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Anti-neutrophil cytoplasmic antibodies predate symptom onset of ANCA-associated vasculitis. A case-control study

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ABSTRACT

Objectives: Anti-neutrophil cytoplasmic autoantibodies [ANCA] are important for diagnosis of ANCA-associated vasculitides (AAV). The timing of antibody development is not well established. To investigate the development of proteinase 3 (PR3)- and myeloperoxidase (MPO)-ANCA, blood samples collected before onset of symptoms of AAV were analysed.

Methods: To identify AAV patients with blood samples predating symptoms, the National Patient Register and Cause of Death register were scrutinized for ICD codes for AAV and linked to the registers of five biobanks. Diagnoses of AAV and time point for symptom onset were confirmed by reviewing 504 case-record. Eighty-five AAV cases (34 males, 51 females) with samples >1 month < 10 years from AAV symptom onset and two controls matched for sex, age, and sampling time for each case were included. Samples were screened using ELISAs for ANCA and further analysed for PR3-or MPO- specificities.

Results: In ANCA-screen 35.7% of the pre-symptomatic cases and 3.5% of controls tested positive ($p < 0.01$). 26.2% of the cases were PR3-ANCA+ and 10.7% MPO-ANCA+. Median (Q1-Q3) predating time for PR3-ANCA+ was 2.7 (0.3–7.7) years and MPO-ANCA+ 2.0 (0.9–3.5) years. PR3-ANCA was demonstrated in samples up to nine years before symptom onset. At symptom onset predating PR3-ANCA+ cases were younger than PR3-ANCA- ($P < 0.01$), and MPO-ANCA+ were older than MPO-ANCA- ($p < 0.05$). Predating MPO-ANCA+ cases vs. MPO-ANCA- and vs. PR3-ANCA+ cases had more often at symptoms onset manifestations from lungs, kidneys or peripheral nervous system ($p < 0.01$ and $p < 0.05$, respectively).

Conclusion: The PR3-and MPO-ANCAs are present years before AAV symptom onset and represent distinct diseases.

1. Introduction

The anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitides (AAV) comprise a group of rare, potentially life-threatening diseases characterized by necrotizing inflammation of small blood vessels and the presence of ANCA [1]. ANCA targeting proteinase 3 (PR3) and myeloperoxidase (MPO) expressed by innate immune cells (neutrophils and monocytes) are salient pathogenic features of the small vessel vasculitides granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). Although GPA and MPA share common immunological and pathological features, such as ANCAs and high degree of renal involvement, they are genetically distinct subsets [1,2].

The mechanisms of tolerance breakdown leading to the generation of ANCA are poorly understood. One model suggests neutrophil

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extracellular trap formation and release to be of importance in the generation of ANCAs, whereas other hypotheses involve the production of alternative and antisense transcripts at the PR3 locus in patients [3–6]. Still, the timing of antibody occurrence and its contribution to disease development is incompletely understood, with only one previous study analysing PR3-ANCA before disease onset in a limited number of serum samples from patients with AAV [7].

In this study we set out to investigate the development of PR3-and MPO-ANCA in AAV and their associations with presenting symptoms of AAV, using serum and plasma samples collected from individuals before onset of symptoms.

2. Material and methods

2.1. Cases and controls

In this case-control study the presence of ANCA predating onset of AAV was analysed in samples from Swedish biobanks. Using the codes of the International Classification of Diseases (ICD)-9 (1987–1997; 446 A, 446.4, 446 E) and ICD-10 (1998–2011; M30.0–30.1, M31.3, M31.7), individuals diagnosed with AAV or polyarteritis nodosa (PAN) were identified from the Swedish National Patient Register of inpatient care (primary diagnosis from discharge summaries was used) and the Cause of Death Register. The PAN diagnosis was included on the suspicion of a misdiagnosed AAV. The personal unique identification numbers of the individuals were then linked to the registers of five different biobanks

