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Is Gianotti–Crosti Syndrome Associated with Atopy? A Case–Control Study and a Postulation on the Intrinsic Host Factors in Gianotti–Crosti Syndrome

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Abstract

Objectives: To investigate whether Gianotti–Crosti syndrome (GCS) in children is associated with atopy.

Methods: The setting was two outpatient clinic. Diagnoses of asthma and atopic dermatitis (AD) were made according to internationally accepted diagnostic criteria. Allergic rhinitis, atopic urticaria, and allergic conjunctivitis were diagnosed clinically. Participants were children with GCS diagnosed over the previous 5 years. For any child with GCS, we extracted the record of the subsequent age and sex pair-matched child seen for problems unrelated to the skin as controls.

Results: We retrieved the records of 37 pairs of study and control subjects; 28 (76%) children with GCS and 9 (24%) controls had AD (risk ratio [RR] = 3.11 [95% confidence interval {CI} 1.73, 5.73]), 31 (84%) children with GCS and 19 (51%) controls had at least one atopic condition (RR = 1.63 [95% CI 1.13, 2.18]) and 11 (30%) children with GCS and 2 (5%) controls had at least three atopic conditions (RR = 5.50 [95% CI 1.29, 35.35]).

Conclusion: GCS is significantly associated with AD and the presence of atopic conditions.

Gianotti–Crosti syndrome (GCS) (1) is a paraviral exanthem known or suspected to be associated with viral infections including hepatitis B virus (2–8), Epstein–Barr virus (9–14), Coxsackie viruses (10, 15), cytomegalovirus (16, 17), enteroviruses (18), hepatitis A virus (19), and herpes simplex virus 1 infections (20).

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We previously reported a case–control study using polymerase chain reaction (PCR) to detect DNA, reverse transcription PCR to detect messenger RNA transcripts, and serology to detect seroconversion in the plasma, sera, and peripheral blood mononuclear cells of children with GCS and found that GCS in Hong Kong might be related to human herpesvirus (HHV) 6B infection (21).

The immunopathogenesis of GCS is largely unknown. Apart from delayed hypersensitivity, a role of immunoglobulin E (IgE)–mediated hypersensitivity has been suspected. Children with histories of GCS were reported to be significantly more likely to have atopic dermatitis (AD) and family histories of atopy than children without GCS (22). Topical (inhalers, sprays) and systemic corticosteroids are the mainstays of treatment for some atopic diseases. Topical (creams, ointments) and systemic corticosteroids have also been reported to be of efficacy in some patients with GCS (23, 24).

GCS has also been reported to be associated with pediatric idiopathic hypereosinophilic syndrome (25), which is intimately related to hyperimmunoglobulinemia (26) and is responsive to treatment with systemic corticosteroids (27, 28). We previously reported a 7-year-old girl with GCS and hyper-IgE syndrome (Job's syndrome) (29). The pertinence of IgE-mediated humoral responses in GCS requires more research.

It is important to determine whether GCS is significantly associated with atopy, because this will enhance our understanding of the immunopathogenesis of GCS. This knowledge might shed light on the prevention and treatment of the paraviral exanthems.

We report here a case–control study investigating the association between atopy and GCS in children.

METHODS

The setting was two outpatient clinic affiliated with a major teaching hospital. The first author, who has training and qualifications in pediatrics and dermatology, provided the services. Patients of all ages could consult us without need for referral. One clinic was located in the Mid-Levels, an affluent residential area in Hong Kong. Most patients were middle class or above. The other clinic was located in the downtown region of the city, with patients from all economic levels.

We stored the clinical reports as hard and electronic copies. During the first consultation with each patient, we took a full medical history. Because the academic interest of the investigator is diseases, we had allocated a separate page to record the dermatologic and atopic histories of all patients.

We searched our diagnostic entries for Gianotti–Crosti syndrome, papular acrodermatitis, and viral rash; reviewed the clinical records; and identified all children (younger than 16 years of age) with GCS diagnosed over the previous 5 years. The diagnoses were made according to a validated diagnostic criteria (32, 33). We excluded adults with GCS, because it has not been determined whether children and adults with GCS are homogeneous (32).

For any child with GCS, we extracted the clinical records of the subsequent child of the same sex and age (within 1 calendar year) who consulted us for problems unrelated to the skin as control subjects.

