EXTENDED REPORT

Henoch–Schönlein purpura in children: an epidemiological study among Dutch paediatricians on incidence and diagnostic criteria

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Background: The aim of the present study on the occurrence of Henoch–Schönlein Purpura (HSP) in Dutch children is to give some insight into the epidemiology of HSP in the Netherlands, to record the diagnostic criteria used by Dutch paediatricians and to evaluate the accuracy of the latter using the presence of IgA in the skin when biopsies are available.

Methods: Each month in 2004, all Dutch paediatricians received an electronic card asking them to mention new diagnosed HSP. Paediatricians reporting one or more new patients with HSP were sent a list of questions concerning various parameters.

Results: 232 patients from 0 to 18 years of age ($6.1/10^5$) were reported as having contracted HSP in 2004. 29% presented renal symptoms. In accordance with the classification criteria of the American College of Rheumatology, 80% of paediatricians consider that isolated purpura (without haematological abnormalities) is sufficient to allow the diagnosis of HSP in children. From the 17 skin biopsies performed, only 9 (53%) presented IgA deposits. The follow-up duration, considered as necessary, was longer in case of renal symptoms at presentation. However, 45% of patients without renal symptoms would be followed for more than 1 year.

Conclusion: Considering the recent (2006) EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides, HSP should have been diagnosed in only 160 of the 179 patients of our study. The use of isolated non-thrombocytopenic purpura as the only criterion to diagnose HSP in children might therefore lead to over diagnosis and unnecessary follow-up.

Heberden[1] was the first to describe the association of macroscopic haematuria with a purpuric rash, colicky pain, bloody stools and arthralgia. Erythaematous or purpuric rash and joint pain was reported again by Schönlein.[2] Schönlein's former pupil, Henoch,[3] described 4 children with the combination of rash, colic, bloody diarrhoea and joint pain, and in a later report added haemorrhagic nephritis to the list of components of the syndrome, thus completing the modern definition of the disease. The latter has been formulated by the International Consensus Conference on Nomenclature of Systemic Vasculatides[4] as ''a vasculitis with IgA-dominant immune deposits affecting small vessels and typically involving skin, gut, and glomeruli and associated with arthralgias or arthritis''. The role of IgA deposition in the pathophysiology of the disease was first suspected in 1968 when Urizar and co-workers[5] showed IgA deposits in renal biopsies of patients with Henoch–Schönlein purpura. In the same year, Berger and Hinglais,[6] reported for the first time a form of glomerulonephritis characterised by mesangial accumulation of IgA which later led to the denomination of IgA nephropathy (IgAN). IgA deposits were also found in other types of tissues such as skin or intestine in both diseases. Henoch–Schonlein purpura nephritis (HSPN) and IgAN are considered nowadays as related diseases, since both have been described in identical twins[7] and bear identical pathological and biological abnormalities.[8] It has become obvious in the last 15 years that the primary process leading to IgA deposition in both IgAN and Henoch–Schonlein purpura (HSP) results from a defect in IgA1 glycosylation that impedes IgA1 clearance by the liver and provokes an accumulation of IgA1 and IgA1-containing complexes in plasma.[8] The denomination HSP should therefore refer nowadays to a well-defined pathophysiological entity leading to tissue lesions induced by IgA deposition and possibly being complicated by chronic renal failure in the long term, particularly during a subsequent pregnancy, even in case of minimal renal symptoms at presentation or apparent complete recovery.[9 10] This possible evolution implies long-term follow-up in case of renal abnormalities and may cause anxiety for patient and family. Following the classification criteria for vasculitis of the American College of Rheumatology (ACR)[11] according to which the presence of palpable purpura in a patient under 16 years of age is sufficient to assess the diagnosis of HSP, paediatricians have been used to set up the diagnosis on the presence of purpura only. This criterion is also used in all epidemiological studies on HSP reported up to now. The latter have been performed in children of various countries in increasing number the last few years. They report annual incidences varying from 6.7 per 10^5 in Saudi children[12] to 20.4 per 10^5 children in the UK.[13]

The aim of the present study on the incidence of HSP in Dutch children is not only to give some insight into the epidemiology of HSP in the Netherlands but also to record the diagnostic criteria used by Dutch paediatricians and to evaluate the accuracy of the latter using the presence of IgA in the skin when biopsies are available.