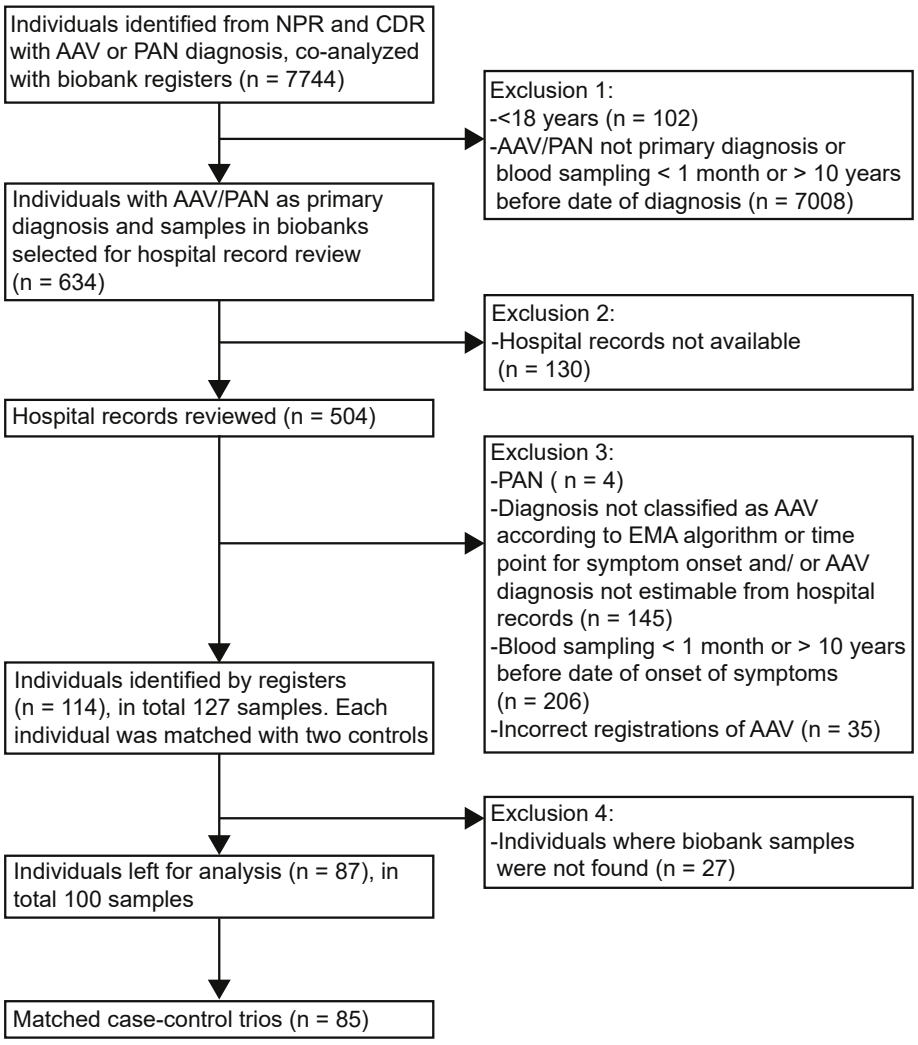

Fig. 1. Flow chart of individuals identified before onset of ANCA associated vasculitis (AAV) or polyarteritis nodosa (PAN). NRP= National Patient Register, CDR= Cause of Death Register. EMA = European Medicines Agency.

(four serological biobanks and one population-based biobank in Sweden) to identify individuals with available blood samples before onset of symptoms. Selection criteria for requisition of medical record were an age ≥18 years and samples >1 month and <10 years before first date of the registered AAV/PAN diagnosis. Thus, 634 individuals were identified of whom 504 had medical records available for confirmation of diagnosis (Fig. 1). Time point for onset of symptoms of AAV was confirmed by reviewing all case-records and AAV diagnoses were confirmed using European Medicines Agency algorithm [8]. In total, 114 cases with 127 samples were identified. For each case, from the same biobank two controls without any of the mentioned diagnoses were matched for age, sex and sampling date. Due to missingness of samples in the biobanks (tubes were empty or not found) samples from 114 cases was reduced to 87 cases (36 males, 51 females; mean age ±SD age 51.9 ± 16.8 years) and from 228 controls to 197 controls (83 males, 114 females; 52.0 ± 16.5 years) that were available for analysis (Fig. 1). Of the originally matched case-control trios, 79 remained with two controls and six more with one matched control. For the six cases with one matched control data of the one control was duplicated to achieve in total 85 matched pairs (presented in Supplementary Table 1). For the 85 cases, 20% were plasma samples (median (Q1-Q3)) predating time 4.9 (3.2–7.0) years) and 80% were serum samples (median (Q1-Q3)) predating time 4.3 (1.2–6.7) years). In the matched controls the distribution between plasma and serum samples was as for the cases. The 85 cases were classified after the disease had developed as 65 cases of GPA, 16 of MPA, and four of eosinophilic GPA (EGPA) [8]. Data on clinical manifestations of the disease at time of symptom onset and at diagnosis and ANCA-positivity at diagnosis were collected from medical records of all patients.

