cells because of the sting or by the resuscitation measures themselves but not by the neuronal or cardiac ischemia.^{4,5} Quite the contrary, the initial shock treatment (epinephrine, antihistamines, corticosteroids) might have even lowered the initial BTC.

In conclusion, it is noteworthy to physicians of all specialties that a thorough dermatologic inspection and specific questions searching for clinical symptoms of mediator release are required in the workup of Hymenoptera-allergic patients with a history of severe reactions because measurement of the BTC alone might not be sufficient to rule out mast cell–derived risk factors.

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SUBCUTANEOUS IMMUNOGLOBULIN INFUSION TO TREAT INFANTS AND TODDLERS WITH ANTIBODY DEFICIENCIES

To the Editor: IgG replacement in children with primary or secondary antibody deficiencies (ADs) clearly prevents recurrent bacterial infections, particularly in the respiratory tract.¹ Although the efficacy and safety of intravenous immunoglobulin (IVIG) replacement have been well documented,² intravenous access, central catheter infections, and systemic untoward effects associated with IVIG^{3–5} can be especially problematic in infants and toddlers with ADs. Although subcutaneous immunoglobulin (SCIG) therapy has gained wider acceptance in the United States, parents of infants and toddlers with ADs are rarely offered SCIG as an alternative to IVIG, and infants younger than 2 years are excluded from pharmaceutical clinical trials of new SCIG preparations, even though SCIG has successfully been given in children and adults since the 1970s.^{4–6}

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SCIG therapy is usually given weekly but can be given more often in small amounts to accommodate the personal preferences of patients with ADs and their families. SCIG therapy provides slow release of IgG into the bloodstream, enabling the provision of appropriate and stable serum IgG levels.⁷ SCIG has been reported to improve the quality of life in AD patients and often at a substantially lower cost than IVIG replacement.⁸ Despite this, little has been written about using SCIG in infants and toddlers with ADs, and our academic practice is often consulted about whether SCIG can be an effective alternative to IVIG in the youngest infants. We have found that infants and toddlers can be effectively treated with SCIG, given their poor venous access and often abundant subcutaneous tissue. We described 3 young children with different ADs as examples, many of whom we have successfully treated with SCIG therapy.

The first child was a 4-month-old (32 week gestation) infant with transient hypogammaglobulinemia of infancy. Three weeks after birth she developed an upper respiratory tract infection complicated by *Haemophilus influenzae* conjunctivitis. At 8 weeks of age, she was hospitalized with respiratory distress and lethargy secondary to pneumonia and *Klebsiella pneumoniae* bacteremia. Immunologic evaluation at 2 months was remarkable for a serum IgG level of 146 mg/dL (reference range at 40 weeks' gestation, 170–595 mg/dL), an IgM level of 22 mg/mL (reference range at 40 weeks' gestation, 6.3–25 mg/dL), a repeat serum IgG value of 89 mg/dL, and an IgA level of 9 mg/dL (reference range at 2 months of age, 2.8–47 mg/dL) at 4 months of age. The patient had normal T- and B-cell numbers for age and T-cell function but had not received any vaccinations. As a result of her clinical course, she was given an empiric prophylactic trial of IVIG, with an initial dose of 400 mg/kg at 4 months of age. She was switched to SCIG at 5 months of age, was thriving, and remained infection free with SCIG therapy for 5 additional months with stable IgG levels (Figure). She is currently not

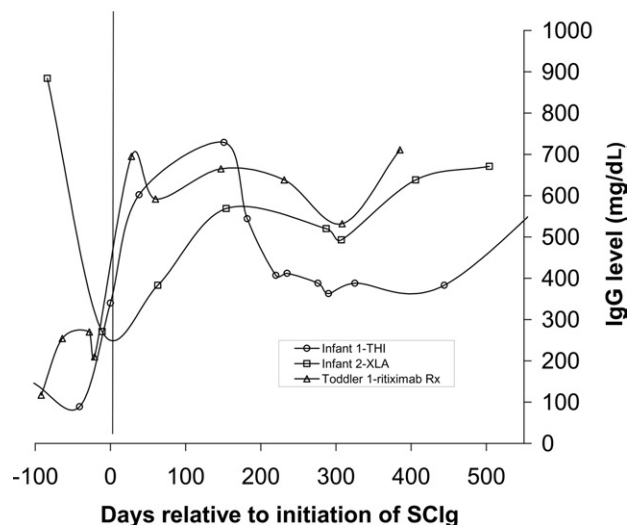


Figure. Serum immunoglobulin levels before and after initiation of subcutaneous immunoglobulin (SCIG) in infants and toddlers. Patient immunoglobulin levels were obtained via the Core Laboratory of the North Shore LIJ Health System and graphed relative to initiation of SCIG treatment. Rx indicates prescription; THI, transient hypogammaglobulinemia of infancy; XLA, X-linked agammaglobulinemia.