METHODS

One of the functions of the Netherlands Pediatric Surveillance Unit (NSCK), hosted by the Netherlands Institute for Applied Scientific Research (TNO) on Quality of Life, is performing epidemiological studies among Dutch paediatricians by electronic cards listing a series of chosen diagnostic items. Those cards are sent monthly to all paediatricians who are requested to

Abbreviations: CSVV, cutaneous small vessel vasculitis; HSP, Henoch–Schönlein purpura; HSPN, Henoch–Schonlein purpura nephritis; IgAN, IgA nephropathy; RTI, respiratory-tract infection

signal cases displaying the listed diagnosis. The responders receive a detailed questionnaire to complete and send back, the patient remaining anonymous.

In 2004, a prospective study was conducted among paediatricians on children diagnosed as having HSP. Paediatricians who reported having diagnosed one or more patients having HSP were sent a list of questions they had to answer with ''yes'', ''no'', ''unknown'' or ''not measured''. The questionnaire included questions on symptoms at presentation, patient and family clinical history, previous and current medication, laboratory measurements and biopsy, diagnostic criteria and the optimal duration of follow-up necessary.

Clinical symptoms tested at presentation included purpura, arthritis, arthralgy, abdominal and testis complaints and renal signs. The abdominal symptoms included colic pain, bloody stools, vomiting and diarrhoea. Renal abnormalities comprised microscopic haematuria, macroscopic haematuria, proteinuria <1 g/24 h, proteinuria >1 g/24 h, renal failure (increased plasma creatinine), nephrotic syndrome, and hypertension.

Previous history of allergy included atopic dermatitis, food allergy, bronchial asthma, wheezing after contact with pollen or animals or recurrent wheezing with respiratory-tract infection (RTI) and rhinoconjunctival symptoms during the pollen season. The questionnaire enquired as to the presence of RTI prior to or at presentation. Specific questions were asked on the use of antibiotics and other medication prior or at presentation, family history concerning chronic renal failure, haematuria; proteinuria, HSP and IgA nephropathy.

Questions on laboratory parameters included ANCA, C3, anti-DNA and IgA. It was also asked if a skin or kidney biopsy was performed and what type of treatment was given. Paediatricians were asked what they consider as an optimal duration of the follow-up period. The main question on diagnostic criteria was: is the finding of a non-thrombopenic purpura sufficient to assert the diagnosis of HSP?

The incidence data were calculated by dividing the number of HSP registered by age category by population numbers according to age provided for 2004 by the Dutch office of population (Centraal Bureau voor Statistiek).

Microsoft Excel 2002 and SPSS 11.0 were used as database. Unreturned questionnaires required paediatricians being telephoned with the request to complete and return the form.

RESULTS

According to the NSCK, 90% of the cards by which paediatricians were monthly asked to report diagnosed HSP were completed and returned. 77% (179/232) of questionnaires were returned by 113 paediatricians.

A total of 232 patients from 0 to 18 years of age were reported as having consulted Dutch paediatricians with HSP in 2004. A completed questionnaire was returned for 179 of them. The yearly incidence in the whole group was 6.1 per 100 000 children versus 14.9 per 100 000 children in the age group of 3–6 years. The average age of signalled patients was 6 years. Sixty percent (107/179) were male.

