Diagnostic Criteria for Gianotti-Crosti Syndrome: A Prospective Case-Control Study for Validity Assessment

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GOAL

To describe a set of diagnostic criteria for Gianotti-Crosti Syndrome (GCS) and assess their validity

OBJECTIVES

Upon completion of this activity, dermatologists and general practitioners should be able to:

1. Describe the positive and negative clinical features of GCS.
2. Identify the differences between GCS and other similar dermatological conditions.
3. Discuss the etiology of GCS and its causal relationship with other events.

CME Test on page 214.

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This activity has been planned and produced in accordance with ACCME Essentials.

No criteria exist for the modern diagnosis of Gianotti-Crosti syndrome (GCS). Our study objectives were to determine diagnostic criteria for GCS and to assess their validity using a prospective case-control design. We reviewed the clinical features of children with GCS who were reported in the literature from 1996 to 2000 and proposed a set of diagnostic criteria. We documented clinical features of children younger than 18 years who were diagnosed over a period of 18 months as having GCS and of control subjects given (over the same period) differential diagnoses of GCS. Forty-two children were recruited (11 with GCS and 31 controls with differential diagnoses of GCS). All children with GCS, and none of the controls, fulfilled the set of diagnostic criteria as a whole. We conclude that the proposed criteria are practical valid criteria for diagnosing GCS.

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Gianotti-Crosti syndrome (GCS), also known as *infantile papular acrodermatitis* and *papular acrodermatitis of childhood*, was first described by Gianotti[1] in 1966. GCS is an acrally distributed papular eruption occurring mainly in infants and children, but it also has been reported in adults.[2,3]

Gianotti[4] identified 3 characteristics of GCS: nonrelapsing erythematopapular dermatitis localized to the face and limbs (lasts about 3 weeks); paracortical hyperplasia of the lymph nodes; and acute hepatitis, usually anicteric (lasts at least 2 months and sometimes progresses to chronic liver disease).

Gianotti[5] wrote that GCS is "always associated with an acute hepatitis, with hepatitis B antigen in the serum," but realized that "in childhood other types of papular or papulovesicular acrolocated eruptions, itching or non-itching, associated with reactive lymphadenitis, are observed, in the course of known diseases and with unknown cause."[5] He preferred using *papulovesicular acrolocated syndrome* to refer to these eruptions.[5-7]

Whereas earlier reports established an association between GCS and hepatitis B virus (HBV) infection,[8-13] recent reports have supported the role of Epstein-Barr virus,[14-18] especially for GCS cases in Western countries. Many other viruses[19-26] and bacteria[27,28] also have been implicated.

As a result, textbooks[29,30] and articles[14-28,31-37] have included all cases of papular or papulovesicular acrolocated eruptions, mainly in childhood, related or unrelated to HBV, under the umbrella of GCS. Lymphadenopathy has been described as sometimes present, and neither lymphadenopathy nor hepatitis has been listed as a clinical feature essential for diagnosis.[29,30] To avoid confusion, some authors coined the term *Gianotti's disease* for GCS cases related to HBV infection.[8-10]

Although the old terminology is no longer used, there are no diagnostic criteria for the modern version of GCS. Having diagnostic criteria allows clinicians, especially relatively inexperienced clinicians, to make more objective diagnoses. Clinicians can then reassure parents of the benign course of their child's disease. Diagnostic criteria also can be used to compare studies involving GCS epidemiology and etiology.

Our study objectives were to determine diagnostic criteria for GCS and to assess their validity using a prospective case-control design.

Patients and Methods

Using MEDLINE, we searched for *Gianotti-Crosti syndrome* and retrieved all January 1996 to December 2000 English-language articles (clinical studies, case reports, review articles) describing clinical features of GCS. We reviewed the reported clinical signs for these cases and listed the positive clinical features; we also reviewed the reported clinical signs for the most common differential diagnoses and listed the negative clinical features.

We then conducted a prospective case-control study for initial assessment of the validity of the diagnostic criteria. We recruited all children (younger than 18 years) diagnosed with GCS at a university teaching clinic for the 18-month period between September 1, 1999, and February 28, 2001. Diagnoses were made clinically by a dermatologist with a special interest in pediatric dermatology. Lesional histopathology was arranged for cases with unclear diagnoses. For controls, we recruited children given (over the same period) any of the differential diagnoses of GCS. Informed consent was obtained from the parents or guardians of all subjects.

