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Original article

Incidence of IgA vasculitis in children estimated by four-source capture–recapture analysis: a population-based study

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Abstract

Objectives. The aim was to describe the epidemiological characteristics of childhood IgA vasculitis (IgAV) defined by the EULAR/PRINTO/Paediatric Rheumatology European Society criteria in a population-based sample from France and ascertain its incidence over 3 years by a four-source capture–recapture analysis.

Methods. Cases were prospectively collected in Val de Marne county, a suburb of Paris, with 263 874 residents <15 years old. Children with incident IgAV living in this area from 2012 to 2014 were identified by four sources of case notification (emergency departments, paediatrics departments, private-practice paediatricians and general practitioners). Annual incidence was calculated, and a capture–recapture analysis was used with log-linear modelling to estimate case-finding completeness.

Results. We identified 147 incident cases [78 boys; mean age 6.5 (s.d.:2.6) years]. The annual incidence (95% CI) was 18.6 (13.6, 24.5)/100 000 children. Although only 10% of children were exclusively identified by non-hospital sources, the completeness of case finding was 62%, with an undercount-corrected annual incidence (95% CI) of 29.9 (23.7, 37.3)/100 000 children. The annual distribution of diagnoses consistently showed a trough in summer months; 72% of children had infectious symptoms (mainly upper respiratory tract) a few days before IgAV onset; and 23% had a North African background.

Conclusion. Our study supports secular and geospatial stability in childhood IgAV incidence and adds further indirect evidence for a possible role of a ubiquitous, non-emerging infectious trigger. Incidence studies from understudied areas are needed to disentangle the role of genetic factors better. Capture–recapture analysis suggests that a substantial portion of IgAV cases may remain unrecognized in epidemiological surveys.

Key words: IgA vasculitis, Henoch–Schönlein purpura, incidence, epidemiology, children, capture–recapture

CLINICAL SCIENCE

Rheumatology key messages

- The estimated incidence of IgA vasculitis is 30/100 000 children/year.
- The epidemiology of IgA vasculitis adds indirect evidence for a role of a communicable respiratory infectious trigger.
- The little secular and geospatial variations in incidence of IgA vasculitis point toward a ubiquitous and non-emerging trigger.

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Introduction

Immunoglobulin A vasculitis (IgAV), formerly named Henoch–Schönlein purpura [1], is the most common vasculitis in childhood in western countries [2] and usually affects children from 3 to 10 years old [2]. This systemic leucocytoclastic small-vessel vasculitis features non-thrombocytopenic purpura with lower-limb predominance associated with joint, gastrointestinal or renal involvement. IgAV is generally self-limiting, but the major long-term complication is the risk of persistent renal involvement [3, 4]. The aetiology of IgAV remains unclear, although the characteristic pathological feature (i.e. the deposition of IgA-containing immune complexes within small vessel walls and renal mesangium) suggests a role of mucosal pathogens [5, 6].

Epidemiological studies have played an elementary role in describing the natural history of diseases and in generating hypotheses in search of a causal pathway [7]. The scarce epidemiological data for childhood IgAV, mainly pertaining to European populations, indicates annual incidence rates from 3 to 27/100 000 children [8]. Criteria used in those studies were heterogeneous and not always appropriate for childhood IgAV [2]. Most of those studies possibly underestimated the true incidence of the disease because they were based on hospital discharge records and therefore failed to identify cases not referred to the hospital [3, 9–15].

We aimed to describe the epidemiological characteristics of IgAV in children in a large French population by using the validated EULAR/PRINTO/Paediatric Rheumatology European Society (EULAR/PRINTO/PReS) criteria for IgAV (Henoch–Schönlein) [16]. We also aimed to ascertain the incidence of IgAV over 3 years by using four sources of case notification and used a four-source capture–recapture analysis to calculate the number of cases not identified by any sources to estimate the total number of cases of the disease.

Methods

Study area

This prospective, population-based study was conducted in Val de Marne county, a highly urbanized southeastern suburb of Paris in France that covers 47 towns, with an area of 245 km^2. According to the national census [17], the population in 2012 was 1 341 831, including 263 874 children <15 years old, with a male-to-female ratio of 1.04.