Symptoms at presentation are given in table 1. Purpura was seen in 99% (177/179) at initial presentation (in the first 2 weeks); arthritis in 46% (82/179) and arthalgia in 73% (130/179). Gastro-intestinal complications were seen in 31% (56/179) of the patients. In 3% (6/179), neurological complications were noticed (headache), and in 7% (8/107) of the males orchitis was diagnosed. In 11% (19/179), purpura was the only presented symptom. Renal symptoms were observed in 29% (51/179) of patients (table 2).

Eighty percent of paediatricians (144/179) stated that isolated purpura on legs and buttocks, without haematological abnormalities, was sufficient for the diagnosis of HSP. Only 11% (20/179)) stated that IgA in a biopsy was necessary for diagnosis.

In children without renal complications, an adequate follow-up was considered to be less than 12 months or more than 12 months in 55% (71/128) and 45% (57/128) of questionnaires returned, respectively. When renal complications were present, the same follow-up durations were reported to be adequate in 39 (20/51) and 61 (31/51)%, respectively, of questionnaires returned.

Prednisone was given to 25% (14/56) of patients with abdominal complications. For renal complications, 10% (5/51) were given medication (prednisone in 4% (2/51), methylprednisone in 4% (2/51) and ACE inhibitors in 2% (1/51)).

A family history of HSP and/or IgAN was reported in 2 patients. Of all HSP cases, 16% (29/179) had manifestations of allergy in their medical history. Upper RTIs prior to or during presentation of purpura were seen in 61% of the patients (109/179), but none of them were treated with antibiotics.

In 27% (49/179) of all cases, IgA was measured in the blood. Only 37% of these values (18/49) were shown to be increased according to normal age-matched values. A skin biopsy was performed in 9.5% of all cases (17/179) and displayed IgA deposits in only 53% (9/17). Among the 8 patients who did not show IgA in the skin biopsy, one had purpura only, three had a combination of purpura and joint symptoms, one had a combination of purpura and abdominal symptoms, and three displayed renal symptoms (one combining nephrotic syndrome, purpura and arthritis; another one showing purpura and macroscopic haematuria and the third displayed purpura, abdominal and joint symptoms, microscopic haematuria and minimal proteinuria).

DISCUSSION

The yearly incidence of HSP found in Dutch children ($6.1/10^5$) is in the same range as that reported in Saudi Arabia ($6.7/10^5$)[12] but is inferior to those of the Czech Republic ($10.2/10^5$),[14] Taiwan ($12.9/10^5$)[15] and the UK ($20.4/10^5$).[13] Reasons for the discrepancy can be related to the methods used. In Taiwan, the records of patients were derived from the research database of the Bureau of National Health Insurance,[15] whereas in the Czech Republic questionnaires were sent to paediatricians[14] as in The Netherlands. In the UK, family doctors were also consulted.[13] Another factor could be bound to the effective participation, which is impossible to determine precisely. Even if 90% of Dutch paediatricians have returned their monthly list properly completed, it is always possible that some cases have not been reported. The diagnostic criteria used might also play a role. The use of overly restrictive diagnostic criteria is not a cause of the relatively low incidence reported in our study, since 80% of participants declare that isolated purpura without haematological abnormalities is sufficient to assess the diagnosis of HSP. The extent to which other factors such as ethnic diversity or environmental factors could also eventually play a role is not possible to determine from actual data.

It is remarkable that 80% of the paediatricians consider that isolated purpura (without haematological abnormalities) is sufficient to allow the diagnosis of HSP in children. This conforms to the ACR criteria of 1990.[11] Several papers have suggested that this criterion is inadequate and should be reviewed.[16 17] Their inadequacy might explain at least partly the discrepancy between studies on annual incidence and proportion of gastro-intestinal, renal and joint involvement. For these reasons, an international committee of paediatric experts has proposed new criteria for the classification of vasculitis in children.[18] According to the latter, aside from palpable purpura, which is a mandatory criterion, one of the following must coexist: (1) any renal symptom; (2) IgA deposition in tissue biopsy; (3) arthalgia or arthritis; (4) abdominal pain. Considering this, HSP should have been diagnosed in only 160 of the 179 patients of our study. Possible overdiagnosis in our series is confirmed by the high percentage of skin biopsies lacking in IgA deposits. The limits of value of those

