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CLINICAL REPORT

Gianotti-Crosti Syndrome and Allergic Background

GIAMPAOLO RICCI[1], ANNALISA PATRIZI[2], IRIA NERI[2], FERNANDO SPECCHIA[1], GIULIO TOSTI[2] and MASSIMO MASI[1]

Departments of [1]Paediatrics and [2]Clinical and Experimental Medicine, Division of Dermatology, University of Bologna, Bologna, Italy

The aim of the study was to verify whether there is a relationship between Gianotti-Crosti syndrome and an allergic background in children. Twenty-nine children affected by Gianotti-Crosti syndrome were first screened for a large panel of microbiological examinations, including serological and cultural tests for viruses and bacteria. A causative agent was identified in only 10 cases (34.4%). In five cases a diagnosis of Epstein—Barr virus infection was made on the basis of significant titres of anti-Epstein-Barr virus antibodies (IgM) associated with constitutional symptoms (fever, pharyngitis – tonsillitis). Our data concur with several clinical studies demonstrating that Epstein-Barr virus is now the most common viral agent associated with Gianotti-Crosti syndrome. For allergic evaluation, a group of 59 age- and sex-matched children investigated for recurrent infections were used as controls. The presence of atopic dermatitis (24.1%) in those with Gianotti-Crosti syndrome was significantly higher ($p < 0.005$) than in the control group (6.8%). In addition, a more common family history for atopy was 51.7% vs. 31% ($p < 0.027$) and the percentage of patients with total IgE greater than +2 SD for age higher than in controls (27.6% vs. 13.7%), as was the percentage of specific IgE present (31% vs. 17.2%). These results indicate that atopy is significantly associated with Gianotti-Crosti syndrome. ***Key words: acrodermatitis; atopic dermatitis; infantile papular eruption; allergy; Epstein-Barr virus.***

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Giampaolo Ricci, Department of Paediatrics, University of Bologna; Via Massarenti 11, IT-40138 Bologna, Italy. E-mail: ricci@med.unibo.it

Papular acrodermatitis of childhood, first described by Gianotti in 1955, is a self-healing papular eruption symmetrically distributed on the face, buttocks and extremities (1). In 1970, an anicteric hepatitis B, Australia antigen-positive (HBSAg), subtype *ayw*, was correlated with this disorder (2, 3). Subsequently, other cases with the same clinical features were observed, although the hepatitis B virus (HBV) could not always be demonstrated to have a causative role. This condition was thus nominated papulo-vesicular acrolocated syndrome by Gianotti (4–6). In the latter cases a different viral infection or recent immunization was indicated as the possible cause of the cutaneous eruption. In 1992, in a retrospective analysis of 308 cases, Caputo et al. (7) affirmed that a clinical distinction between different aetiologic varieties of papular acrolocated eruptions was not possible based solely on cutaneous features, and suggested that the term "Gianotti-Crosti syndrome" (GCS) should be utilized for all acrolocated papular eruptions (7). Why different aetiologic agents should produce the same clinical picture remains an open question. In this retrospective study, a group of children affected by GCS were examined in order to identify various aetiological factors and to assess atopy as a possible predisposing factor.

MATERIAL AND METHODS

Patients

Twenty-nine children (15 boys and 14 girls, mean age 2 years and 7 months, range 1–9 years) with a diagnosis of GCS examined between November 1990 and December 1999 were included in this study. They were all Caucasians. Two cases were observed in 1994, 3 in 1995, 6 in 1996, 7 in 1997, 7 in 1998 and 4 in 1999. GCS occurred between January and March in 10 cases, between April and June in 13, between July and September in 1 case and between October and December in 5 cases.

The following data were recorded: sex and age of the patients at onset; the season of occurrence of GCS; the presence of associated prodromes or previous immunizations; the presence of systemic constitutional symptoms or other associated conditions and duration of the rash.

We compared these patients with a control group referred to us for recurrent infections: we studied 59 children (30 boys and 29 girls; mean age 2 years and 4 months, range 1–9 years); in patients and controls the anamnesis was aimed to analyse personal and family history of atopic diseases including asthma, hay fever, allergic conjunctivitis, atopic dermatitis (AD) and allergic urticaria.

Methods

Biochemical and bacterio-virological investigations. Laboratory tests performed in all patients affected by GCS included complete blood cell counts, liver function tests, ESR, total serum protein and immunoglobulin IgG, IgA, IgM evaluation.

Microbiological studies included serologies to hepatitis A, B and C viruses, Adenovirus, Parainfluenza virus I and III, Poliovirus, Coxsackie B virus, Cytomegalovirus, Epstein-Barr virus (EBV), Respiratory syncytial virus, Herpes simplex virus I, II and VI, Herpes zoster virus, Parvovirus B19, *B. burgdorferi, M. pneumoniae, Rickettsia* and *T. gondii.*

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Screening for HIV infection was not performed since the patients' personal and family histories did not justify this. Cultures for bacteria were taken from throat swabs and stool samples. Throat swabs and stool samples were examined in accordance with a conventional procedure used in our microbiological laboratory for viral (Rotavirus, Enterovirus and Adenovirus) and parasite isolation.