For each study subject and each control subject, we documented the presence or absence of each positive and each negative clinical feature. We then calculated the sensitivity, specificity, predictive value, and correlation coefficient of each clinical feature. We used the phi coefficient test to analyze the correlation and the Fisher exact test, 1-tailed, to calculate *P* values.

Results

Seventeen articles were reviewed.[14-18,23-27,31-37] Four positive clinical features and 2 negative clinical features were identified and listed as diagnostic criteria (Table 1). Forty-two children were recruited—11 with GCS and 31 controls with differential diagnoses of GCS. All diagnoses were made clinically, and no lesional biopsies were performed.

All 11 children with GCS were Chinese. Six (54.5%) were boys; 5 (45.5%) were girls. Ages ranged from 7 months to 15.17 years (mean, 5.58 years). Ten of these 11 patients were recruited into another study to evaluate the association of GCS and human herpesvirus 6. Clinical features of a patient are shown in Figures 1 through 3.

All 31 control subjects were Chinese. Thirteen (41.9%) were boys; 18 (58.1%) were girls, with ages ranging from 4 months to 16 years (mean, 7.39 years). Age distributions of the study and control subjects were comparable (Mann-Whitney test, z=.96, 2-tailed, P=.3371). Ten controls had papular urticaria, 8 had hand-foot-and-mouth disease, 5 had erythema infectiosum, 4 had scabies (diagnosed clinically, supported by contact history, 3 from the same family), 2 had erythema multiforme, 1 had Henoch-Schönlein purpura, and 1 had lichen planus (lichenoid rash in adolescent, with lichen planus being the most likely diagnosis, lesional biopsy declined by patient).

Analysis of the positive clinical features is shown in Table 2. All the positive clinical features are 100.0% sensitive for GCS. Rash duration of at least 10 days is most specific (61.3%) and most predictive (47.8%) for GCS, as many children had

Table 1.

Diagnostic Criteria for Gianotti-Crosti Syndrome

Proposed Diagnostic Criteria
Patient exhibits all positive clinical features on at least one occasion or clinical encounter, and
Patient does not exhibit any negative clinical feature on any occasion or clinical encounter related to rash, and
No differential diagnosis is considered more likely than diagnosis of GCS based on clinical judgment, and
If lesional biopsy is performed, findings are consistent with GCS
Positive Clinical Features
Monomorphous, flat-topped, pink-brown papules or papulovesicles 1–10 mm in diameter
Any 3 or all 4 sites involved: cheeks, buttocks, extensor surfaces of forearms, extensor surfaces of legs
Symmetry
Duration of 10 days or more
Negative Clinical Features
Extensive truncal lesions
Scaly lesions
Differential Diagnoses
Acrodermatitis enteropathica, erythema infectiosum, erythema multiforme,[34] hand-foot-and-mouth disease, Henoch-Schönlein purpura, Kawasaki disease, lichen planus,[34] papular purpuric gloves-and-socks syndrome,[34] papular urticaria, scabies

Figure not available online

Figure 1. Monomorphous flat-topped papules on the face of a 3-year-old girl with Gianotti-Crosti syndrome.

short-lasting papular urticaria. Symmetry is least specific (19.4%) and least predictive (30.6%) for GCS. All positive clinical features were positively correlated with GCS, except for symmetry (P=.1404), as most of the differential diagnoses are symmetrical rashes.

Analysis of the negative clinical features is shown in Table 3. Absence of extensive truncal lesions is 35.5% specific for GCS. Absence of scaly lesions has low specificity (3.2%) for GCS. Extensive truncal lesions are negatively correlated with GCS (P=.0198). However, for scaly lesions the correlation with GCS is insignificant (P=.7381) because, among the differential diagnoses, only lichen planus (a condition uncommonly seen in children and adolescents) is likely to be scaly.

All children with GCS—and none of the controls—fulfilled the set of diagnostic criteria as a whole.