Table 1 Symptoms reported in 179 patients diagnosed as HSP by Dutch paediatricians in 2004

Symptoms	No./total no. of patients with HSP	%
Purpura	177/179	99
Arthritis	82/179	46
Arthralgia	130/179	73
Orchitis	8/107	7
Gastrointestinal	56/179	31
Neurological	6/179	3
Renal	51/179	29

Table 2 Renal symptoms in 51 Dutch patients diagnosed as HSP nephritis in 2004

Symptoms	No./total no. of patients with HSP	%
Microscopic haematuria	45/179	25
Macroscopic haematuria	5/179	3
Proteinuria (<1 g/l)	26/179	15
Proteinuria (>1 g/l)	6/179	3
Renal insufficiency	1/179	1
Nephrotic syndrome	3/179	2
Hypertension	5/179	3

new classification criteria[18] for HSP are suggested by the lack of IgA deposits not only in case of isolated purpura but also when other symptoms were associated. In contrast to internists, paediatricians are not used to perform a skin biopsy in case of non-thrombocytopenic purpura. It is therefore not astonishing that the paediatric literature lacks a series of skin biopsies devoted to differentiate HSP (characterised by a leucocytoclastic vasculitis with IgA deposits) from another common cause of vasculitis such as hypersensitivity vasculitis (more recently called idiopathic cutaneous small-vessel vasculitis: CSVV) which is well recognised in adult medicine. Consequently, every non-thrombocytopenic palpable purpura found on legs and buttocks in children leads nowadays to the diagnosis of HSP (except, of course, in the presence of specific clinical and biological features pleading for some rare causes of vasculitis such as systemic lupus erythaematosus, polyarteritis nodosa and so on), and no epidemiological study in children has been able so far to differentiate HSP from CSVV. Idiopathic CSVV is well documented in adults[19] and is also characterised histologically by a leucocytoclastic vasculitis but without IgA deposits. Based on a series of skin biopsies, it is estimated that 10% of patients with CSVV are children.[20 21] Cutaneous symptoms are similar to those of HSP. Arthralgia, gastro-intestinal pain and renal involvement may also be present. However, complete recovery is the rule.[22] Idiopathic cutaneous small-vessel vasculitis has not been described as a cause of chronic renal disease in children so far. Viral (flu, hepatitis C and B) and bacterial (Group A beta haemolytic *Streptococcus*, *Staphylococcus aureus* and so on) infections are considered to constitute the most frequent cause.[19] Since most studies mention that an RTI precedes or accompanies HSP in a high percentage of patients[8] and that skin biopsy is rarely done for diagnostic confirmation, it could be reasonably postulated that a number of patients classified as HSP present in fact with CSVV. Knowing that HSP nephritis on the contrary to CSVV can lead to chronic renal failure at long term even after apparent complete recovery[9] and in case of mild symptoms especially when pregnancy occurs,[10] the assessment of the correct diagnosis has important consequences on prognosis and follow-up.

In conclusion, considering the recent (2006) EULAR/PReS endorsed consensus criteria for the classification of childhood vasculitides,[18] HSP should have been diagnosed in only 160 of the 179 patients of our study. The use of isolated non-thrombocytopenic purpura as the only criterion to diagnose HSP in children might therefore lead to overdiagnosis and unnecessary follow-up. Although technical problems can be eventually argued to explain the lack of dermal IgA observed in a high percentage of patients diagnosed as having HSP, inclusively in some having renal involvement, this finding suggests that the diagnosis of HSP cannot always be ascertained on the basis of clinical symptoms only. Physicians should take into consideration the prognostic and therapeutic implications of their diagnosis to decide whether or not to perform a skin biopsy.

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