



Long-Term Risk of Comorbidity after IgA Vasculitis in Childhood: A Population-Based Cohort Study

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ABSTRACT

Introduction: Patients with IgA vasculitis (IgAV) may require aggressive treatment and are prone to disease relapses, and IgA deposition in tissues can persist. We investigated whether these factors predispose to long-term morbidity in children with IgAV.

Methods: Observational cohort study comparing rates for comorbidity development by Charlson comorbidity index (CCI) and rates for hospitalization, procedures, and emergency department (ED) visits over a 20-year period for IgAV patients < 20 years ($n = 494$) and matched

hospital-based controls ($n = 1385$). Odds (OR) for events and rate ratios (RR) for event rates per 1000 person-years were derived from maximum likelihood estimates.

Results: Patient survival (99.1 vs. 99.7%, $p = 0.6$) and overall comorbidity accrual CCI (0.21 vs. 0.23, $p = 0.7$) were similar for IgAV patients and hospital-based controls after 20 years. IgAV patients did not develop other rheumatic diseases, but more often were diagnosed with peptic ulcer and end-stage renal failure. Hospitalization rates were three times higher for IgAV patients (RR 3.41 CI 3.04–3.82) in the first year following diagnosis, while ED attendance rates were higher in subsequent years (RR 1.29; 1.02–1.04; $p < 0.01$) for IgAV patients.

Conclusions: Childhood IgAV patients have good long-term prognosis despite the occurrence of end-stage renal failure and compared to hospital-based controls are at not at increased risk for other comorbidity or rheumatic disease.

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Keywords: IgA vasculitis; Longitudinal; Morbidity; Procedures; Readmissions

Key Summary Points

Why carry out this study?

Little is known about the long-term risk of developing comorbid conditions other than renal failure in patients presenting with IgA vasculitis (IgAV) in childhood.

Using the prognostically important Charlson Comorbidity Index we investigated the risk and type of comorbid conditions during more than 20 years follow-up of childhood IgAV patients.

What was learned from the study?

IgAV vasculitis in children does not increase the risk of other rheumatic disease or diabetes mellitus over the next 20 years.

With current management options, the increased risk of renal failure and peptic ulcer disease in childhood IgAV vasculitis does not impact on survival prognosis over 20 years.

disease presents more severe in adults [3]. Childhood IgAV is considered a self-limiting condition, but severe polyarthritis, gastrointestinal hemorrhage, and/or renal disease may require treatment with corticosteroids and/or immunosuppressive drugs and disease relapses occur in up to a third of patients [4, 5]. Similar to other rheumatic diseases, systemic inflammation, drug toxicity, and disease relapse contribute to the potential for organ damage in IgAV in the longer term [6]. While chronic kidney disease results from disease relapses and/or natural progression of IgA associated nephritis (IgAN) it is unclear whether the deposition of pathogenic IgA in other tissues carries long-term risks [7]. We have recently described increased rates of pregnancy complications and infections following the onset of IgAV in childhood [8, 9], but there is a paucity of data on the long-term risk of developing other autoimmune conditions or common comorbidities, such as diabetes mellitus, vascular, or chronic pulmonary disease following IgAV diagnosis. We therefore investigated the long-term development of such comorbidity requiring hospital admission or and emergency department (ED) care in IgAV patients diagnosed in childhood.

DIGITAL FEATURES

This article is published with digital features to facilitate understanding of the article. To view digital features for this article go to <https://doi.org/10.6084/m9.figshare.12981575>.

INTRODUCTION

IgA vasculitis (IgAV) is a small vessel vasculitis that occurs when an unknown trigger stimulates production and deposition of polyclonal IgA immune complexes in vessel walls that set off an inflammatory process. Clinical manifestations involve cutaneous purpura, arthralgias and/or arthritis, gastrointestinal hemorrhage and enteritis, glomerulonephritis, and less frequently neurological abnormalities [1, 2]. While IgAV is more common among children, the

METHODS

Design

A retrospective cohort study of administrative health data extracted from the Hospital Morbidity Data Collection (HMDC) (1980–2015), Emergency Department Data Collection (EDDC) (2002–2015), WA Cancer Registry (1982–2014) and the WA Death Registry (1980–2014) which contain routinely collected data from all private and public hospitals in Western Australia (WA). Data were linked through a validated process of probabilistic matching and clerical review by the WA Data Linkage Branch at the Department of Health, which resulted in deidentified individual longitudinal health data for each participant with 99.7% accuracy in identifying individuals across four linked datasets [10, 11]. Detailed

information on the process and quality insurance of health data linkage in WA is publicly available at <https://www.datalinkage-wa.org.au>.