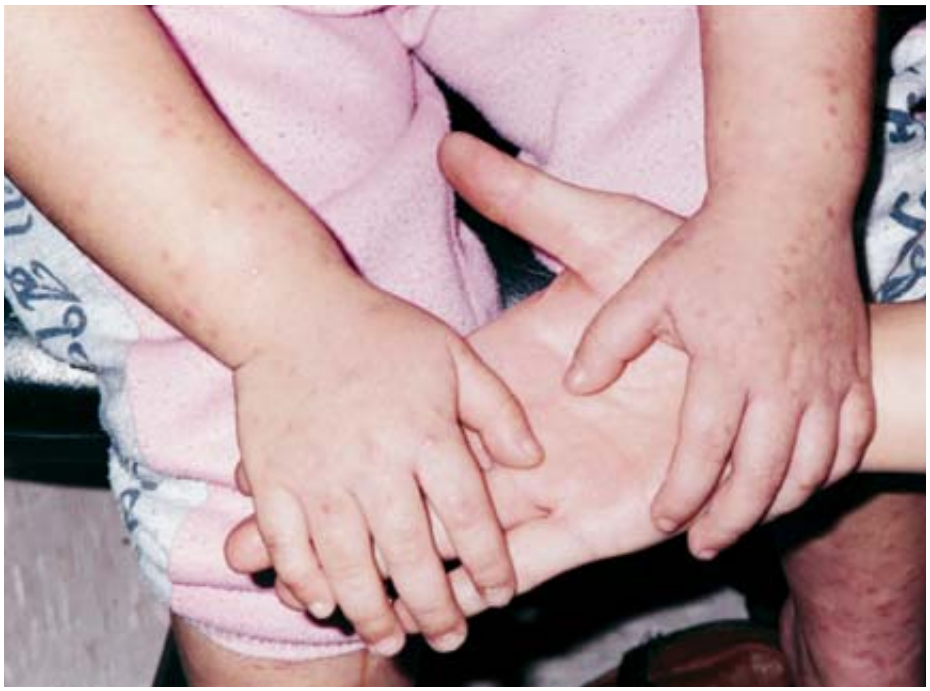

Figure 2. Papular lesions on the extensor surface of the forearms and dorsum of hands.

Comment

We have found the diagnostic criteria identified here to be practical and helpful in working with children who have a rash for which GCS is one of the differential diagnoses. In this study, we established the validity of these diagnostic criteria. Owing to practical constraints, however, we did not attempt to establish their reliability. We believe that a determination of reliability is possible only in centers with several pediatric dermatologists seeing many children with GCS and its differential diagnoses every year.

Although rash is characteristic of GCS, the extent of involvement necessary to make a diagnosis of GCS is debatable. Regions commonly involved are the cheeks, buttocks, extensor surfaces of the forearms, and extensor surfaces of the legs. Extent of involvement seems to be less for older individuals.[33] We believe that, with the characteristic rash present, diagnosis can be made if any 3 or all 4 of the regions are involved. This was confirmed by our results. By itself, presence of truncal lesions does not exclude a diagnosis of GCS, as such lesions have been described.[15] Involvement of the trunk, however, is usually less than that of the face and the extremities.[15]

The Köbner phenomenon, which has been reported for many GCS cases,[23,26] is usually described as a linear array of small papules, presumably precipitated by trauma. When many papules are clustered, determining whether the

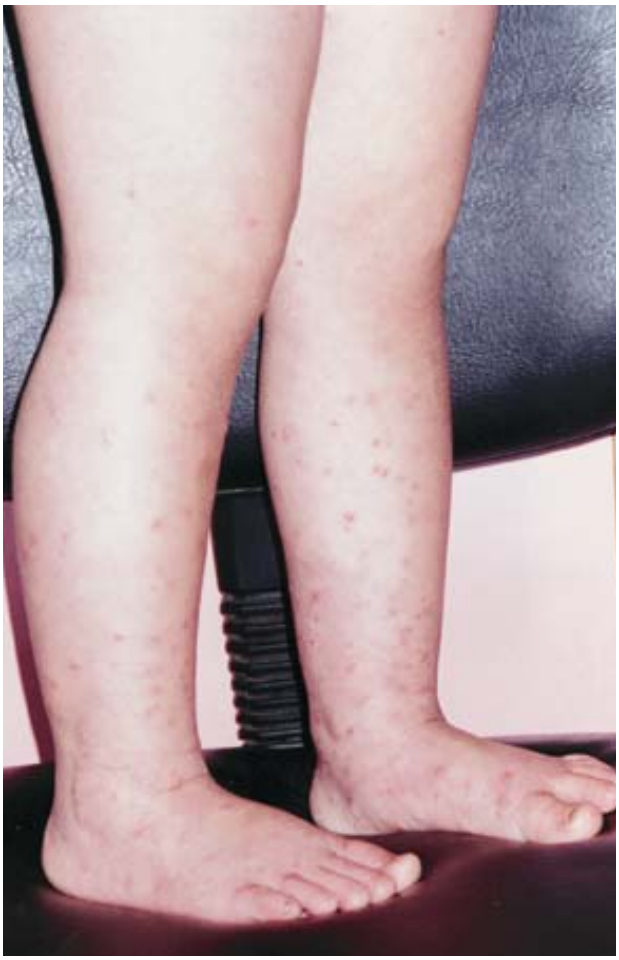

Figure 3. Papular lesions on the legs and feet.