We charted histories of atopic conditions. We diagnosed AD according to the UK Working Party's Diagnostic Criteria for Atopic Dermatitis (34–36). For asthma, we followed the consecutive versions of diagnostic criteria of the British Thoracic Society (37, 38). Allergic rhinitis and allergic conjunctivitis were diagnosed clinically. We diagnosed atopic urticaria as a subset of AD with an urticarial component.

Because the numerical values of several entries might be less than five, we used the Fisher exact probability test to calculate two-sided p-values. Risk ratios (RRs) with 95% confidence intervals (CIs) were calculated where applicable. Because we would have had missing data if we had extended the period of our retrospective recruitment, it was not feasible to estimate the number of subjects for a power of 0.80 for all parameters. We therefore employed McNemar's Z-test to back-calculate the powers.

RESULTS

We retrieved medical records of 37 children diagnosed with GCS (n = 23 boys, n = 14 girls, ages 7 months–14 years, mean age 4.5 ± 3.5 years) and 37 control subjects (ages 9 months–13 years, mean age 4.3 ± 3.4 years). All study and control subjects were Chinese, so subgroup analyses according to race were not performed.

Our findings are shown in Table 1. Fourteen (38%) children with GCS and 6 (16%) control subjects had asthma (RR = 2.33 [95% CI 0.95, 6.31]), 18 (49%) children with GCS and 11 (30%) controls had allergic rhinitis (RR = 1.64 [95% CI 0.86, 3.22]), and 28 (76%) children with GCS and 9 (24%) controls had AD (RR = 3.11 [95% CI 1.73, 5.73]). The differences were insignificant for atopic urticaria and allergic conjunctivitis.

Although a significant difference was found only for AD, aggregation of results demonstrated statistically and clinically significant differences; 31 (84%) children with GCS and 19 (51%) controls had at least

TABLE 1. *Comparison of Atopic Tendencies of 37 Children with Gianotti–Crosti Syndrome and 37 Age and Sex Pair-Matched Control Subjects*

Atopic tendency	Children with Gianotti–Crosti syndrome (n = 37)	Age and sex pair-matched controls (n = 37)	Risk ratio (95% confidence interval)	p -Value (Fisher exact probability test; two-tailed)	Power (McNemar Z-test)
	n (%)				
Asthma	14 (38)	6 (16)	2.33 (0.95–6.31)	.06	0.57
Allergic rhinitis	18 (49)	11 (30)	1.64 (0.86–3.22)	.15	0.54
Atopic dermatitis	28 (76)	9 (24)	3.11 (1.73–5.73)	<.001	1.00
Atopic urticaria	4 (11)	0 (0)	Infinity (0.69–infinity)	.11	Inapplicable
Allergic conjunctivitis	2 (5)	4 (11)	0.50 (0.07–3.03)	.67	0.21
At least one atopic condition	31 (84)	19 (51)	1.63 (1.14–2.18)	.006	0.87
At least two atopic conditions	21 (57)	9 (24)	2.33 (1.20–4.80)	.009	0.91
At least three atopic conditions	11 (30)	2 (5)	5.50 (1.29–35.35)	.01	0.88
At least four atopic conditions	3 (8)	0 (0)	Infinity (0.463–infinity)	.24	Inapplicable
All five atopic conditions	0 (0)	0 (0)	Inapplicable	>.99	Inapplicable

one atopic condition (RR = 1.63 [95% CI 1.13, 2.18]). The greatest difference was found in children with at least three atopic conditions (11 [30%] study subjects, 2 [5%] controls; RR = 5.50 [95% CI 1.29, 35.35]).

The powers for association between individual atopic conditions and GCS reached 0.80 only for AD (power = 1.00). The powers were greater than 0.80 for the associations between GCS and at least one (power = 0.87), two (power = 0.91), and three (power = 0.88) atopic conditions.

DISCUSSION

Interpretation of the Results

The prevalences of atopic conditions in children without GCS were similar to previously reported prevalences of atopic conditions in children in Hong Kong (39). For dermatitis, the prevalence was 24% for our control subjects and 30.7% (life time dermatitis) for patients, as previously reported (39). For allergic rhinitis, the prevalence was 30% for our control subjects and 42.4% (life time rhinitis) for patients, and 37.5% (current rhinitis) as reported previously.