Study period and case definition

We studied incident IgAV occurring from 1 January 2012 to 31 December 2014 among children <15 years old residing in Val de Marne at disease onset. Residency in Val de Marne was defined by the dwelling postal code. Diagnoses were verified by EULAR/PRINTO/PReS criteria for IgAV [16]: purpura with lower-limb predominance plus at least one of acute diffuse abdominal pain, leucocytoclastic vasculitis or proliferative glomerulonephritis with pre-dominant IgA deposit; arthritis or arthralgia of acute onset; renal involvement defined by proteinuria >0.3 g/24 h (urine albumin/creatinine ratio >30 mmol/mg) or haematuria ⩾2+ on dipstick testing.

Case notification

Patients were identified from four sources: paediatric emergency departments, paediatric departments, private-practice paediatricians and general practitioners (GPs). We approached seven paediatric emergency departments and eight inpatient hospital departments of medical specialties that were likely to diagnose IgAV or treat children with IgAV (general paediatrics, paediatric rheumatology, paediatric nephrology and paediatric gastroenterology) located in or near to Val de Marne. Also, we contacted by telephone all 95 private-practice paediatricians working in the study area. Before the study launch, the contacted physicians were informed about the study during face-to-face meetings in each department or by telephone. From early 2012 until 2 months after the end of 2014, emails were sent to all these paediatricians on a quarterly basis to inquire if they were aware of children with newly diagnosed IgAV who resided in the study area. Recipients were asked to reply to emails even if they had no patient to report.

Moreover, in 2014 and early 2015, the 1018 GPs working in the study area were asked to participate in two mail surveys. The first survey asked GPs to report retrospectively all childhood cases with newly diagnosed IgAV occurring since 2012. The second survey was sent to retrieve new cases diagnosed during the interval between the two surveys and to increase the response rate for non-responders. The mail surveys included a self-addressed stamped return envelope, and GPs were asked to reply even if they were not aware of any case fulfilling our search criteria.

Demographic and clinical information

For each potentially relevant case with IgAV, a study-specific case report form was completed to retrieve the main demographic and clinical characteristics. The case report form was completed by the emergency physician, treating hospital paediatrician, private-practice paediatrician or the principal investigator (M.P.). The collected data included information to check for the study-specific inclusion criteria and IgAV classification criteria, date of disease onset, date of diagnosis, date of birth, dwelling postal code, ethnic background, relevant personal or familial medical history, 30 clinical variables related to IgAV, imaging and laboratory results and potential triggers occurring within 3 weeks before disease onset (i.e. infections, drug intake or other relevant information given by parents).

Ethnicity was defined by country of birth of at least three of the patient's grandparents and classified into eight groups: European, North African, Afro-Caribbean, Middle Eastern, Asian (Far East), Oceanic or American; children with grandparents from different areas were classified as having mixed ethnicity. To encourage a high response rate, the questionnaire sent to GPs was deliberately

limited to the crucial clinical and demographic information for the incidence study. Duplicate cases were identified by using a 13-character alphanumeric code (ID code) generated by using the first two letters of the patient's last name, the initial of the first name, sex, month and year of birth, and dwelling postal code.

Statistical and capture–recapture analysis

The annual incidence rate was calculated by using the number of incident cases per year as the numerator and the population of children <15 years old living in Val de Marne in 2012 as the denominator. Incidence rates were calculated for the entire study area population and study period and stratified by age, sex and calendar year of onset. The 95% CIs for incidence rates were calculated under the assumption of a Poisson distribution.

The distribution of IgAV diagnoses over months or astronomical seasons was examined for uniformity by comparing observed with expected frequencies by one-way goodness-of-fit χ^2 testing. Two-tailed $P < 0.05$ was considered statistically significant.

A four-source capture–recapture analysis was used to assess the completeness of our case finding. Briefly, this technique takes advantage of the overlap of patient data collected by two or more sources of information from the same population to estimate the number of cases missed by any source and therefore the total number of cases. Log-linear modelling was used to adjust for possible between-source dependencies. Among the 113 possible log-linear models including single-, second- or third-order interactions between the four sources, the best-fitting model was selected from the results of maximum likelihood statistics (deviance G^2, Akaike information criterion and Bayesian information criterion [16]). To assess the possibility of heterogeneous case-capture across sources, we performed stratified capture–recapture analyses in the overall sample based on two dichotomous patient characteristics: age at diagnosis (defined by the mean patient age at diagnosis) and IgAV severity (defined by the presence of at least one of the following features: proteinuria, macroscopic haematuria, anorexia, gastrointestinal bleeding and intussusception). We compared the expected distributions with the distributions observed within each of the sources by χ^2 test. In the event of heterogeneous case-capture within a source, we introduced in the best-fitted model a term of interaction between the corresponding characteristic and the source to adjust for potential bias [18]. Analyses involved use of Stata 12 (StataCorp, College Station, TX, USA), the Rcapture package [19] in R statistical software (R Project for Statistical Computing, Vienna, Austria) and SAS Studio v3.5 (Cary, NC, USA).