Allergometric assessment. GCS patients and the control group were studied for the following parameters: total IgE serum level detected using an ELISA method; circulating specific IgE determined using RAST CAP-System (Pharmacia, Sweden) for the main food (hen's egg, cow's milk, soy, wheat, fish, tomatoes, peanuts) and inhalant allergens (timothy grass, *D. pteronyssinus, D. farinae*, cat dander, *Alternaria tenuis*).

Detection limit of the CAP system was 0.35 kU/l IgE; the specific IgE values were divided into classes as follows: P0 = <0.35 kU/l; P1 = 0.35 – 0.69; P2 = 0.70 – 3.40; P3 = 3.50 – 17.40; P4 = 17.50 – 49.90; P5 = 50.0 – 99.9; P6 > 100 kU/l. Children with specific IgE levels above the detection limits were regarded as sensitized.

Statistical analysis. Differences between GCS patients and control group were compared using χ^2 tests. A p value of 0.05 or less was regarded as significant.

The study was approved by the local University Research Fund Committee and supported by grant no. 2.09.2.171 from the Ministry for University and Research.

RESULTS

Clinical and microbiological data

The main clinical and microbiological data for GCS cases are summarized in Fig. 1. Prodromes occurred in 8 patients. These consisted of mild to moderate fever in 2 cases and cough in 3 cases; one child was referred as suffering from stomach-ache followed by vomiting and diarrhoea throughout the whole month before the skin eruption occurred (other members of his family were also affected); one presented influenza-like symptoms and one pharyngotonsillitis as a prodrome of mononucleosis. One patient had been immunized 3 days before the skin eruption with a combined measles-mumps-rubella vaccine.

At the time of the skin eruption, constitutional symptoms were present in 10 patients: 6 cases showed respiratory tract infection (rhinitis and/or pharyngitis-tonsillitis, bronchitis), 2 cases had isolated moderate fever, 2 children complained of mild pruritus; the other children were in good general health. Physical examination of all GCS patients showed a symmetrical skin eruption consisting of monomorphous, erythematous sometimes purpuric, flat-topped, 2 – 6 mm diameter papules that involved the face, buttocks and limbs. In all cases the dermatosis had a self-limiting course lasting from 3 to 8 weeks, without recurrences.

Laboratory investigations revealed that one patient had lymphocytosis, 5 had eosinophilia, one had a slightly raised ESR and 4 had slightly raised levels of aminotransferases.

Microbiological investigations, including serologies and cultures, revealed that: one patient had a positive throat swab for *S. pyogenes*; in two patients stool samples were positive for viruses (Adenovirus, Enterovirus) and in one patient for bacterial agents (enterotoxic *E. coli*). Viral investigations showed the presence of anti-EBV (IgG, IgM, EBNA) diagnostic for a recent infection by EBV in 5 cases; Ab anti-cytomegalovirus and virus detection suggested a concomitant cytomegalovirus infection in one patient. Finally, in one patient anti parvovirus B19 IgM antibodies were detected. The causative agent was clearly identified in only 10 cases (34.4%). In all the remaining patients microbiological investigations were negative or not significant, showing low titres of specific antibodies or only the presence of IgG antibodies that are not significant for a recent infection.

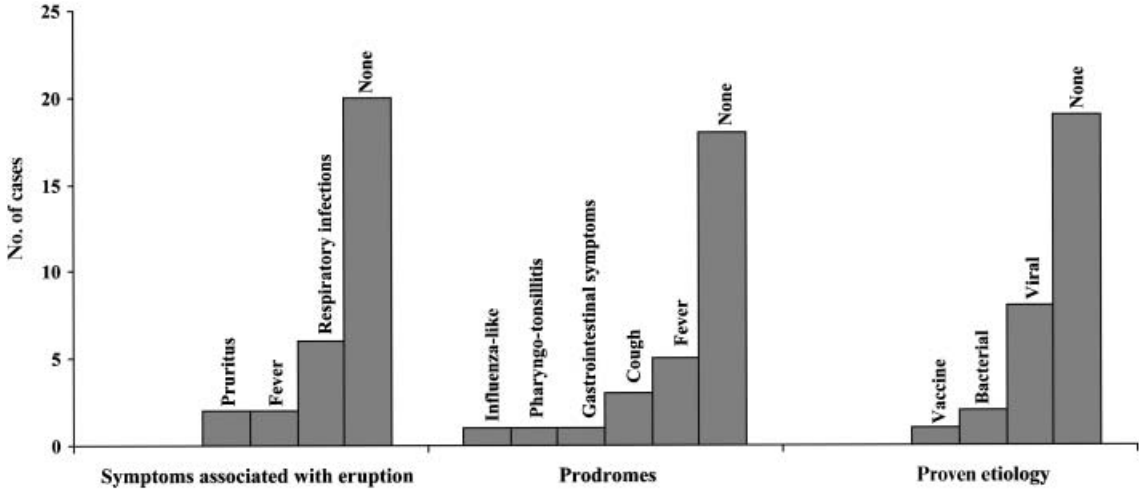

Fig. 1. Main clinical and laboratory data in 29 children with Gianotti-Crosti syndrome.

