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A Model Predicting Short Term Severity of IgA Vasculitis in Adults

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Abstract

Background: Predictors of short term severity of adult immunoglobulin A vasculitis (IgAV) are unknown. We aimed to determine clinical features predicting the severity of acute adult IgAV and thus to aid the management of adult IgAV in daily practice.

Methods: Medical records of adult, histologically proven IgAV cases, diagnosed between 01.01.2010 and 30.06.2016 at our secondary/tertiary rheumatology centre were reviewed.

The disease activity was assessed using Birmingham vasculitis activity score-3. Renal disease was defined severe when nephrotic syndrome or nephritic syndrome with acute renal failure developed. Gastrointestinal (GI) disease was severe in case of bloody diarrhoea, ileus or bowel perforation.

Results: During the 78-month observation period, we identified 184 new IgAV cases (57.1% male; 43.5% ever smokers). Skin, GI, renal and joint involvement were present in 184 (generalized purpura above the waist in 47.8%), 63 (severe in 16), 88 (severe in 23), and 81 patients, respectively. Four patients died during acute disease due to vasculitis. Patients with generalized skin lesions had more commonly GI tract, severe GI tract, and kidney involvement. Current smoking was strongly associated with severity of kidney disease. In logistic regression and classification tree model the history of new onset abdominal pain or the presence of generalized purpura in ever smoker emerged as the best predictors of severe GI or renal disease.

Conclusions: Based on clinical characteristics only, the presence of abdominal pain, purpura above the waist and smoking history, seem to be good predictors of short term severity of adult IgAV.

Keywords: IgA Vasculitis; Henoch-Schönlein purpura; Disease severity; Smoking; Generalized purpura

What's Already Known About This Topic?

The two most frequent, and potentially life or organ threatening acute manifestations of IgAV in adults are intestinal ischemia leading to bowel perforation, and renal involvement with acute kidney injury. Previous studies suggested that patient age predicted renal involvement.

What Does This Study Add?

No other study thus far examined the potential predictors of severity of the entire clinical spectrum of acute adult IgAV that could be useful for the management of the acute phase of the disease in daily clinical practice. We found that the abdominal pain, purpura above the waist-line, and smoking history reliably predict short term severity of adult IgAV.

Introduction

Immunoglobulin A vasculitis (IgAV; formerly known as the Henoch-Schönlein purpura) is a small vessel leucocytoclastic vasculitis characterized clinically by skin (palpable purpura), joint (arthritis and arthralgia), gastrointestinal, and renal involvement and histologically by the predominantly IgA deposits in the inflamed vascular wall [1]. It is considered a typical childhood disease. Clinical data of adult IgAV are scarce and mostly limited to cases with significant renal disease [2,3]. We have previously shown IgAV is common and can be severe in adults [4,5].

Predictors of severity of acute IgAV have not been extensively studied in the past. Cao et al. found that the risk of significant renal disease increases with patient age, and the presence of necrotic or bullous skin lesions [6]. Patient age was additionally associated with visceral involvement in the study by Poterucha et al. Adults aged 40 years or less had an increased risk of gastrointestinal tract (GI) involvement. An increased risk of renal involvement was observed in those over 40 years with leuccocytoclastic vasculitis without eosinophils on skin biopsy [7].

The objective of our present study was to determine factors that forecast the severity of acute disease in unselected adult IgAV population.

Methods

Setting and patient selection

The cross-sectional study was conducted at the Department of Rheumatology, University Medical Centre Ljubljana, Slovenia. University Medical Centre Ljubljana is an integrated teaching hospital, serving approximately 1,060,000 of adult residents on the tertiary level, and is the only secondary level referral hospital in the Ljubljana region, serving approximately 530,000 adult residents. Patients with suspected vasculitis are regularly referred by their general practitioners to our early interventional clinic where they are examined without any waiting list on the referral day.

Adults (i.e. persons aged ≥ 18 years), with symptoms, and signs compatible with the definition of IgAV according to the 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides, with histologically proven disease diagnosed for the first time during the observation period, between January 2010 and June 2016 were included. Data were collected in a partially retrospective (from 1 January 2010 to 31 December 2012), and partially prospective (from 1 January 2013 to 30 June 2016) manner. For the retrospective part of the study IgAV cases were ascertained by searching electronic medical records for the 10th Revision of the International Statistical Classification of Diseases code D69.0.

Clinical assessment

After detailed clinical evaluation including smoking history, patients underwent an extensive laboratory work-up as described previously [4]. Definitions of the extent of purpura, renal and gastrointestinal involvement, and severe IgAV are listed in (Table 1). Skin or renal biopsies were evaluated using bright field microscopy, and direct immunofluorescence. IgAV activity was assessed using the Birmingham Vasculitis Activity Score (BVAS, version 3) [8]. Treatment and outcomes of the acute phase of the disease were scrutinized.