Ethics

The study was approved by the Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé (Advisory Committee on Information Processing in Research in the field of Health no. 12–146 bis) and the Commission Nationale de l'Informatique et des Libertés (National Commission of Informatics and Freedom no. 914148). Parents of patients were informed of the study and signed a consent form.

Results

Response rate

All seven paediatric emergency departments and six of the eight inpatient hospital departments approached participated in the study. Among the private-practice paediatricians, 48% replied to emails at least once, and 33% of GPs returned the questionnaire.

Figure 1 shows the flow of patients in the study. Overall, 243 patients were reported by the four sources; 65 did not fulfil demographic, geographical or EULAR/PRINTO/PReS classification criteria or their disease onset was outside the study period. Among the remaining patients, 31 were intersource duplicates. We retained 147 children with incident IgAV in Val de Marne between 1 January 2012 and 31 December 2014.

Patient characteristics

The main demographic and clinical characteristics of the 147 patients are summarized in Table 1. They included 78 boys (male-to-female ratio: 1.1) with a mean (S.D.) age of 6.5 (2.6) years (range 2.2–14.7) at disease onset (Fig. 2). The mean interval from symptom onset to diagnosis was 3 days (0–41 days), with one-third of patients diagnosed on the day of the disease onset. Overall, 72% (87/121) of children showed infectious symptoms a few days before the disease onset, which consisted mainly of rhinitis (n = 40), tonsillitis (n = 23), fever (n = 14), cough (n = 14), otitis (n = 7), gastroenteritis (n = 4), cystitis (n = 2), laryngitis (n = 1) and skin eruption or infection (n = 5). During the 3 weeks before disease onset, 37% of children took drugs, generally (94%) related to the infectious symptoms.

The ethnic origin of most children was European (44%), and North African for 23%, Asian for 4%, Afro-Caribbean for 3% and Middle Eastern for 2%; 24% had mixed origins.

Incidence estimates

The overall annual incidence (95% CI) of IgAV in Val de Marne (per 100 000 children <15 years old) was 18.6 (13.6, 24.5): 19.3 (12.6, 28.3) for boys and 17.8 (95% CI: 12.8, 26.7) for girls. The estimated annual incidence differed by age groups: 32.6 (22.1, 47.3) for 5–10 years, 16.7 (9.7, 27.7) for <5 years and 5.7 (2.0, 14.2) for >10 years. The incidence varied slightly between years: 16.3 (11.8, 22.0) for 2012, 15.5 (11.2, 21.1) for 2013 and 23.9 (18.4, 30.6) for 2014.

The monthly and seasonal distribution of diagnoses deviated from a random distribution (P = 0.004), with a nadir in July and August (Fig. 3) and a significantly lower incidence in summer than other seasons (spring: 29%; summer: 12%; autumn: 28%; winter: 31%; P = 0.03).

FIG. 1 Flow of ascertainment of cases with incident childhood IgA vasculitis reported by four sources

