

## SHORT COMMUNICATION

### Cold Contact Urticaria Following Vaccination: Four Cases

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Cold contact urticaria (CCU) is a physical urticaria, also called inducible urticaria, which is triggered by exposure of the skin to cold air, surfaces or fluids. Clinical manifestations of CCU range from mild, localized whealing to life-threatening anaphylactic shock. CCU is mostly idiopathic (primary), but in rare cases it is secondary to infectious disease, with or without cryoproteins. We report here, for the first time, 4 cases of CCU that developed following vaccination, which suggests a link between these events.

#### CASE REPORT

**Case 1.** A 4-year-old boy presented with severe CCU of 3 months' duration. Symptoms had begun suddenly in the summer, 5 days after first-time vaccination with Meningitec<sup>®</sup> (anti-*Neisseria meningitidis* serogroup C conjugate vaccine), when his extremities came into contact with cold water. He presented secondary generalized hives with malaise and experienced pharyngeal discomfort on drinking cold beverages. Following this episode, typical urticarial eruptions on cold-exposed areas reoccurred every time he came into contact with cold air outdoors (Fig. 1). No other symptoms, including recurrent fever episodes, arthralgias or Raynaud's phenomenon, were noted. He had no personal or familial atopic background or familial history of CCU. Clinical examination was normal. The ice-cube test (ICT) was carried out for 3 min on the volar aspect of the patient's forearm and resulted in a large wheal within 10 min of removal (Fig. 2). Evaporative cooling was excluded. Blood test results were normal or negative: haemogram, C-reactive protein, C-reactive protein, complement C3 and C4 levels, cryoglobulins, cryo-

fibrinogen, cold agglutinins, and Epstein-Barr virus serology. Management of his condition consisted of no swimming in cold water and avoidance of both long periods in cold atmospheres and ingestion of cold liquids and foods. He was treated with high doses of desloratadine, 5 mg per day, and montelukast, 4 mg per day, with partial remission 6 months later. An epinephrine auto-injector was also prescribed.

**Case 2.** A 29-year-old man with no past medical history was referred for CCU. Symptoms had appeared 3 years earlier, 3 weeks after being vaccinated against yellow fever (Stamarile<sup>®</sup>) and hepatitis A (Havrix<sup>®</sup>). At that time, he experienced generalized urticaria with faintness and dizziness when bathing in a lake in Senegal. Thereafter, he developed hives every time he swam in fresh water or was exposed to cold air or rain, and reported having oropharyngeal angioedema when he ate ice-cream. ICT was positive at 5-min exposure and within 10 min of removal when he was tested in our unit. Blood tests were normal or negative: complete blood cell count, C-reactive protein, C3 and C4 levels, cryoglobulins and cold agglutinins. He was advised to avoid swimming in cold water, remaining in cold atmospheres for long periods, and ingesting cold liquids and foods. He was treated with high doses of desloratadine, 80 mg per day, with partial improvement and an adrenaline auto-injector was prescribed.

**Case 3.** A 2-year-old girl with no past medical history was seen for urticaria localized on cold air-exposed areas, 7 days after vaccination with Prevenar<sup>®</sup>, a *Streptococcus pneumoniae* vaccine, combined with Pentavac<sup>®</sup>, a diphtheria, tetanus, poliomyelitis/*Haemophilus influenzae* type b/pertussis vaccine. Clinical examination was within normal limits. Blood tests were normal or negative: haemogram, sedimentation rate, C3 and C4 levels and total haemolytic complement activity (CH50), renal and hepatic function tests, immunoglobulins (IgG, IgA, IgM), antinuclear antibodies, cryoglobulinaemia, and Epstein-Barr and hepatitis C virus serologies. A combination of dexchlorpheniramine and hydroxyzine were partially efficient 5 months later.



Fig. 1. Urticaria on cold air-exposed area (face) in Case 1.



Fig. 2. Positive ice-cube test (ICT) within 3 min in Case 1.

*Case 4.* A 37-year-old woman was referred for urticaria localized on cold air-exposed areas 3 weeks after vaccination for the first time with Pandemrix® to protect against the pandemic H1N1/09 influenza virus. She also experienced pharyngeal discomfort when she drank cold beverages. She had a past history of attacks of renal nephrolithiasis, uterine cervix conization, cotrimoxazole allergy and no atopy background. ICT was positive at 5-min exposure. Blood tests were normal or negative: haemogram, sedimentation rate, renal and hepatic function tests, serum protein electrophoresis test, serology for syphilis and hepatitis B (positive anti-HBs), and thyroid-function hormones. Cryoglobulins and cryofibrinogen were negative. Circulating immune complexes were slightly increased (6.4 µg/ml IgG; normal values <4) without complement consumption. She was first treated with high doses of prednisolone and antihistamine drugs (desloratadine, 20 mg per day) for 10 days with a rebound after withdrawal. She then received high doses of desloratadine, 80 mg per day, and was free of symptoms 3 months later. One year later, ICT was negative and she was vaccinated with Vaxigrip® (A/H1N1, A/H3N2, B strains of seasonal flu viruses) with no recurrence of CCU.

## DISCUSSION

CCU is mostly idiopathic (primary), but in rare cases it can be associated with cryoglobulinaemia, haematological disorders and various viral, parasitic or bacterial infections with or without cryoproteins (1). Rare cases of CCU associated with or starting shortly after, the intake of oral contraceptives (2), griseofulvin (3), angiotensin converting enzyme inhibitor (4) and alprazolam (5) have also been reported. According to the French causality assessment method, the 4 cases reported here suggest that CCU may be induced by vaccinations because of the sequence of events: absence of symptoms or laboratory abnormalities suggesting an underlying disease, onset shortly after exposure to

vaccine, and partial regression of symptoms over time with antihistamine treatment.

An immune allergic reaction to a component of the vaccines is suspected, probably to the vaccine viral strain itself because of the wide variety of incriminated vaccines. Subsequent mast cell activation is probable, but, as yet, the mechanisms and signals for cold-dependent mast cell activation have not been identified. Although our observations do not prove a causal association between vaccination and CCU, the observation that CCU is associated with infectious diseases (6, 7) and the suggestive chronology, lead us to caution physicians to keep in mind that, in rare cases, vaccination may induce CCU.

*The authors declare no conflicts of interest.*

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