

Case Report

Cardiac failure in an infant with Chediak–Higashi syndrome: A hypothesis of the effect of diadenosine polyphosphates

Ganschow R, Grabhorn E, Lemke J, Lepler R. Cardiac failure in an infant with Chediak–Higashi syndrome: A hypothesis of the effect of diadenosine polyphosphates.

Pediatr Allergy Immunol 2002; 13: 307–310. © 2002 Blackwell Munksgaard

A 14-week-old boy with undiagnosed Chediak–Higashi syndrome developed fever with a high temperature and acute cardiac failure after having received a scheduled vaccination. We hypothesize that decreased concentrations and receptor binding of serum and tissue diadenosine polyphosphates, such as AP₄A, AP₅A, or AP₆A, which are stored in various tissues and serve as extra-cellular signaling molecules or are secreted by cells in response to physiologically stressful stimuli, lead to the observed severe tachyarrhythmia.

Diadenosine polyphosphates normally have a negative chronotropic and inotropic effect. This is the first report of severe cardiac failure in a child with Chediak–Higashi syndrome and we suggest that cardiac arrhythmias should be considered in such children in the event of high fever. Our hypothesis requires further investigation in other patients.

**Rainer Ganschow¹, Enke Grabhorn¹,
Joachim Lemke² and Rudolf Lepler²**

¹Department of Pediatrics, University of Hamburg, Hamburg, Germany, ²Children's Hospital Wilhelmstift, Hamburg, Germany

Key words: Chediak–Higashi syndrome; cardiac failure; diadenosine polyphosphates; fever

Dr Rainer Ganschow, University Hospital Hamburg Eppendorf, Department of Pediatrics, Pediatric Immunology, Martinistraße 52, 20246 Hamburg, Germany

Tel.: +49-40-42803-8037

Fax: +49-40-42803-9646

E-mail: ganschow@uke.uni-hamburg.de

Accepted 1 November 2001

Chediak–Higashi syndrome (CHS) is a rare, autosomal-recessive immune-deficiency disorder, first described in 1943 (1) and characterized by recurrent pyogenic infections, giant cytoplasmic granules in neutrophils, impaired chemotaxis and bactericidal activity of neutrophils, and partial oculocutaneous albinism. Fewer than 300 cases of CHS have been reported worldwide, although some affected individuals may remain unreported or unrecognized. The hallmark of CHS is the presence of huge peroxidase-positive cytoplasmic granules in peripheral leucocytes, their bone marrow precursors, and many other cell types. The multi-system defect is caused by mutations in a single gene, located on chromosome 1q42–43. This gene was isolated in 1996 by Nagle et al. (2) and is responsible for encoding a granule-associated protein that regulates the intracellular trafficking of many proteins as well as the granule fusion. The disorder can be considered as a model for defects in vesicle formation, fusion, or trafficking. Membranes of the melanosomes,

lysosomes, and platelet-dense bodies, which have a common genesis, are involved. Some of the affected individuals undergo an 'accelerated phase', which is characterized by a non-malignant lymphohistiocytic infiltration of multiple organs, resembling lymphoma. Typical findings in these patients are fever, pancytopenia, hepatosplenomegaly, lymphadenopathy, and jaundice (3). This might be accompanied by a high mortality rate, especially as a result of severe bleeding diathesis and infections. Most of the therapy available in CHS is symptomatic and the response to appropriate antibiotics used to treat infections is often slow. The only treatment that appears to be curative in CHS is bone marrow transplantation, which has been performed in a couple of patients (4).

No cases of CHS with electrophysiological alterations of the heart have been described previously. We here report on a case of severe cardiac failure in a febrile infant with undiagnosed CHS after having received a routine

vaccination, providing a speculative hypothesis for the underlying pathophysiological mechanisms.