Table 2.

Positive Clinical Features of Gianotti-Crosti Syndrome: Sensitivities, Specificities, Predictive Values, and Correlations*

Feature	No. GCS Patients With Feature (n=11)	No. Control Patients With Feature (n=31)	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Phi Co-efficient	Fisher Exact Test†
Mono-morphous, flat-topped, pink-brown papules or papulovesicles 1–10 mm in diameter	11	17	100	45.2	39.3	+.42	.0050
Any 3 or all 4 sites involved	11	19	100	38.7	36.7	+.38	.0128
Symmetry	11	25	100	19.4	30.6	+.24	.1404 (NS)
Duration of 10 days	11	12	100	61.3	47.8	+.54	.0003

*GCS indicates Gianotti-Crosti syndrome; NS, not significant.
†1-tailed *P*.

Table 3.

Negative Clinical Features of Gianotti-Crosti Syndrome: Sensitivities, Specificities, Predictive Values, and Correlations*

Feature	No. GCS Patients With Feature (n=11)	No. Control Patients With Feature (n=31)	Sensitivity,† %	Specificity,† %	Predictive Value,‡ %	Phi Coefficient	Fisher Exact Test§
Extensive truncal lesions	0	11	100	35.5	35.5	-.35	.0198
Scaly lesions (NS)	0	1	100	3.2	26.8	-.09	.7381

*GCS indicates Gianotti-Crosti syndrome; NS, not significant.
†Absence of feature in supporting diagnosis of GCS.
‡Absence of clinical feature.
§1-tailed *P*.

arrangement is genuine or due to random chance can sometimes be difficult. Moreover, not every GCS case involves the Köbner phenomenon. As a result, we did not include this feature among our diagnostic criteria.

GCS lesions are usually "blanchable," at least to some extent. Occasionally, they may be hemorrhagic[34] or petechial[16] and therefore not blanchable. These atypical lesions do not exclude a diagnosis of GCS, although they may make differential diagnoses such as Henoch-Schönlein purpura more likely. GCS also has been reported to present as a lichenoid form.[37] Under these circumstances, the entire clinical picture must be taken into account, with lesional histopathology considered if indicated.

Presence of another dermatologic condition does not exclude a diagnosis of GCS.[25] Absent compelling evidence, however, an association should not be inferred. This is especially true for subacute or chronic skin conditions. For example, GCS was reported to be related to poxvirus infection—a 5-year-old girl had both GCS rash and molluscum contagiosum.[25] Molluscum is common in children of this age and may last for months to more than one year. The safest assumption—again, lacking evidence suggesting otherwise—is that GCS and molluscum are independent events occurring together by chance.

Lymphadenopathy, hepatomegaly, and splenomegaly are classic signs for the old, hepatitis-related diagnosis of GCS. These features are seen in many modern cases unrelated to hepatitis or HBV.[15,36] Although their presence may add more weight to a diagnosis of GCS, their absence does not exclude a diagnosis of GCS. These features are thus not included among the diagnostic criteria. In the presence of prominent lymphadenopathy or large hepatosplenomegaly, investigations should be considered to exclude other differential diagnoses, including tumors and Langerhans cell histiocytosis.

Identification of or failure to identify a pathogen, usually a virus, does not affect a diagnosis of GCS. Many cases with or without elevated liver enzymes have a causative factor unidentified even after detailed history-taking and extensive investigations.[15,36]

Further, we recommend caution when considering GCS rashes in relation to specific events. A rash appearing soon after an event does not necessarily mean that the rash is related to the event. An example involves immunization.[31,35] GCS is most common in children younger than 4 years. Based on random chance alone, many infants and children are bound to develop GCS within one month of receiving any immunization. Assuming that this temporal relationship is a causal relationship might generate parental anxiety toward further immunizations.

Conclusion

Using the clinical features of children with GCS—as reported in the literature from 1996 to 2000—we proposed diagnostic criteria for the modern version of GCS. Our prospective case-control study established the validity but not the reliability of these criteria. We have found the criteria identified here to be practical and helpful in working with children who have a rash for which GCS is one of the differential diagnoses.

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