The association between GCS and atopic diseases has been previously reported (22). We have also reported a 7-month-old girl with known hyper-IgE syndrome and GCS (29), the severity of the latter being among the highest we have seen. She had AD and asthma. Her father also had AD, recurrent skin abscesses in childhood, and very high IgE levels. We thus postulated that immunodeficiency coupled with atopy could have contributed to the severe GCS eruption.

In our present study, we found that GCS was significantly associated with AD, whereas the associations with asthma, allergic rhinitis, atopic urticaria, and allergic conjunctivitis were insignificant, although the risk of asthma (RR = 2.33) was rather high. The wide 95% CI (0.95, 6.31) might be related to the small sample size.

Implications for Practicing Clinicians

The results of this study have some implications for clinicians who are managing children with GCS. Our results highlight the association between GCS and atopy, in line with the known difficulty in differentiating AD from AD with overlying GCS (40), although this knowledge linking GCS to atopy does not enable us to treat or prevent GCS. GCS is mostly a benign condition. Moreover, the fact that we identified only 37 children with GCS in 5 years indicates that GCS is not particularly common in our population.

Implications for Investigators

We urge other investigators to explore the immunopathogenesis of GCS, focusing on atopies and hyper-IgE states. Because the extreme hyper-IgE state is hyper-IgE syndrome, immunomodulations in this syndrome might parallel the immunopathogenesis of GCS to a certain extent. The significant association between GCS and atopic tendencies indicates that GCS might be a common pathway for the body's impaired cell-mediated, humoral, and local immunologic responses against pathogens, particularly hepatitis B and Epstein–Barr viruses.

Other investigators might explore whether the three known single-nucleotide polymorphisms (rs2897442199 [*KIF3A*], rs479844 [*OVOL1*], rs2164983 [*ACTL9*]) are associated with children with AD and GCS.

Limitations

The most important limitation of our study is that, because of the retrospective design, data on total IgE levels and radioallergosorbent test results were not available. PCR in plasma and peripheral blood mononuclear cells and serologic investigations in acute and convalescent sera for viruses were also not conducted.

Moreover, the numbers of study and control subjects were small. Thus type II errors were possible. The powers for the associations between individual atopic states and GCS were less than 0.80, except for AD, although upon aggregation of atopic states, the powers were strong.

Another limitation might be whether our results for Chinese children can be compared with those of a study in Italy with Caucasian children (22). Different phenotypes have been reported for Asian children with AD (44,45). Sandpaper-like skin lesions on the elbow, knee, and lateral malleolus; hangnails; and ventral wrist dermatitis are more frequently seen in patients with AD in Korea (45), but the diagnostic criteria of AD of the UK Working Party are applicable to children of different ethnicities (34–36). The extent of the generalizability of our results and those of the Italian study (22) to other populations remains to be seen.

We recruited control subjects from our clinics only, not by randomly selecting healthy children. Selective bias is possible, although because the study subjects were diagnosed in our two clinics, the most valid control subjects should be age and sex pair-matched children who consulted us for problems unrelated to the skin. Recruiting healthy children randomly might serve as a second control group to minimize selection bias, although these children would not be pair-matched to the study subjects and thus would be more heterogeneous. Moreover, the criteria to diagnose atopic conditions might not be similar to those in our study in terms of validity, interrater reliability, and intrarater reliability.

We believe that the retrospective nature of our study, which minimizes systemic bias in diagnosing GCS and atopic conditions, the availability of age and sex pair-matched controls, and data recruitment in a primary care setting incorporating children representative of the entire clinical spectrum of GCS partly compensate for these shortcomings.

CONCLUSIONS

GCS is significantly associated with AD and the presence of atopic conditions. Atopy seems to be an important host factor in the immunopathogenesis of GCS.