Cohort Selection

We included patients under 20 years at the time of a diagnostic code for IgAV/allergic purpura (ICD-9-CM 287.0; ICD-10-AM D69.0) in the linked dataset during the period 1980 to 2000. Each IgAV-patient was assigned up to three individuals from HMDC without rheumatic disease (‘hospital-based controls’) matched by age (by birth year), gender, and year of index hospitalization. Details on the medical conditions at study inclusion for hospital-based controls are given in Fig. 1.

Outcomes

Hospitalization and ED visit rates per 1000 person-years, accrual of comorbidity according to a modified Charlson Comorbidity Index (m-CCI) without the rheumatic disease domain and the number and type of hospital-based

interventions (ICD-9 and ACHI procedure codes) performed up to 2016 broadly categorized as diagnostic, medical, surgical, obstetrical, odontology, or other support (allied health) services.

Statistics

Descriptive statistics were calculated for cohort characteristics and all outcome measures. Continuous variables are presented as a median and interquartile range (IQR) and were compared using Mann–Whitney *U* test. Categorical variables presented as frequency and proportion were compared by Chi-square test or Fisher’s exact test ($n < 5$). A modified CCI at last observation was calculated with exclusion of rheumatic disease scores [12]. All-cause hospitalization and ED visit rates are expressed as number per 1000 person-years at risk and compared by conditional maximum likelihood estimates of odds (OR) and rate ratios (RR) with 95% confidence intervals (CI). Logistic regression was applied to investigate predictors for m-CCI scores > 0 . Statistical analyses were

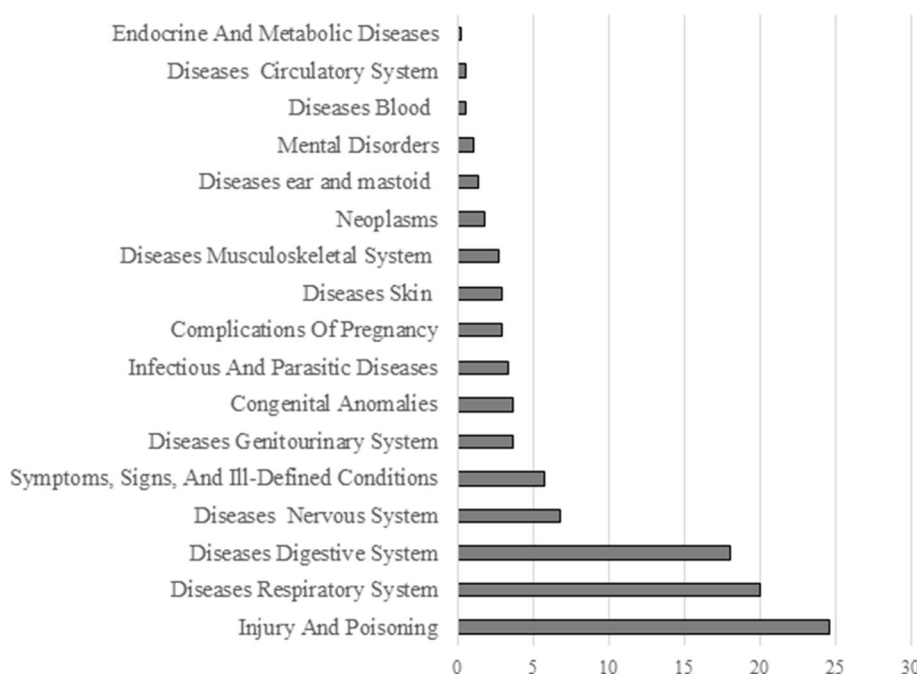


Fig. 1 Distribution of conditions (by main ICD category for primary diagnosis) at the time of study inclusion (time zero) in hospital-based matched controls

undertaken using IBM SPSS v24.0 and Open-Epi software with two-sided p values < 0.05 considered statistically significant.

Ethics

This data linkage project has been approved by the Human Research Ethics Committees at the WA Department of Health (HREC# 2016.24).

RESULTS

At diagnosis there was no significant age difference between IgAV patients and hospital-based controls (3.9 ± 4.5 vs. 4.4 ± 5.1 , $p = 0.06$), although the IgAV cohort contained fewer males (57 vs. 65%, $p = 0.02$). Renal disease was more frequent in IgAV patients (1.0 vs. 0.1%, $p < 0.01$), but there was no significant difference in the proportion of patients with non-renal manifestations (Table 1).

