Concise Report

Coeliac disease in patients with Kawasaki disease. Is there a link?

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Objective. Kawasaki disease (KD) is an acute febrile systemic vasculitis, mainly affecting infants and young children. Immunological abnormalities during the acute phase of KD have been described extensively. However, the occurrence of a second immunological disorder in a patient with a history of KD is rarely reported. We evaluated the presence of autoimmune thyroiditis and coeliac disease (CD) in patients with KD diagnosis.

Methods. Ninety consecutive children (57 males and 33 females, median age 5.2 yr, age range 1.6–14.1 yr) with KD were evaluated. All patients were evaluated for thyroid function (thyroid-stimulating hormone, thyroxine and triiodothyronine), antithyroglobulin (TgA) and anti-peroxidase (TPOA) antibodies, and antigliadin, anti-endomysium and antitransglutaminase antibodies. CD was confirmed by jejunal biopsy if the specific antibody profile was positive. One hundred and fifty Italian children, matched for age and sex and from the same geographic area, acted as controls.

Results. A total of five patients (three boys, two girls; 5.5%; \( P < 0.05 \)) were found positive for coeliac antibodies. In all of these patients the diagnosis of CD was confirmed histologically. Regarding thyroid function and autoantibodies, no patient showed subclinical hypothyroidism or autoimmune thyroiditis. No differences in the familial occurrence of autoimmune diseases between KD patients and controls were found (9.1 and 7.9%, respectively).

Conclusions. Our data showed a higher prevalence of CD in children with KD, and this suggests that children with KD should be monitored carefully for CD. However, there was no increase in the prevalence of autoimmune thyroid diseases in patients with KD or the familial occurrence of autoimmune diseases.

Key words: Kawasaki disease, Thyroid function, Thyroid autoantibodies, Coeliac disease, Vasculitis.
and other rheumatological disorders, CD, type 1 diabetes mellitus (T1DM), vitiligo, alopecia, multiple sclerosis and inflammatory bowel disease.

Complete KD was defined as the occurrence of at least five of the following six principal symptoms: (i) fever persisting for 5 or more days; (ii) bilateral conjunctivitis; (iii) changes in lips and oral mucosa; (iv) polymorphous exanthema; (v) extremity changes; and (vi) acute non-purulent cervical lymphoadenopathy.

The study protocol was approved by the ethics committee of A. Meyer Children’s Hospital. The procedures followed were in accordance with institutional guidelines. Written informed consent was obtained from each patient and/or his or her parents.

Methods

Thyroid function and autoantibody screening. Free T₄, free T₃ and TSH serum levels were determined by immunometric assays (Immuliite™ 2000 Third Generation; DPC Diagnostic Products Corporation, Los Angeles, CA, USA). Within- and between-run coefficients of variation were less than 8.5% for TSH, less than 7.5% for T₄, and less than 9.1% for T₃. We took the normal ranges of concentrations to be as follows: T₄, 0.8–1.9 ng/dl; T₃, 1.9–4.8 pg/ml; TSH, 0.4–4.0 μIU/ml, respectively.

Thyroid autoimmunity was evaluated by fluorescence enzymatic immunoassays of TgA and TPOA antibodies, considering as positive TgA values ≥50 IU/ml and TPOA ≥100 IU/ml.

Coeliac disease screening. IgA and IgG AGA were measured using an enzyme-linked immunosorbent assay (ELISA). IgA EmA was assayed with a standard immunofluorescence method using cryostatic sections of monkey oesophagus. Serum IgA tTG antibodies were assayed with specific ELISA. CD diagnosis was confirmed by performing a small intestine biopsy if a specific autoantibody profile was positive.

Controls. One hundred and fifty Italian children (95 males, 55 females, median age 5.7 yr; range 1.3–14.9 yr), matched for age and sex and from the same geographic area, admitted to our hospital for minor surgery (adenotonsillectomy, phimosis, dermoid cyst, herniotomy, etc.), and studied before surgery, acted as controls. Sixty-two of these subjects were also part of a previously reported control group [13].

Statistical analysis

The χ² test or Fisher’s exact test and the Mantel–Haenszel test, when appropriate, were used to compare differences between cases and controls. Bonferroni’s correction for multiple comparisons was applied where appropriate. Statistical tests were two-tailed and were considered significant when P < 0.05.

Results

The results are summarized in Tables 1 and 2.