Purpura	
limited	lesions present only on skin below the waistline
generalised	skin lesions extending above the waistline
Renal involvement	
haematuria	>5 red blood cells per high power field or red blood cells casts in the urinary sediment or haemoglobinuria ≥ 2+ on dipstick
macroscopic haematuria	>1500 red blood cells/mm^3 of urine
proteinuria	urine protein excretion >300 mg/day
severe	when the patient had nephrotic or nephritic syndrome with acute worsening of renal function, defined as either an increase in serum creatinine concentration or a decrease of the glomerular filtration rate estimated by the four-variable Modification of Diet in Renal Disease Study Equation >25% from patient's baseline
Gastrointestinal involvement	new onset of diffuse abdominal pain or gastrointestinal bleeding
severe	bloody diarrhoea, ileus or bowel perforation

Table 1: Clinical definitions used in patient assessment.

Statistical analysis

We compared subgroups of patients considering the extent of the purpura, smoking history, and disease severity. The results were expressed as medians and IQRs for metric or as percentages for categorical variables. To test for differences between subgroups we used Mann-Whitney test for metric, and Chi-square test or Fisher's exact test for categorical variables. Being aware of the limited number of severe cases, we selected four potential predictors of severe IgAV based on univariate logistic regression results. We used multiple logistic regression and classification tree (R package rpart) to assess the strength of the covariates predicting disease severity [9].

Ethics Committee Approval

The study was approved by the Slovenian National medical ethics committee.

Results

Demographic, epidemiological and clinical data

During the 78-month observation period we encountered 184 (57% male) new IgAV cases. The median patient age at the time of diagnosis was 65.5 (interquartile range (IQR) (44.5–77.3), range 18–92) years. There were 36 (19.6%) current, and 44 (23.9%) past smokers. A hundred and sixty-nine patients presented with purpura for the first time, while 15 recalled previous episodes of similar skin lesions without a definitive diagnosis in the past. Clinical characteristics of our IgAV cohort are presented in (Table 2).

Characteristics	All IgAV	Generalized purpura			Ever smoking			Severe IgAV		
		YES	NO	P value$	YES	NO	P value$	YES	NO	P value$
Number of cases	184	88	96	-	80	104	-	36	148	-
Male / Female gender	105 / 79	57 / 31	48 / 48	0.053	58 / 22	47 / 57	<0.001	24 / 12	81 / 67	0.260
Age (years)#	65.5 (44.5-77.3)	63.4 (43.4;76.8)	66.8 (45.2-78.2)	0.581	62.2 (50.3-74.9)	71.0 (41.4-81.7)	0.090	62.1 (47.3-77.2)	65.8 (44.5-77.4)	0.623
Symptom duration (d)#	8 (5-17)	9 (5-21)	8 (5-14)	0.363	8 (5-14)	8 (5-21)	0.451	14 (5-24)	8 (5-14)	0.238
Prior infection	63	32	31	0.641	27	36	1.0	14	49	0.559
New medication	48	25	23	0.507	21	27	1.0	7	41	0.339
Prior malignancy	20	9	11	0.817	9	11	1.0	3	17	0.769
Smoking (ever)	80	39	41	0.882	-	-	-	22	58	0.024
Smoking (active)	36	18	18	0.853	-	-	-	13	23	0.009
General symptoms	32	21	11	0.032	14	18	1.0	-	-	-
Necroses	84	37	46	0.235	37	47	1.0	-	-	-
Generalized purpura	88	-	-	-	39	49	0.882	25	63	0.005
Isolated skin	41	10	31	<0.001	14	27	0.213	-	-	-
Joint symptoms	81	45	36	0.075	37	44	0.654	-	-	-
Arthritis	32	16	16	0.848	16	16	0.438	-	-	-
GI	63	47	16	<0.001	28	35	0.876	-	-	-
Severe GI	16	12	4	0.034	8	8	0.607	-	-	-
Renal	88	50	38	0.026	42	46	0.299	-	-	-
Severe renal	23	15	8	0.117	16	7	0.012	-	-	-
BVAS	9 (4-15)	12 (6-18)	7(3-13)	<0.001	11(4;16)	8(3;15)	0.323	-	-	-
Severe IgAV	36	25	11	0.005	22	14	0.024	-	-	-
Serum IgA (g/l)#	3.9 (3.1-5.3)	3.7 (2.8-5.2)	4.0 (3.5-5.7)	0.139	4.2 (3.0-5.7)	3.8 (3.1-4.9)	0.264	3.9 (2.5-5.3)	3.9 (3.1-5.2)	0.506
ESR (mm/h)#	35 (20-52)	35 (18-54)	34 (20-50)	0.973	31 (18-54)	35 (20-51)	0.741	38 (21-56)	34 (19-51)	0.554
CRP (mg/l)#	28 (11-55)	32 (18-66)	24 (6-47)	0.018	32 (12-68)	25 (8-52)	0.086	39 (21-85)	25 (8-51)	0.017