With 24.4 (± 5.5) years of follow-up most patients had reached early adulthood, crude

mortality rates in both groups were very low and similar (0.9 vs. 0.4%, $p = 0.6$) and we observed no registered comorbidity in the domains of cardiac, peripheral vascular, severe liver disease, complicated diabetes mellitus, HIV or other rheumatic disease (Table 2). There was, however, increased accrual of peptic ulcer and renal disease and lower accrual of chronic pulmonary disease in IgAV patients (Table 2). The average CCI at last observation for IgAV patients (0.23; CI 0.18–0.28) was not different from hospital-based controls (0.23; CI 0.18–0.28 versus 0.20 CI 0.17–0.22) ($p = 0.68$) with some comorbidity seen in 89 (18.0%) IgAV patients and 242 (17.5%) hospital-based controls ($p = 0.72$). Multi-organ morbidity (CCI scores ≥ 3 , which indicate affection of at least two organ systems) was rare and slightly more often (1.2 vs. 0.2%, $p = 0.08$) seen in IgAV patients. Logistic regression modeling showed a borderline impact of increasing age at diagnosis (Exp B 0.953, 95% CI 0.909–0.998; $p = 0.043$) on comorbidity development (CCI > 0) with no influence on CCI seen for gender, rural

Table 1 Demographic data for IgAV patients and controls

	IgAV ($n = 494$)	Controls ($n = 1385$)	p value
Average age (year) (SD)	3.94 (4.46)	4.44 (5.09)	0.06
Male gender (%)	283 (57.3)	910 (65.2)	0.02
Non-metropolitan residence (%)	135 (27.3)	380 (27.4)	0.51
<i>Baseline findings</i>			
Arthralgia or arthritis (%)	73 (14.8)	145 (10.8)	0.11
<i>Glomerul</i>			
Glomerulonephritis/hematuria (%)	5 (1.0)	< 5 (0.1)	< 0.01
Non-infectious enteritis (%)	< 5 (0.8)	< 5 (0.2)	0.21
Constitutional symptoms (%)	6 (1.2)	8 (0.6)	0.21
Increased ESR (%)	25 (5.1)	69 (5.0)	0.91
Mean observation period (years)(SD)	24.4 (5.52)	26.6 (5.69)	0.01
Total person-years observation	76.662	149.955	

Small numbers ($n < 5$) have been confidentialized due to HREC requirements

SD standard deviation, ESR erythrocyte sedimentation rate, IgAV immunoglobulin A vasculitis

Table 2 Frequency and rate per 1000 person-years for new comorbidities in IgAV patients and hospital-based controls

	IgAV (<i>n</i> = 494)		Controls (<i>n</i> = 1385)		Rate ratio	<i>p</i> value
	No. of patients	Rate/1000 years	No. of patients	Rate/1000 years		
Myocardial infarction (1)	–	–	–	–	–	NA
Congestive heart failure (1)	–	–	–	–	–	NA
Peripheral vascular disease (1)	–	–	–	–	–	NA
Cerebral vascular accident (1)	–	–	< 5 (0.1%)	–	–	0.7
Dementia (1)	–	–	–	–	–	NA
Pulmonary disease (1)	48 (9.7%)	0.61 (0.45–0.81)	189 (13.6%)	1.26 (1.09–1.45)	0.49 (0.35–0.69)	< 0.001
Other rheumatic disorders (1)	–	–	–	–	–	NA
Peptic ulcer (1)	5 (1%)	0.064 (0.002–0.15)	< 5 (0.07%)	0.006 (0.0008–0.03)	9.64 (1.34–229.0)	0.02
Liver disease (1)	27 (5.5%)	0.035 (0.022–0.05)	49 (3.5%)	0.033 (0.024–0.43)	1.06 (0.6–1.69)	0.8
Diabetes (1)	< 5 (0.4%)	0.026 (0.003–0.09)	< 5 (< 0.2%)	0.02 (0.004–0.058)	1.28 (0.15–8.6)	0.77
Diabetes-complications (2)	–	–	–	–	–	NA
Paraplegia (2)	< 5 (< 0.4%)	0.012 (0.0001–0.07)	5 (0.3%)	0.03 (0.01–0.77)	0.39 (0.02–2.78)	0.42
Renal disease (2)	13 (2.6%)	0.17 (0.08–0.29)	< 5 (< 0.2%)	0.02 (0.004–0.06)	8.36 (2.56–36.7)	< 0.001
Cancer (2)	< 5 (< 0.4%)	0.025 (0.002–0.09)	< 5 (< 0.2%)	0.02 (0.004–0.058)	1.28 (0.15–8.65)	0.77
Metastatic cancer (3)	–	–	< 5 (< 0.1%)	0.034	–	NA
Severe liver disease (3)	–	–	–	–	–	NA