The median age at the time of KD diagnosis was 31 months (range 3–196). The median follow-up was 22 months (range 6–163). The median age of children with KD at the diagnosis of CD was 50 months (range 25–71) and the median follow-up was 14 months (range 1–41 months).

| Table 1. Demographic data, familial occurrence of autoimmune diseases and CD prevalence in patients with KD and controls |
|-----------------|-----------------|-----------------|
|                  | KD              | Controls        | P   |
| Subjects (n)     | 90              | 150             |     |
| Males:females    | 57:33           | 95:55           |     |
| Median age (yr)  | 5.2             | 5.7             |     |
| Familial occurrence of autoimmune diseases | 9.1% | 7.9% | NS |
| CD prevalence    | 5.5%            | 0.6%            | <0.05 |

NS, not significant.

| Table 2. Patients with KD and CD: main characteristics |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                  | Patient 1       | Patient 2       | Patient 3       | Patient 4       | Patient 5       |
| Sex (M:F)        | Male            | Male            | Male            | Female          | Female          |
| Age at KD diagnosis (yr:months) | 0:11            | 2:6             | 3:4             | 7:1             | 3:5             |
| Fever (days)     | 10              | 9               | 7               | 8               | 9               |
| Conjunctivitis   | +               | +               | +               | +               | +               |
| Lymphoadenopathy | +               | +               | +               | +               | +               |
| Rash             | +               | +               | +               | +               | +               |
| Changes of lips or oral mucosa | –               | +               | +               | –               | –               |
| Changes of extremities | +               | +               | –               | +               | +               |
| Age at CD diagnosis (yr:months) | 2:1             | 5:1             | 4:2             | 3:8             | 5:9             |
| Familial occurrence of autoimmune diseases | +               | +               | +               | +               | +               |
| Thyroid functiona | Triiodothyronine (pg/ml) | 4.28           | 5.15           | 4.01           | 3.66           | –               |
| Thyroxine (ng/dl) | 1.15            | 1.28            | 1.40            | 1.05            | 1.25            |                  |
| Thyroid-stimulating hormone (μIU/ml) | 0.83          | 1.60            | 1.61            | 2.12            | 0.51            |                  |
| CD antibodies    |                 |                 |                 |                 |                 |                  |
| IgA and IgG agliadin (AGA) antibodies | 12/47          | 7/30           | 9/27           | 1/80            | 21/39           |                  |
| Antiendomysial antibodies (EMA) | +               | +               | +               | –e             | +               |                  |
| Transglutaminase antibodies (tTG)d | 10             | 15             | 21             | –              | 18              |                  |
| Clinical symptoms |                 |                 |                 |                 |                 |                  |
| Small intestine biopsy | Villous atrophy | Villous atrophy | Villous atrophy | Villous atrophy | Villous atrophy |                  |

+, present; –, absent.

aNormal range: thyroxine, 0.8–1.9 ng/dl; triiodothyronine, 1.9–4.8 pg/ml; thyroid-stimulating hormone 0.4–4.0 μIU/ml.

bNormal value <7 IU.

cNormal value 15 IU.

dNormal value <7 IU.

ePatient with serum IgA deficiency. She exhibited strong positivity for antigliadin IgG antibody (80 IU).
Familial autoimmunity

No statistically significant differences were detected between KD patients and controls as regards the familial occurrence of autoimmune diseases (9.1 and 7.9%, respectively).

Interestingly, all patients with KD and CD showed a strongly positive familial history of autoimmune diseases, in particular T1DM, autoimmune thyroiditis, rheumatoid arthritis and vitiligo.

Thyroid function and autoimmune thyroid disease

Patients with KD showed, during the follow-up, thyroid hormones and TSH levels in the normal range. No cases of subclinical or overt hypothyroidism were found. Thyroid antibodies were negative in all patients. No cases of autoimmune thyroiditis were observed.

Coeliac disease

A total of five patients (three boys, two girls; 5.5%; P < 0.05) were found to have significantly elevated titres of CD antibodies. In all of these patients the diagnosis was confirmed histologically. Of these, CD was diagnosed after KD in four patients and before KD in one patient. The latter patient exhibited IgA deficiency, and CD was suspected due to the high titre of IgG antigliadin antibodies. At CD diagnosis, the patient showed some typical manifestations of CD in children: failure to thrive and abdominal distension (Table 2). At the time of KD, he was on a gluten-free regimen.

All the other patients, except one who exhibited persistent iron deficiency anaemia during KD follow-up, were asymptomatic for CD (Table 2).