Table 2: Characteristic of IgAV (generalized *versus* limited purpura; ever-smokers *versus* non-smokers, severe *versus* non severe). [BVAS-3: Birmingham Vasculitis Activity Score-3; GI: gastrointestinal; severe GI – bloody diarrhea or ileus or surgical intervention; severe renal – nephritic syndrome with acute renal failure or nephrotic syndrome; CRP: C-reactive protein; ESR: Erythrocyte Sedimentation Rate; # : median and IQR; $p-values were used to assist the exploratory results].

Treatment

We managed 126 (68.5%) patients as inpatients and the rest as outpatients. We treated the patients in line with common local practice. IgAV spontaneously remitted in 42 (22.8%) cases. Topical steroids were the only treatment in 6.5% of patients. Indications for systemic immunosuppressive treatment were necrotic purpura, bowel involvement of any type, or severe kidney involvement. We treated 42 (22.8%) patients with intravenous methylprednisolone pulses (MP; 125–1000 mg qd, for three consecutive days). In ten patients MP pulses were the only treatment, while the remaining 32 patients continued with oral glucocorticoids. We treated a total of 124 patients with oral MP in a median (IQR; range) initial dose of 40 (32–60; 16–96) mg qd. We used cyclophosphamide in 15 (8.1%), mycophenolate mofetil in

one (0.5%), and hyperimmune gammaglobulins in five (2.7%) cases. Two (1%) patients had plasma exchange. None of the patients required haemodialysis. Two patients with ischemic bowel perforation and one patient with intractable gastrointestinal haemorrhage needed surgical intervention. Another patient had explorative laparoscopy. Four patients (2.2%) died in the acute phase of the disease. One due to diffuse alveolar haemorrhage (IgA vasculitis was demonstrated in the lung post mortem), and three succumbed to severe GI tract involvement.

Disease severity

Thirty-six (19.6%) patients fulfilled our definition of severe disease (5 had severe GI tract involvement, 20 severe renal involvement, 11 a combination of severe GI tract and severe renal involvement). Clinical characteristics of severe *versus* non severe IgAV are shown in the (Table 2).

Severe disease was more common in past or current smokers (p=0.024) and commonly presented with generalized purpura (p=0.005).

The patients with generalized purpura more commonly had general symptoms (relative risk (RR) 2.1 (95% CI 1.1–4.1)), GI tract involvement (RR 3.2 (95% CI 2.0–5.2)), severe GI tract involvement (RR 3.3 (95% CI 1.1–9.8)), as well as kidney involvement (RR 1.4 (95% CI 1.1–2.0)). Severe renal involvement was twice as common in this group (17.0% *vs.* 8.3%), but it did not reach the level of significance.

Severe renal disease was significantly more frequent in ever smokers than in non-smokers (RR 3.0 (95% CI 1.3-6.9)). This relationship was even more profound in current smokers (RR 4.1 (95% CI 1.7-10.0)). Other IgAV presentations were not associated with the positive smoking history.

Abdominal pain was reported in 51 (27.7%) patients. It was significantly more common in severe disease (55.6% *vs.* 20.9%; RR 3.3 (95% CI 1.8-5.8).

Predicting IgAV severity

We created a logistic model predicting disease severity that included smoking status, new onset abdominal pain, CRP and extent of purpura. The presence of abdominal pain identified 20/36 cases with severe disease. Eight additional patients with severe IgAV had generalized purpura and positive history of past or current smoking. CRP did not contribute significantly to the model and was therefore withdrawn the final scheme. The allocation of patients according to our model is shown in (Table 3 and Figure 1). Our model predicted 77.8% severe episodes: 16/16 severe GI tract cases and 15/23 severe renal cases. All the results about the logistic model and regression tree with complete criteria for severe disease prognosis can be found in the Supplementary material.

Characteristic	Number	GI	Severe GI	Renal	Severe renal	BVAS	Severe IgAV
(a) Abdominal pain	51	51	15	31	7	17 (11-21)	20
(b) Ever smoker with generalized purpura	21	2	1	14	8	9 (4-14)	8
(a) and (b) negative	112	10	0	43	8	6 (3-12)	8

Table 3: IgA vasculitis severity model. (GI gastrointestinal; severe GI – bloody diarrhea or ileus or surgical intervention; severe renal – nephritic syndrome with acute renal failure or nephrotic syndrome; BVAS-3 Birmingham vasculitis activity score-3).