Case report

A newborn male from consanguineous parents, who was diagnosed (prior to birth) to have fetal tachycardia, was delivered at term. His heart rate had occasionally ranged from 175–245/min during the last 2 weeks of pregnancy. The child was monitored for 3 days after birth, but no abnormal cardiac rate or rhythm was found. An electrocardiogram and cardiac ultrasound were unremarkable. The following course was uneventful until the age of 14 weeks, when a scheduled vaccination (Diphtheria, Pertussis, Tetanus, Polio, and *Haemophilus influenzae*) was administered. Five hours after the intramuscular injection, the child began to suffer from high temperatures ($>40^{\circ}\text{C}$) and, after a further 5 h, from dyspnea and somnolence. After transfer to the emergency department of a nearby hospital, the child was diagnosed to have ventricular tachycardia, at a rate of 235 beats per minute in the electrocardiogram, and cardiogenic shock. The child was pale, and blood gas analysis showed a severe acidosis (pH 7.0, pCO_2 121 mmHg). After cardioversion, application of epinephrine and lidocaine boluses, intubation, and mechanical ventilation, the child improved and was weaned from mechanical ventilation after 18 h. There were no imbalances of blood electrolytes at the time of admission, and no signs of bacterial, viral, or fungal infections. The patient stayed in the hospital for 3 weeks, was discharged in good condition, and was followed-up as an out-patient. Several electrocardiograms showed an incomplete right-bundle branch block for 8 weeks. Echocardiographies in the following months did not show any significant pathologic findings. Unfortunately, no manual blood smear was undertaken during the former hospital stay, so the pathognomic findings of the later-diagnosed CHS were missed.

In the following course, the child was doing well except for a high frequency of respiratory tract, ear, and cutaneous infections, mostly occurring without fever. Four years after the cardiac failure, our patient was re-admitted with a severe lobar pneumonia caused by *Staphylococcus aureus* with atelectasis of the right upper lobe. After 2 weeks of conservative therapy, including administration of gentamicin and clindamycin with no significant improvement, there was a need for lobectomy of the right upper lobe. Mechanical ventilation was per-

formed for 3 days. The diagnosis of CHS was made on the typical giant granules of neutrophils seen in the peripheral blood smear. Additional typical findings for CHS were present in the boy, such as partial oculocutaneous albinism, photophobia, easy bruisability, and a mild mental retardation. There have been no pancytopenia or signs of involvement of other organs in the patient to date, so no 'accelerated phase' of the disease can be assumed. Serum immunoglobulin concentrations, quantification of lymphocyte subsets, and mitogen stimulation of lymphocytes were normal. Analysis of the oxidative metabolism (chemiluminescence) of polymorphonuclear leucocytes showed a 30% reduction, and chemotaxis a 40% reduction (Boyden chamber), compared to normal controls. The activity of natural killer cells was found to be normal, which is an unusual finding in CHS.

In the following course, no further severe infections occurred in the patient receiving antibiotic prophylaxis with trimethoprim/sulfamethoxazole. No progression of the disease has been reported to date and therefore a bone marrow transplantation has not been performed. At present, the patient has a normal electrocardiogram and a normal echocardiogram. The electroencephalogram shows mild, generalized pathologic signs. There are no enlarged lymph nodes, and no hepatosplenomegaly has been identified by clinical investigation or abdominal ultrasound. Laboratory studies revealed a hemoglobin of 12.9 g/dl, platelets of $321,000/\text{mm}^3$, and a leucocyte count of $5,900/\text{mm}^3$. If infection occurs, the parents perform an aggressive antipyresis in order to prevent recurrence of the former events.

Discussion

We present a case of an infant who developed high fever and cardiac failure after a routine vaccination as the first clinical manifestation of CHS. Review of the literature did not explain the cardiogenic shock based on side-effects of the vaccines given. There was no evidence for the suspected direct correlation between the vaccination and the subsequent cardiac failure. Additionally, a database search by the drug companies who provided the vaccines was uninformative. Side-effects after vaccinations have not been reported previously in any patient with CHS. According to Blume et al., childhood immunizations are well tolerated and should be performed in patients with CHS (3).