REFERENCES

1. Gianotti F. Viral anicteric hepatitis in infantile papular acrodermatitis. Epatologia 1966;12:171–191.
2. De Gaspari G, Bardare M, Costantino D. Au antigen in Crosti-Gianotti acrodermatitis. Lancet 1970;1:1116–1117.
3. Ishimaru Y, Ishimaru H, Toda G et al. An epidemic of infantile papular acrodermatitis (Gianotti's disease) in Japan associated with hepatitis-B surface antigen subtype ayw. Lancet 1976;1:707–709.
4. Colombo M, Gerber MA, Vernace SJ et al. Immune response to hepatitis B virus in children with papular acrodermatitis. Gastroenterology 1977;73:1103–1106.
5. Toda G, Ishimaru Y, Mayumi M et al. Infantile papular acrodermatitis (Gianotti's disease) and intrafamilial occurrence of acute hepatitis B with jaundice: age dependency of clinical manifestations of hepatitis B virus infection. J Infect Dis 1978;138:211–216.
6. Kanzaki S, Kanda S, Terada K et al. Detection of hepatitis B surface antigen subtype adr in an epidemic of papular acrodermatitis of childhood (Gianotti's disease). Acta Med Okayama 1981;35:407–410.
7. Ono E. Natural history of infantile papular acrodermatitis (Gianotti's disease) with HBsAg subtype adw. Kurume Med J 1988;35:147–157.
8. Spear KL, Winkelmann RK. Gianotti-Crosti syndrome. A review of ten cases not associated with hepatitis B. Arch Dermatol 1984;120:891–896.
9. Ehringhaus C, Happle R, Dominick HC et al. Gianotti-Crosti syndrome. HBsAG-negative papular acrodermatitis, an infantile papulovesicular acrolocalized syndrome. Monatsschr Kinderheilkd 1985;133:111–113.
10. Taïeb A, Plantin P, Du Pasquier P et al. Gianotti-Crosti syndrome: a study of 26 cases. Br J Dermatol 1986;115:49–59.
11. Drago F, Crovato F, Rebora A. Gianotti-Crosti syndrome as a presenting sign of EBV-induced acute infectious mononucleosis. Clin Exp Dermatol 1997;22:301–302.
12. Hofmann B, Schuppe HC, Adams O et al. Gianotti-Crosti syndrome associated with Epstein-Barr virus infection. Pediatr Dermatol 1997;14:273–277.
13. Terasaki K, Koura S, Tachikura T et al. Gianotti-Crosti syndrome associated with endogenous reactivation of Epstein-Barr virus. Dermatology 2003;207:68–71.
14. Hall LD, Eminger LA, Hesterman KS et al. Epstein-Barr virus: dermatologic associations and implications: part I. Mucocutaneous manifestations of Epstein-Barr virus and nonmalignant disorders. J Am Acad Dermatol 2015;72:1–19.
15. James WD, Odom RB, Hatch MH. Gianotti-Crosti-like eruption associated with coxsackievirus A-16 infection. J Am Acad Dermatol 1982;6:862–866.
16. Berant M, Naveh Y, Weissman I. Papular acrodermatitis with cytomegalovirus hepatitis. Arch Dis Child 1983;58:1024–1025.