Small numbers (*n* < 5) have been confidentialized due to HREC requirements

residence, or the baseline presence of arthritis, nephritis, or enteritis (all *p* > 0.3).

During follow-up, there were 1683 subsequent hospital admissions for 362 IgAV patients

Table 3 Frequency of hospital events for IgAV patients and hospital-based controls during > 20 years of follow-up after index admission

	IgAV (<i>n</i> = 494) (<i>n</i> = 1395)	Controls (<i>n</i> = 1385) (<i>n</i> = 2395)	Odds ratio	Rate ratio	<i>p</i> value
Patients admitted to hospital	362 (73.3)	710 (51.3)	2.61 (2.08, 3.27) 3.266) 2.47)	–	< 0.001
Total number of admissions	1683	2819	–	–	
Average length of stay (SD)	3.07 (4.65)	2.4 (4.47)			< 0.001
Overall admission rate	21.64 (20.6, 22.7)	18.8 (18.1–19.5)	–	1.15 (1.08, 1.22)	< 0.001
Admissions ≤ 1 year after diagnosis	659 (39.2)	542 (19.1)			< 0.001
Admission rate first year after diagnosis	1334.8 (1234.1–1440)	391.3 (359.1–425.7)		3.41 (3.04–3.82)	< 0.001
Admissions > 1 year after diagnosis	1024 (60.8)	2277 (80.7)			
Admission rate > 1 year after diagnosis	13.4 (12.7–14.3)	15.3 (14.7–15.9)		0.88 (0.82–0.94)	0.004
Patients attending ED	183 (37)	336 (24.3)	1.83 (1.47, 2.29)	–	< 0.001
Total ED visits	845	1269	–	–	
Patients with >1 ED visit	126 (25.5)	231 (16.7)	1.71 (1.34, 2.19)	–	< 0.001
ED visit rate/1000 person-years	10.9 (10.2–11.7)	8.5 (8.0–8.9)	–	1.28 (1.18, 1.40)	< 0.001
<i>m</i> -CCI at last observation	0.23 (0.18–0.28)	0.20 (0.17–0.22)	–	–	0.68
Nr with <i>m</i> -CCI > 0 at last observation	89 (18.0%)	242 (17.5%)			0.71 (0.55–0.90)
Nr with <i>m</i> -CCI ≥ 3	6 (1.2%)	< 5 (< 0.2%)			0.08 (0.79–11.6)

Admission rates are number of admissions per 1000 person-years

m-CCI modified Charlson morbidity index without rheumatic disease category, *SD* standard deviation, *ED* emergency department

and 2819 admissions in 710 hospital-based controls during 26.6 (± 5.7) years of follow-up (Table 3). Length of hospital stay was slightly longer in IgAV patients (3.1 vs. 2.4 days, *p* < 0.01). Both the overall proportion of admitted patients (73.3 vs. 51.3%) and

admission rate per 1000 person-years were higher in IgAV patients (rate ratio 1.15, 95% CI 1.08–1.22; both *p* < 0.01). However, this was due to a higher proportion of patients (39.2 vs. 19.2%) and admission rate (RR 3.41 CI 3.04–3.82)) (both *p* < 0.01) for IgAV patients in

the first year following diagnosis. A total of 120 (18.5%) admissions were readmissions for IgAV. In contrast, in subsequent years the proportion (60.8 vs. 80.7%) and admission rate (RR 0.88, CI 0.82–0.94) was lower for IgAV patients. During hospital admission IgAV patients had an overweight of diagnostic and medical procedures performed compared to hospital-based controls especially in the first years following diagnosis, and this did not completely even out during the subsequent years (Suppl Fig. 1).