Allergologic data

Seven out of 29 children with GCS (24.1%) presented with AD, according to the criteria of Hanifin & Rajka (8); of these, 2 had normal allergological laboratory values, while the remaining 5 presented altered IgE values. One patient had high IgE serum levels, and two had both high IgE serum levels and specific IgE antibodies. Three of the 7 children in this group also have a positive family history of atopic diseases.

Among all 29 patients, family history for atopy in first-degree relatives was positive in 15 (51.7%); of these 15 families, 9 had one atopic member, while 6 presented 2 atopic members; IgE serum levels were elevated in 8 children (27.6%) and specific IgE for food or inhalant allergens were positive in 9 out of 29 patients (31%).

In the control group, 4 children showed AD (6.8%); family history was positive for atopy in first-degree relatives in 15 children (25%) the IgE serum levels were elevated in 6 children (10%), and specific IgE for food or inhalant allergens were positive in 11 children (18%).

None of the patients with GCS or the control group presented atopic respiratory diseases. A comparison of the study group with the control group shows higher percentages of allergometric parameters in the GCS (Fig. 2).

DISCUSSION

In the 3rd millennium, GCS remains an enigmatic reaction to different agents, even if the link between the rash and infections has now been firmly established (9). Nevertheless, an aetiologic diagnosis may only be reached in less than half of the patients even using a large range of microbiological investigations (10), as proposed in this study where the causative agent was identified in 10 cases (34.4%). In one of these patients, immunization had been performed a few days prior to the rash and in 9 patients a microbiologic agent was identified as a possible aetiologic agent.

In 5 patients a diagnosis of GCS related to EBV infection was made on the basis of the evidence of significant titres of anti-EBV antibodies (IgM) associated with constitutional symptoms (fever, pharyngo-tonsillitis).

Our data agree with studies in the literature that EBV is now the most common viral agent associated with GCS (11–17). However, symptoms and signs suggestive of an associated infection were observed in a further nine patients where no microbiological evidence of an associated infection was identified. In these patients, we cannot exclude the possibility that other, still unknown, infectious agents may be the cause.

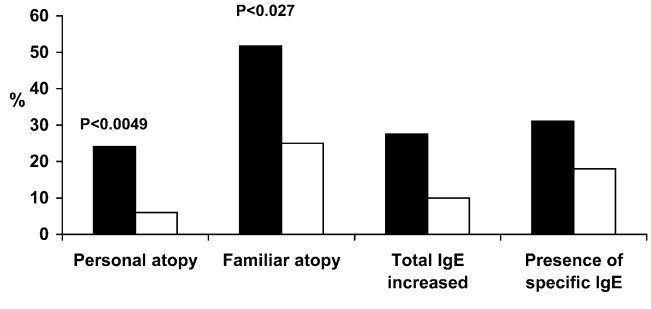

Fig. 2. Main allergologic data in 29 children with Gianotti-Crosti syndrome (■) and in the control group (□). Percentage of personal atopic dermatitis, familiar atopy, increased IgE and presence of specific IgE.

Atopic relationship

In our initial studies of GSC we observed that many patients presented allergic diseases or laboratory results indicating atopy. We therefore began to investigate more systematically whether there was a tendency to allergy in our patients. AD was observed in 7 (24.1%) of the children with GCS, a statistically significant higher percentage than in our control group (6.8%). The frequency found in the control group is similar to that reported by the International Study of Asthma and Allergies in Childhood in our region (Emilia-Romagna, Italy) showing a presence of AD of almost 5.4% (18).

Typically, an atopic patient develops a spectrum of age-correlated "atopic diseases" (19) during the first years of life; gastrointestinal and skin symptoms predominate, often caused by food allergens, while asthma and rhinitis due to inhalant allergens tend to develop later. Our GCS patients and control group (mean age 2.5 years) with atopy were characterized by skin symptoms. Interestingly, two of the AD children in the GCS group were negative in the allergic laboratory tests; it is thus possible to hypothesize that both the "intrinsic form" (i.e. without positive allergic laboratory tests) and the "extrinsic form" (i.e. with positive allergic laboratory tests) of AD may be involved in this syndrome.

The risk of developing an IgE-mediated allergy is 40%–60% for a child if both parents have atopy (19, 20). Therefore, among the atopic group we may also add the IgE-sensitized and the children with a positive family history of atopy, especially the six cases with a history of two first-degree family members. Furthermore, we have to bear in mind that our children were at the age when atopic diseases are not yet fully expressed clinically.

We therefore consider that atopy may play an important role in conditioning the onset of the clinical papular eruption features of GCS in children exposed to different microbiological agents. Furthermore, the hypothesis that atopic subjects, particularly during the first years of life, may express a "papular prone" phenotype when exposed to different external stimuli is confirmed by reports of a high percentage of atopy in patients with papular dermatoses such as frictional lichenoid eruption or lichen striatus (21–23). These

dermatoses resemble GCS regarding clinical features (morphology of lesions, papules with typical distribution), and age range and spontaneously regressing evolution.

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