Symptoms and signs at presentation were defined according to surrogate markers for vasculitis and further for pulmonary involvements (e.g. severe cough, dyspnea, hemoptysis, results of X-ray examination or auscultation) and mononeuritis [8]. At diagnosis biopsy had been performed in 81% of the cases, of which pulmonary or renal biopsy was performed in 67% and the remaining biopsies were from the nasal mucosa or skin.

The study approved by the locally appointed ethics committee and complies with the Declaration of Helsinki.

2.2. ANCA analyses

The samples were screened for IgG class ANCA using high sensitivity ELISA (ORGENTEC Diagnostika, Germany) with the cut-off for positivity set by the manufacturer as ≥1. Samples were further analysed using previously evaluated second-generation (capture-based) PR3-and MPO-ANCA ELISAs (SVAR Life Science, formerly EuroDiagnostica, Sweden) with cut-off at 7 and 8 IU/mL, respectively according to the manufacturer selected as suggested by the International consensus statement and recommendations [9,10]. In the present study, no significant differences between the levels in serum and plasma were found for the cases but in controls the plasma levels of MPO-ANCA were significantly lower compared to serum (data not shown). Thus, the specificities were adjusted and were for serum and plasma PR3-ANCA 99.4% and 97.9%, respectively and for MPO-ANCA 98.7% and 97.9%, respectively.

2.3. Statistical analysis

Statistical calculations were performed using SPSS software (v. 25.0 IBM Corp, USA). Descriptive data for cases and controls were summarized and presented as proportions, means and medians as appropriate. Frequencies were compared using Chi-square test or Fisher's exact test when appropriate and for continuous data Student's T-test and non-parametric tests were used. Normally distributed data were presented with mean and standard deviation (SD) or standard error of mean (SEM) and median and inter quartiles range (Q1-Q3) for skewed data. Conditional logistic regression analyses were performed for matched pairs and logistic regression analyses including adjustments for sex and age for analysing stratified data among the cases and the risk was presented with odds ratio (OR) and 95% confidence intervals (CI). Sensitivity analyses have been performed on the original matched groups (114 cases vs. 228 controls) versus the remaining matched pairs, 85 cases and 170 controls. Furthermore, sensitivity analyses have been performed before and after the duplication of the six controls for cases (n = 79) and their controls (n = 158), presented in the supplementary file (Supplementary Table 1). P ≤ 0.05, two sided was considered as statistically significant.

3. Results

3.1. Autoantibodies

All samples were analysed for presence of ANCA, revealing a significantly higher frequency of ANCA positivity (+) in pre-symptomatic cases compared to controls, 30/85, 35.7% (95%CI 25.2–46.2% versus 3.5% (95%CI 0.7–6.4%) (p < 0.001); with a risk ratio for being a pre-symptomatic AAV individual compared to control of OR = 27.53, 95%CI 6.56–115.57, p < 0.001. The increase of positivity during the predating time was significant until symptom onset (p < 0.001) (Fig. 2). The level of antibodies detected by ANCA screen increased significantly during the predating time until symptom onset (p < 0.05, Supplementary Fig. 1).

PR3-ANCA was positive in 22 of 84 (26.2%, 95%CI 16.6–35.8%) and MPO-ANCA in 9 of 84 pre-symptomatic cases (10.7%, 95%CI 4.0–17.5%), significantly increased compared to controls, (p < 0.001 and p < 0.001, respectively). No individual was positive for both antibodies. PR3-and MPO-ANCA were each associated with being pre-symptomatic for AAV compared with controls, OR = 159.48, 95%CI 3.16–9102.91, (p < 0.01) and OR = 16.54, 95%CI 2.08–131.42, (p < 0.01), respectively. The positive predictive value was highest for PR3-ANCA, 0.917 as was the Likelihood ratio positive 21.74 (Table 1). The frequencies of positive PR3-and MPO-ANCA increased during the predating time (p < 0.001 and p = 0.001, respectively) (Fig. 2).