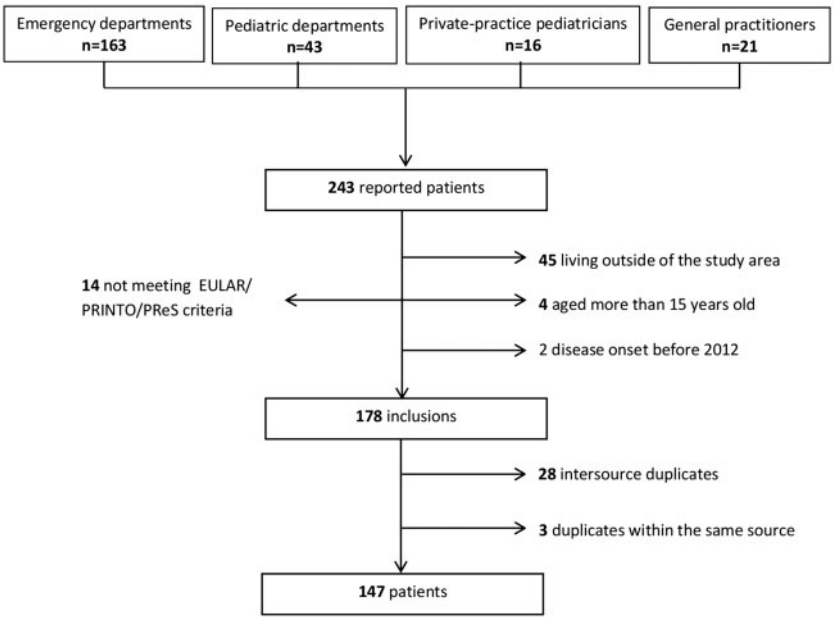


TABLE 1 Characteristics of 147 patients with incident IgA vasculitis

Variable	Value
Male/female, n	78/69
Age at disease onset, mean (S.D.), years	6.5 (2.6)
Delay between onset and diagnosis, mean (S.D.), days	3.1 (5.2)
Interval between onset and inclusion, mean (S.D.), days	22.8 (93.8)
Clinical manifestations at diagnosis, n (%)[a]	
Purpura	147/147 (100)
Palpable purpura	142/147 (97)
Necrotic or bullous purpura	14/131 (11)
Urticaria	15/123 (12)
Acral oedema	93/130 (72)
Limb pain	136/146 (93)
Arthritis	24/131 (18)
Abdominal involvement	85/146 (58)
Abdominal pain	75/139 (54)
Vomiting	36/138 (26)
Anorexia	41/135 (30)
Diarrhoea	18/138 (13)
Haemorrhage	10/138 (7)
Intussusception	3/146 (2)
Renal involvement	28/142 (20)
Proteinuria	16/141 (11)
Haematuria	18/142 (13)
Scrotal oedema	9/74 (12)

[a]Denominators excluded patients with missing or irrelevant information.

Capture–recapture analysis

Figure 4 shows the number of incident cases ascertained by each of the four sources and the among-source overlap: 123 cases (84%) were identified by one source, 20 (14%) by two sources and 4 (3%) by three sources; no patients were identified by all four sources. Emergency departments were the most effective source, identifying 118 (80%) of the 147 patients. Only 16 patients (9.5%) were reported by private practitioners and were not identified by hospital data.

Comparisons of the goodness of fit of the different log-linear regression models suggested that the model with interaction between emergency departments and private-practice paediatricians had the best fit (Table 2). This model had low deviance ($G^2 = 8.44$), with smaller Akaike information criterion (55.97) and Bayesian information criterion (73.91). According to this model, an estimated 90 patients were missed, for a total of 237 (95% CI: 179.6, 294.4) patients with IgAV. The non-saturated model estimated a total of missed cases of 112, which suggested a negative interaction between emergency departments and private-practice paediatricians.

As expected, the stratified capture–recapture analyses revealed a higher percentage of children with severe IgAV among the paediatric departments (70 *vs* 36%, $P < 0.001$). The addition of a relevant interaction term (between IgAV severity and paediatric departments) in the previously selected, best-fit model generated the same estimate of missing cases. In contrast, we found no differences in distribution of age at diagnosis for any of the sources compared with the expected distribution.

Fig. 2 Age distribution for 147 children with incident childhood IgA vasculitis at disease onset