With the gluten-free diet, specific antibody profiles for CD were negative and the symptomatic patient recovered.

KD patients vs controls

We did not observe significant differences relating to thyroid function and autoimmune thyroiditis in KD patients when compared with controls. CD showed a significantly increased prevalence in KD patients compared with controls (P < 0.05).

Interestingly, one girl developed vitiligo (4 yr after KD; the mother also showed vitiligo) during the follow-up. In one girl, T1DM (with positive autoantibodies) was diagnosed 3.2 yr before KD. In this patient, the family history of autoimmune diseases was negative.

Discussion

Our data suggest a higher prevalence of CD in KD compared with controls. In one patient CD was diagnosed before KD, whilst in four it was recognized after the acute phase of the disease. However, KD does not seem to predispose towards and/or to be associated with other autoimmune diseases, such as autoimmune thyroiditis. Otherwise, in our cohort, the family history of autoimmune diseases does not differ from the general population.

The aetiology of KD is still uncertain: it has been supposed that, in susceptible subjects, a possible ubiquitous agent causes the disease through a striking immune activation sustained by marked cytokine production and endothelial activation [14].

We could hypothesize that these reported immune alterations in KD subjects might favour the development of several autoimmune diseases. However, the occurrence of a second immunological disorder in a patient with a history of KD has rarely been noted [9–12]. Fukuhara et al. [9] reported a 3-yr-old girl with chronic thyroiditis who presented hypothyroidism during the acute phase of KD. Some reports also emphasize the occurrence of autoimmune haemolytic anaemia in KD patients [10, 11]. Laxer et al. [12] described a girl who developed systemic lupus erythematosus 3.5 yr after KD.

In addition, T1DM has been reported in children after KD [15], and a diffuse macrophage infiltration of the pancreas has been detected in a patient with acute fatal pancreatitis during KD [16]. Although the two girls described by Bhowmick et al. [15] did not show immune markers for T1DM, evidence for pancreatic involvement in KD could be claimed and an immune-mediated process cannot be completely excluded. In our study, we report a girl with T1DM who successively developed KD. The occurrence of this association may be merely coincidental, but T1DM and KD might be two disorders possibly triggered by an unknown aetiological agent in a genetically susceptible individual.

As far as we know, no cases of CD have been reported in subjects with a history of KD. The reason for this occurrence in our study is obscure. Since KD is a frequent condition in the general population, this association might be coincidental. However, our data compellingly suggest that patients with KD display a significantly increased prevalence of associated CD, compared with controls. Addressing this potential association, sharing a common genetic background and/or common immunological mechanisms might provide possible clues to the aetopathogenesis of both disorders. Several studies have demonstrated a close association between CD and autoimmune disorders, such as T1DM, autoimmune thyroid diseases, inflammatory bowel diseases, Addison’s disease, connective tissue disorders, and juvenile idiopathic arthritis [13]. Interestingly, Kuipers et al. [17] reported the presence of prominent nodular infiltrates in the artery adventitia of a KD patient, closely resembling the B-cell reactivity and the follicular lymphoid hyperplasia seen in autoimmune diseases (e.g. Crohn’s disease, Hashimoto thyroiditis and rheumatoid arthritis) [18]. These hypothetical mechanisms may not be mutually exclusive and may be particularly relevant at different stages of disease development. For instance, molecular mimicry could trigger the initial activation of autoreactive T cells and/or induce the expansion of a memory T-cell population, while superantigens could reactivate autoreactive T cells and induce relapses. Impairment of regulatory T cells, as described in KD [19], could help to explain this association.

In addition, involvement of the intestinal mucosa during KD could determine changes in its permeability and, in predisposed subjects, could participate in inducing CD development. Otherwise, the increased gut permeability is already thought to be a key event in other gastrointestinal disorders: inflammatory bowel disease, food allergy and CD itself [20].

Several additional hypotheses cannot be excluded. However, our study, in simply reporting an observed association, is clearly not a proper tool and does not attempt to speculate about these pathogenetic issues.

In conclusion, we report a higher prevalence of CD in children with KD, and suggest that children with KD should be monitored carefully for CD. However, there was no increase in the prevalence of autoimmune thyroid diseases in patients with KD or with familial occurrence of autoimmune diseases. Additional and more extensive studies are necessary to clarify possible underlying mechanisms linking CD and/or other possible autoimmune diseases in KD patients.

The authors have declared no conflicts of interest.

Reference