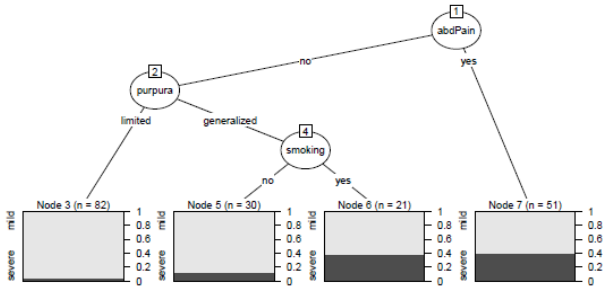

Figure 1: Classification tree - IgA vasculitis severity model

Discussion

Current understanding of the IgAV in adults is limited. Reports focus mainly on the long term outcome of IgAV subgroup with major renal involvement. In many settings, IgAV is perceived a rare disease. In contrast, we found it to be the second most common systemic vasculitis in adults with a 3–6-times higher incidence rate than previously reported [4]. One plausible explanation for this discrepancy might be that in most settings mild cases are managed solely by general practitioners, and pass under the radar of the systemic vasculitis experts on the tertiary level. However, in our recent thorough study of the clinical spectrum of the acute phase of IgAV in unselected adult cohort we found that not all cases have a favourable outcome, e.g. an unrecognized gastrointestinal involvement may rapidly result in irreparable bowel ischemia and even patient death [5,10].

In the present study we aimed to identify clinical predictors of severe IgAV in the acute phase of the disease. Using logistic regression analysis, and classification tree we developed a simple model that could help the first responders, e.g. general practitioners or dermatologists, to recognize patients with probable adverse short-term outcomes based solely on clinical assessment when the results of laboratory, patohistological or imaging studies are pending. The presence of new onset abdominal pain or the presence of generalized skin lesions in an ever smoker emerged as the best predictors of severe gastrointestinal and renal disease. The model enables a reasonably good discrimination between IgAV cases with mild, uneventful disease and more severe acute disease course. Considering only these three characteristics the model recognized over 75% of patients with severe IgAV. We are aware that renal involvement may present with a delay of several weeks or even months therefore we suggest regular repetition of urine analysis, and renal function tests in all IgAV patient during this period [11].

Except for statistical analyses the following observations support the choice of the clinical parameter in our model. First, 93.8% of patients with a history of new onset abdominal pain had severe gastrointestinal involvement which was responsible for three of the four deaths in our cohort. Second, current smokers presenting with generalized purpura had a relative risk of 4.1 (95% CI 1.7–10.0) for severe kidney involvement. The association of smoking and the progress of chronic kidney disease is appreciated in diabetic and several non-diabetic chronic kidney diseases, including IgA nephropathy [12,13]. Cha YJ demonstrated a link between the progression of renal disease in IgA nephropathy and smoking-related injury of microvasculature, glomeruli and arterioles [14]. In animal and *in vitro* models nicotine activates inflammatory mediators, induces mesangial cell proliferation, and fibronectin production [15].

In our cohort, we found no difference in the frequency, and severity of GI involvement among ever smokers. However, the role of smoking in gut inflammation is not straightforward. Under physiological conditions, cigarette smoking does not appear to cause macro-or micro-scopic damage to the gut. On the other hand, animal studies show that smoking renders the small intestine more susceptible to inflammation, while its effect on colon could be both pro- and anti-inflammatory [16]. This divergent impact of smoking on small and large intestine is well documented in Crohn's disease where worse outcome is reported in Crohn's ileitis than in Crohn's colitis [17]. IgAV most commonly involves the small intestine, thus one might expect that smoking may worsen GI inflammation.

We are aware of limitations of our study. Most obvious seem to be its partly retrospective design. The study also provided no information on the smoking pattern (intermittently or daily) and on cumulative cigarette exposure. Looking at a potential dose dependency and asking patients about passive cigarette smoke exposure would have certainly increased the quality of the study. The relative paucity of severe cases limited the number of predictors that could be included in the model. However, the potential clinical IgAV triggers, such as antecedent infection, use of new medication, history of cancer and disease duration before the diagnosis had no significant impact on disease severity.

The major strength of our study is that we based our findings on the observations from the largest known unselected adult IgAV cohort. The decision to include histologically established IgAV cases only could be interpreted as a drawback on one side but it increases the reliability of the diagnosis on the other side.

In conclusion, based on the presence of abdominal pain, generalized purpura, and smoking history we correctly predicted three quarters of IgAV patients with acutely adverse outcomes. Our findings could help primary care physicians identify patients that require careful short-term follow-up or even inpatient management.

Conflict of Interest

Authors have no conflicts of interest to declare.

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