Retrospectively, we have to assume cardiac involvement of the CHS which led to the cardiac

failure after vaccination. In a recently published study, the effects of diadenosine polyphosphates on the cardiovascular system were investigated (5). Diadenosine polyphosphates are members of a group of dinucleoside polyphosphates that are ubiquitous, naturally occurring molecules. Diadenosine triphosphates, such as AP₄A, AP₅A, or AP₆A, are stored in various tissues and serve as neurotransmitters, extra-cellular signaling molecules or 'alarmones', secreted by cells in response to physiologically stressful stimuli (metabolic or oxidative stress). In plasma, AP₄A is cleaved to ATP and AMP, which are subsequently metabolized to adenosine and inosine. Adenosine and inosine can then be taken up via nucleoside transporters present in endothelial cells, erythrocytes, and cardiac myocytes (6). Diadenosine polyphosphates generally produce vasodilation via mechanisms which seem to result in the release of nitric oxide or prostacyclin. They produce cardiac electrophysiologic effects by altering ventricular refractoriness at sub-micromolar concentrations and influence coronary resistance (7). Heart rate and cardiac output increase with lower concentrations of AP₄A and decrease with higher concentrations via negative chronotropic and inotropic effects (8). Diadenosine polyphosphates are structurally related to ATP and their influences on cardiac electrophysiological and hemodynamic effects are comparable. The effects of AP₄A have been studied in detail in a mouse model. Hildermann et al. (9) identified a specific receptor to AP₄A on the surface of isolated cardiac myocytes dissociated from mouse hearts, and Walker et al. agree with those data by demonstrating that AP₄A binding can be antagonized by a monoclonal antibody raised against the receptor (10).

It has been clearly shown that platelets from patients with CHS have a functional defect resulting in a bleeding tendency (11). Kim et al. demonstrated a 99% lower AP₄A and a 53% lower ATP concentration in platelets from patients with CHS compared to platelets from normal subjects (12). Diadenosine polyphosphates promote platelet aggregation, which is partly a result of their slow hydrolysis to ADP and their synergy with other agonists such as platelet-activating factor. Interestingly, the negative chronotropic and inotropic actions of adenosine have important clinical implications in the treatment of tachyarrhythmias in infancy, such as the Wolff–Parkinson–White (pre-excitation) syndrome. In our patient, we speculate that a significantly decreased tissue and serum concentration of diadenosine polyphosphates predis-

posed to ventricular tachyarrhythmia. An additional factor, such as rapidly rising temperature (>40°C) after a routine vaccination, may have resulted in the observed severe cardiac failure. The binding of AP₄A to its receptor on the cell surface of the cardiac myocytes seems to be temperature dependent: optimal at 20°C and 40% less at 37°C, as found by Walker et al. (13). This phenomenon suggests that in our patient the binding of diadenosine polyphosphates was significantly defective owing to a high temperature of >40°C, leading to the lack of negative chronotropic and inotropic effects. The factors causing prenatal tachycardia episodes in our patient still remain unclear. Our findings are limited by the fact that we can only assume, as we were unable to prove, a relationship between diadenosine polyphosphates and the cardiac event. Additionally, it should be stressed that this might be an effect which does not occur in all patients with CHS, as tachyarrhythmias have not been reported in the literature to date. However, our unsubstantiated and speculative hypothesis requires investigation in other patients with CHS. Our report may be helpful in directing attention to the possibility of cardiac failure in patients with CHS who develop fever with a high temperature.

In summary, we describe a clinical case of severe cardiac failure in a child with CHS, and fever with a high temperature, after a routine vaccination. An impaired negative chronotropic effect of diadenosine polyphosphates on the cardiovascular system is hypothesized to be the underlying cause. Further studies are needed to prove this suggested link.

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