Subsequent emergency department (ED) visits (registered since 2002) were more frequent for IgAV patients (37 vs. 24%, $p < 0.01$) and occurred at a higher time adjusted rate (10.8 vs. 8.43 per 1000 person-years, rate ratio 1.29; 1.02–1.04; $p < 0.01$). ED visits resulted in hospital admission for 12.1% of IgAV patients and 10.4% for hospital-based controls ($p = 0.83$). The main diagnostic categories for ED visits did not differ significantly between the two groups with only two ED visits for a flare of IgAV and two visits for unspecified arthritis (Suppl Fig. 1).

DISCUSSION

The results from this study suggest that patients diagnosed with IgAV in childhood do not acquire more comorbidity than matched hospital-based controls and despite a higher occurrence of chronic renal failure and peptic ulcer disease have an excellent prognosis during more than 20 years of follow-up.

IgA deposition in IgAV is thought to be triggered by external factors (e.g., infections, medication use, vaccinations, or insect bites) and once these triggers subside IgAV symptoms often resolve, leading to the concept of IgAV as a self-limiting condition [2, 13]. A significant number of IgAV patients require ongoing symptomatic and/or immune modulating treatment and disease relapses have been described in up to 30% of patients [14, 15]. Earlier work has shown that the typical abnormalities in IgA glycosylation in IgAV may have a hereditary base [16] leading to possibly continued production of abnormally glycosylated IgA1 and increased risk for conditions associated with abnormal IgA levels and/or

function [17–20]. The two pathways combined constitute risk factors for subsequent development of comorbidity in IgAV patients. A recent large study of childhood IgAV patients (aged < 16 years) and matched controls seen in General Practices across the United Kingdom reported a 52% increased relative risk of hypertension and a 89% increased risk of chronic kidney disease after a mean follow-up of 5 years in IgAV patients, although the absolute risks were low (1.34 and 0.31%, respectively) [21]. We confirm this long-term risk of renal disease in IgAV, although we found a higher rate most likely due to the different patient selection. Our data also indicate a higher rate of peptic ulcer disease in childhood IgAV patients. Although we cannot exclude that this could be due to disease manifestations, that can be hard to distinguish from peptic ulcer disease on a clinical basis [22, 23], this complication most likely represents the use of anti-inflammatory drugs to reduce symptoms.

We have earlier reported increased respiratory infections in IgAV patients after disease onset [8], but did not observe a deleterious effect on the occurrence of chronic pulmonary disease in the longer-term. Reassuringly, the occurrence of immune complex mediated IgAV in childhood was not followed by an increased rate of chronic arthritis or connective tissue disease later in life. Even though the occurrence of a systemic vasculitis and its therapy has been shown to predispose to accelerated atherosclerosis, we observed no increase in the rate of thromboembolic and/or cardiovascular complications in IgAV patients, similar to what was reported by Tracy et al. [6, 21, 24].

The hospitalization rate for IgAV patients normalized after 1 year and although IgAV patients had more ED visits over the subsequent years than hospital-based controls, there was no obvious difference in the reasons for nor in the admission rate resulting from ED attendance. This suggests that the increased ED attendance was not due to specific IgAV complications but possibly reflects a more cautious attitude in IgAV patients, based on previous experiences surrounding IgAV.

The limitations of this study regard selection of patients managed in an ED or hospital setting,

which potentially skews this cohort toward patients with more severe disease. The use of administrative health data precluded the study of detailed clinical and laboratory characteristics. Also, while the CCI is a validated prognostic tool for adult patients, comorbidity development may differ in children [25]. Finally, while our data demonstrate straightforward rates and risks for comorbidity in IgAV patients, the comparative rates and risk are based on data from hospital-based controls and odds and rate-ratios should be considered in that light. The inclusion and very long-term follow-up of a fully matched completely healthy control group was beyond the limits of our data similar to many other IgAV-based studies. While our hospital-based controls cannot be fully considered a healthy comparator group, the majority were included at the time of a common acute presentation in this age group (see Fig. 1) suggesting they were not a severely ill group. The strength of the presented data is the sizeable and population-based IgAV cohort with long-term capture of comorbidity development.

CONCLUSIONS

In conclusion, childhood IgAV patients have no increased risk of rheumatic disease or other comorbidity over a twenty period, apart from end-stage renal failure, which does not impact survival.

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Compliance with Ethic Guidelines. This data linkage project has been approved by the Human Research Ethics Committees at the WA Department of Health (HREC# 2016.24).

Data Availability. WA Health is proprietor of this administrative dataset to whom queries for data sharing must be addressed. The manuscript has been reviewed by the custodians of the WA Health Data Linkage Branch registries for appropriateness.

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