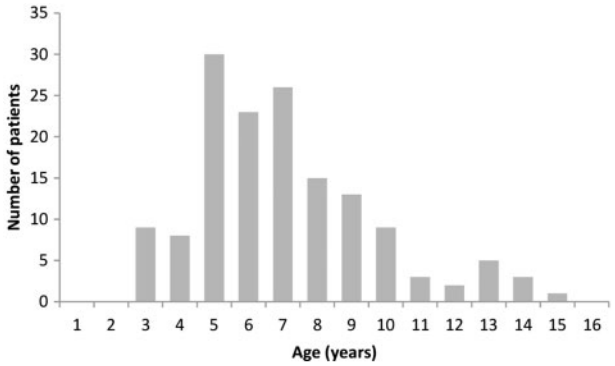
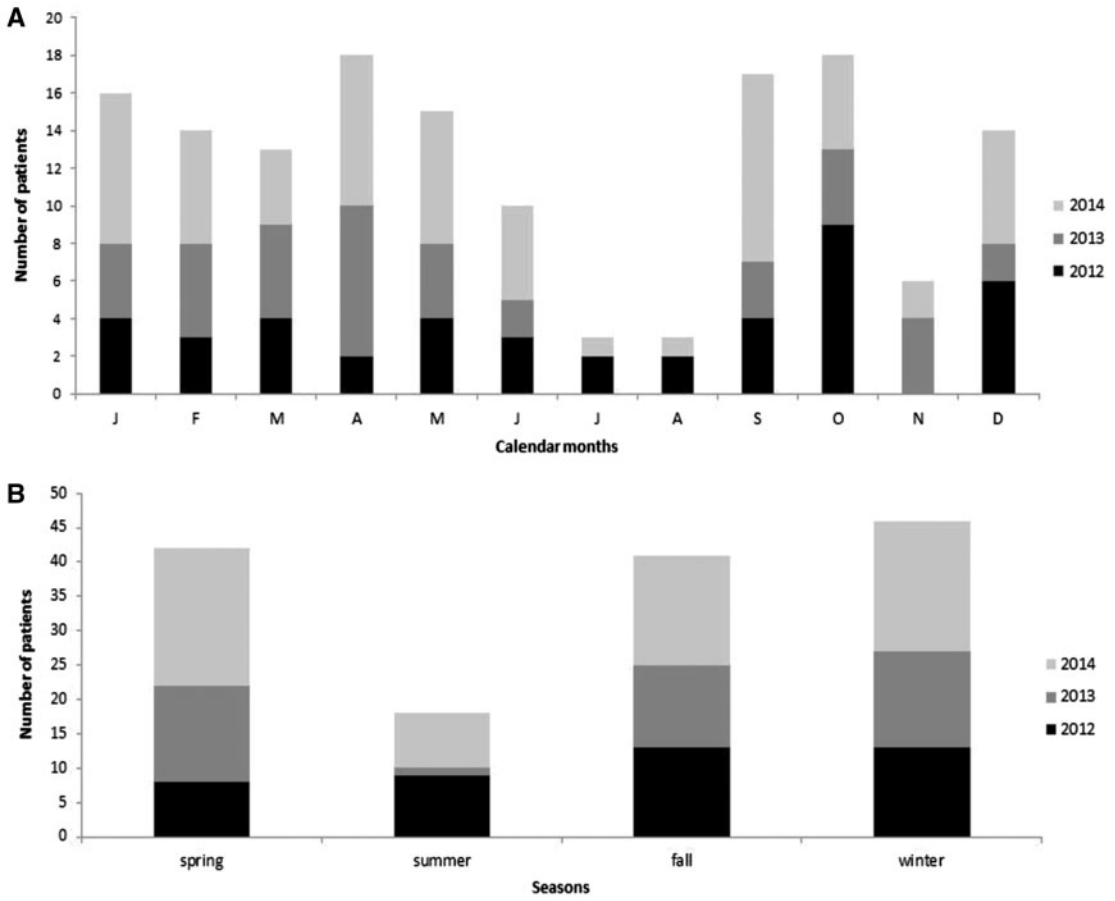


Fig. 3 Monthly (A) and seasonal (B) distribution of incident IgA vasculitis over the period 2012–14



Thus, the estimated completeness (95% CI) of the combined four sources was 62 (50, 82)%. From the estimated number of new diagnoses obtained, the annual incidence (95% CI) of IgAV per 100 000 children <15 years old living in Val de Marne was 29.9 (23.7, 37.3).

Discussion

This prospective population-based study assessed the incidence of IgAV at 18.6/100 000 children <15 years old in a defined population in France for 2012–2014. Using

FIG. 4 Venn diagram of the sources of ascertainment of the 147 cases with incident childhood IgA vasculitis