17. Tzeng GH, Hsu CY, Chen HC. Gianotti-Crosti syndrome associated with cytomegalovirus infection: report of one case. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1995;36:139–141.
18. Draelos ZK, Hansen RC, James WD. Gianotti-Crosti syndrome associated with infections other than hepatitis B. JAMA 1986;256:2386–2388.
19. Pouillaude JM, Moulin G, Morlat C et al. Gianotti-Crosti's infantile papular acrodermatitis. Nosological relationship with viral hepatitis. A fatal outcome. Pediatrie 1975;30:351–360.
20. Dauendorffer JN, Dupuy A. Gianotti-Crosti syndrome associated with herpes simplex virus type 1 gingivostomatitis. J Am Acad Dermatol 2011;64:450–451.
21. Chuh AA, Chan HH, Chiu SS et al. A prospective case control study of the association of Gianotti-Crosti syndrome with human herpesvirus 6 and human herpesvirus 7 infections. Pediatr Dermatol 2002;19:492–497.
22. Ricci G, Patrizi A, Neri I et al. Gianotti-Crosti syndrome and allergic background. Acta Derm Venereol 2003;83:202–205.
23. Iorizzo LJ III, Scott G, Tausk FA. Gianotti-Crosti syndrome: a case report in an adult. Cutis 2012;89:169–172.
24. Stojkovic-Filipovic J, Skiljevic D, Brasanac D et al. Gianotti-Crosti syndrome associated with Epstein-Barr virus and parvovirus B-19 co-infection in a male adult: case report and review of the literature. G Ital Dermatol Venereol 2016;151:106–111.
25. Molvi MA, Sharma YK, Dash K et al. Pediatric idiopathic hypereosinophilic syndrome with Gianotti-Crosti syndrome: a novel presentation. Int J Dermatol 2015;54:1416–1419.
26. Hosoki K, Nagao M, Iguchi K et al. An 8-year-old boy with hypereosinophilic syndrome. Int Arch Allergy Immunol 2011;155:117–122.
27. Farruggia P, D'Angelo P, Acquaviva A et al. Hypereosinophilic syndrome in childhood: clinical and molecular features of two cases. Pediatr Hematol Oncol 2009;26:129–135.
28. Kao CC, Ou LS, Lin SJ et al. Childhood idiopathic hypereosinophilic syndrome: report of a case. Asian Pac J Allergy Immunol 2002;20:121–126.
29. Chuh A. The association of hyperimmunoglobulin E syndrome and Gianotti-Crosti syndrome—speculations on the roles of atopy and immunoglobulin E in a viral exanthem. Pediatr Infect Dis J 2005;24:942.
30. Drago F, Ciccarese G, Rebora A et al. Relapsing pityriasis rosea. Dermatology 2014;229:316–318.
31. Drago F, Broccolo F, Ciccarese G et al. Persistent pityriasis rosea: an unusual form of pityriasis rosea with persistent active HHV-6 and HHV-7 infection. Dermatology 2015;230:23–26.
32. Chuh AAT. Diagnostic criteria for Gianotti-Crosti syndrome—a prospective case control study for validity assessment. Cutis 2001;68:207–213.
33. Chuh A, Lee A, Zawar V. The diagnostic criteria of Gianotti-Crosti syndrome—are they applicable to children in India? Pediatr Dermatol 2004;21:542–547.
34. Williams HC, Burney PG, Hay RJ et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. I. Derivation of a minimum set of discriminators for atopic dermatitis. Br J Dermatol 1994;131:383–396.
35. Williams HC, Burney PG, Strachan D et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. II. Observer variation of clinical diagnosis and signs of atopic dermatitis. Br J Dermatol 1994;131:397–405.
36. Williams HC, Burney PG, Pembroke AC et al. The U.K. Working Party's Diagnostic Criteria for Atopic Dermatitis. III. Independent hospital validation. Br J Dermatol 1994;131:406–416.
37. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Thorax 2003;58(Suppl 1):i1–i94.
38. British Thoracic Society Scottish Intercollegiate Guidelines Network. British Guideline on the Management of Asthma. Thorax 2008;63(Suppl 4):iv1–iv121.
39. Lee SL, Wong W, Lau YL. Increasing prevalence of allergic rhinitis but not asthma among children in Hong Kong from 1995 to 2001 (phase 3 international study of asthma and allergies in childhood). Pediatr Allergy Immunol 2004;15:72–78.
40. Llanora GV, Tay CM, van Bever HP. Gianotti-Crosti syndrome: case report of a pruritic acral exanthema in a child. Asia Pac Allergy 2012;2:223–226.
41. Paternoster L, Standl M, Chen CM et al. Meta-analysis of genome-wide association studies identifies three new risk loci for atopic dermatitis. Nat Genet 2011;44:187–192.
42. Lepre T, Cascella R, Ragazzo M et al. Association of *KIF3A*, but not *OVOL1* and *ACTL9*, with atopic eczema in Italian patients. Br J Dermatol 2013;168:1106–1108.
43. Kang Z, Li Q, Fu P et al. Correlation of *KIF3A* and *OVOL1*, but not *ACTL9*, with atopic dermatitis in Chinese pediatric patients. Gene 2015;571:249–251.
44. Loo EX, Shek LP, Goh A et al. Atopic dermatitis in early life: evidence for at least three phenotypes? Results from the GUSTO Study. Int Arch Allergy Immunol 2015;166:273–279.
45. Lee HJ, Cho SH, Ha SJ et al. Minor cutaneous features of atopic dermatitis in South Korea. Int J Dermatol 2000;39:337–342.