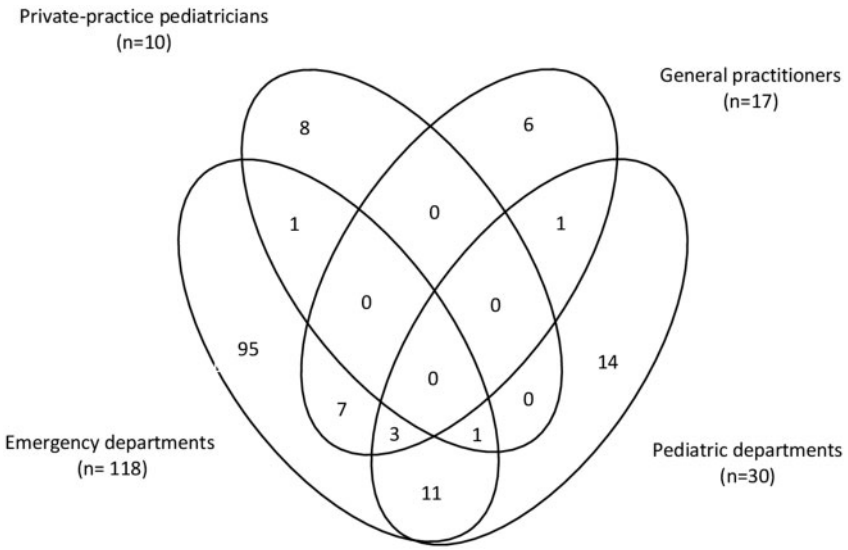


TABLE 2 Numbers of IgA vasculitis estimate by the 10 best log-linear models fitted to the four sources

Models	df	G^2	P-value	AIC	BIC	X	N	95% CI
ED, PPP, HD, GP	10	11.88	0.29	57.41	72.36	111.9	258.9	193.8, 324.0
HD, GP, ED × PPP	**9**	**8.44**	**0.49**	**55.97**	**73.91**	**90**	**237.0**	**179.6, 294.4**
ED, PPP, HD × GP	9	9.71	0.37	57.24	75.18	123.7	270.7	196.4, 345.0
PPP, HD, ED × GP	9	10.17	0.34	57.69	75.64	140.2	287.2	193.3, 381.1
HD, ED, PPP × GP	9	10.48	0.31	58.01	79.95	108.8	255.8	192.3, 319.3
GP, ED, HD × PPP	9	11.85	0.22	59.38	77.32	111.1	258.1	192.8, 323.4
PPP, GP, ED × HD	9	11.38	0.25	58.91	76.85	136.2	283.2	175.2, 391.2
ED × PPP, HD × GP	8	6.71	0.57	56.24	77.17	99.3	246.3	181.0, 311.6
PPP, ED × HD, ED × GP	8	6.84	0.55	56.36	77.70	364.3	511.3	28.7, 993.9
HD, ED × PPP, PPP × GP	8	6.91	0.55	56.44	77.37	87.1	234.1	178.4, 289.8

The model with interaction between emergency departments and private-practice paediatricians (in bold) had the best fit. AIC: Akaike information criterion; BIC: Bayesian information criterion; df: degrees of freedom; ED: emergency department; G^2: deviance; GPs: general practitioners; HD: paediatric department; N: estimate of the total number of cases; PPP: private-practice paediatricians; X: estimate of the number of cases missed.

capture–recapture analysis, we adjusted this estimate to 29.9/100 000 children <15 years old.

This first estimate falls within the range of previously reported incidence rates from studies conducted between 1970 and 2010 in Europe, Asia and North America [8] and is remarkably close to an estimate of 21.7/100 000 children <15 years old from a former French study conducted in a less urbanized area in France between 1992 and 1995 [20]. Collectively, these findings add to the view of a relative stability of the occurrence of IgAV across different geographical areas and reinforce study findings with long observation periods conducted in Spain [10], Scotland [21] and Denmark [9], showing no significant secular variations in the incidence of IgAV.

Furthermore, we addressed the general issue that IgAV incidence rates reported in epidemiological surveys represent only conservative estimates because of potential under-reporting of cases by treating physicians. Using capture–recapture analysis [22], we estimated the completeness of case ascertainment at 62%. With a similar approach, Gardner-Medwin *et al.* [2] estimated a completeness of case finding for incident childhood IgAV of only 38% in the West Midlands, UK. In contrast to our first hypothesis, our observations suggest that estimates relying merely on hospital-based data could be relatively accurate compared with estimates also including non-hospital data. In our study, only 10% (14/147) of the patients identified were reported exclusively by primary care physicians, which indicates that children with IgAV are usually seen in hospitals, particularly emergency departments. In the study by Gardner-Medwin *et al.* [2], based on three sources (GPs, consultants and discharge

diagnostic index from hospitals), only 3% of patients were reported by GPs exclusively [2]. These observations suggest that hospital data provide most of the information on newly diagnosed childhood IgAV and that the true incidence of IgAV might still be 2- to 3-fold higher than incidence rate calculations based on the number of actually identified cases.

Our incidence study is the first to use the validated EULAR/PRINTO/PReS classification criteria for childhood IgAV, with sensitivity and specificity of 100 and 87%, respectively [16]. Previous studies were based on physician diagnoses [9, 12, 20, 21, 23] or non-validated criteria and/or criteria inappropriate for paediatric populations, such as the ACR criteria [13, 24], Michel *et al.* criteria [25] or study-specific criteria [2, 3, 11, 14, 15]. Despite the heterogeneous classification criteria used, the narrow range of published incidence rates suggests only a modest impact of the classification criteria chosen on incidence estimates. However, the EULAR/PRINTO/PReS classification criteria can help to homogenize patient populations with IgAV and increase the comparability between studies in the future.

The current aetiopathogenic paradigm for IgAV involves an abnormal immune response to various antigenic stimuli in genetically susceptible individuals [8, 26]. In particular, clinical and epidemiological data provide several lines of indirect evidence for a pivotal role of infectious triggers in the pathogenesis of the disease. IgAV affects children $<$10 years old in 75–90% of cases [27, 28], and the incidence peak between the ages of 4 and 7 years matches the age of admission into school, where children are exposed to many communicable infectious diseases. In our series, and in previous reports [8, 26], symptoms of an infection, mainly in the upper respiratory tract, were reported in at least 60% of cases within days before the onset of IgAV symptoms. Moreover, in line with other studies [10, 11, 20, 21, 24, 28–32], we found a trough in IgAV incidence during summer months, which concurs with the season of lower incidence of respiratory virus infections and with reduced transmission of microbes during school closure [33, 34]. A reporting bias during summer months seems unlikely in light of the large number of studies that have consistently reported the same summer incidence trough and because cases during the summer months are unlikely to be completely unrecognized by all the caregivers we approached. The role of non-infectious antigenic stimuli, such as vaccines and other medications [8, 35], remains to be elucidated.

Multi-ethnic populations provide information about the role of genetic factors in disease risk. Our observation of 23% of children with IgAV having parents from North Africa seems striking. Although this number is difficult to interpret because of the lack of accurate information on the ethnic characteristics of infants in the general population in France, it appears to be higher than expected as compared with the 13% North African background in the general adult population reported for another county of the greater Paris area [36] or with the 8% North African migrants 25–54 years old living in Val de Marne in 2012 [17]. Indeed, data from other multi-ethnic populations suggested inter-ethnic differences in childhood IgAV risk, with 3- to 4-fold higher incidence for white or Asian than black children [2] and a possibly higher incidence among Hispanics than white Americans [23]. Genetic association studies identified predisposing or protective loci within and outside the HLA region, such as *HLA-DRB1*01* [odds ratio (OR) = 2.03], *HLA-DRB1*11* (OR = 2.00), *HLA-DRB1*07* (OR = 0.67) [8, 37, 38] or polymorphisms in functional angiotensin-converting enzyme insertion/deletion (OR = 1.56–1.88) [39, 40]. Some of these polymorphisms are frequent; one example is *HLA-DRB1*01*, present in 43% of IgAV patients *vs* 27% of controls [41]. Interestingly, IgAV develops in 3–7% of children with FMF [42, 43], but the population risk of IgAV attributable to *MEFV*, the gene implicated in FMF, is unknown. However, the idea that IgAV has a strong genetic underpinning is mitigated by the scarcity of familial aggregation of IgAV, and the short interval between the index and secondary familial cases points to an environmental transmission rather than heritability [8].

In summary, this study supports relatively little secular and geospatial variation in the incidence of childhood IgAV. When considering that environmental and, in particular, upper respiratory-tract infectious factors play an important role, paediatric IgAV might be triggered or caused by an ubiquitous and non-emerging infectious pathogen. To disentangle the role of genetics in this disease better, incidence studies are required in understudied areas and populations, such as countries where FMF is frequent. Our findings confidently indicate that methodological differences are not very important even though a substantial part of IgAV may be left unrecognized in epidemiological surveys.

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