The levels of PR3-ANCA and MPO-ANCA were increased in cases compared with controls (median (Q1-Q3) PR3-ANCA; 1.56 (1.1–5.9) IU/mL vs. 1.11 (0.9–1.1) IU/mL, p < 0.001 and MPO-ANCA 1.51 (1.0–2.7) IU/mL vs. 1.17 (0.9–1.7) IU/mL, p < 0.01) (Fig. 3). The levels of PR3-and MPO-ANCA in the cases increased closer to symptom onset although non-significantly (p = 0.082 and 0.087, respectively) (Supplementary Fig. 1).

The median (Q1-Q3) predating time for PR3-ANCA+ was 2.7 (0.3–7.7) years and for MPO-ANCA+ 2.0 (0.9–3.5) years. The first antibody to appear positive was PR3-ANCA, 9.7 years before symptom

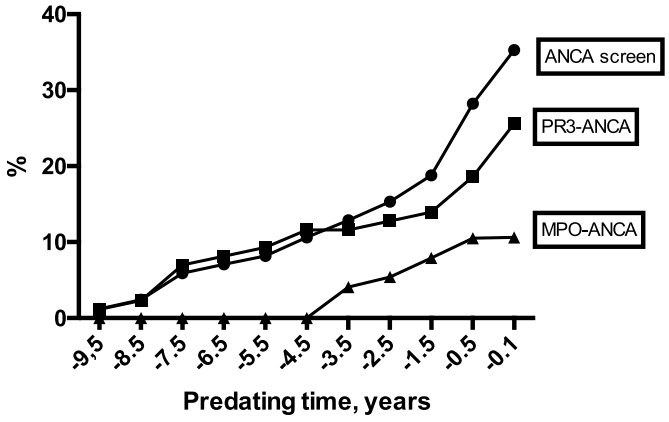

Fig. 2. Accumulated frequencies of antibody positivity in percent (y-axis) during predating time (x-axis) analysed using ANCA screen (p < 0.001), and PR3-and MPO-ANCA ELISAs (p < 0.001 and p = 0.001, respectively).

Table 1
Descriptive data of matched cases and controls and cases stratified for ANCA analysed before symptom onset.

	Controls N=170	Summary of all cases N=85	Stratification of cases according to ANCA testing:					
			ANCA screen cases N=85		PR3-ANCA ELISA analyses N=84[a]		MPO-ANCA ELISA analyses N=84[a]	
			Negative N=55	Positive n=30	Cases negative N=62	Cases positive n=22	Cases negative N=75	Cases positive n=9
ANCA frequency, %	3.5[b]	35.7[b]	0	35.3	0	26.2	0	10.7
PPV			0.833		0.917		0.818	
NPV			0.749		0.725		0.686	
LR+			10.0		21.74		9.95	
Age at sampling, mean ±SD, years	52.0±16.5	52.2±16.7	52.8±14.5	50.2±20.6	55.2±14.7	42.8±19.3*	50.7±16.2	65.0±15.6*‡
Age at symptom onset, mean ±SD, years	-	56.1±17.0	57.4±15.1	52.5±20.2	59.3±15.0	46.7±19.1**	54.3±17.0	67.0±15.7*‡
Age at diagnosis, mean ±SD, years	-	56.6±16.9	58.1±14.8	53.0±20.2	60.0±14.8	47.0±19.1**	55.3±16.7	67.6±15.5*‡
Sex, female, n (%)	98 (57.6)	49 (57.6)	31 (56.4)	19 (61.3)	37 (58.7)	13 (56.5)	43 (55.8)	7 (77.8)
Storage time, mean ±SD years	21.9±7.3	21.8±7.4	22.7±7.0	19.9±7.8	22.5±7.2	19.5±7.5	21.7±7.0	21.2±10.6
Predating time from sample collection until symptom onset, median (Q1-Q3), years	-	4.7 (1.39-6.7)	5.3 (2.7-7.4)	1.9 (0.8-5.3) **	4.7 (2.0-6.7)	2.7 (0.3-7.7)	4.9 (1.6-7.4)	2.0 (0.9-3.5) *
Involvement of kidney, lung or peripheral nervous system, n (%)	-		15/51 (29.4)	12/29 (41.4)	21/59 (35.6)	6/21 (28.6)	20/71 (28.2)	7/9 (77.8) **†
Pulmonary and/or kidney manifestations at diagnosis, n (%)	-		42 (76.4)	27 (84.4)	48 (75.0)	21 (91.3)	60 (76.9)	9 (100)
EMA classification after onset at diagnosis[3], n (%)								
EGPA	-	4 (4.7)	4 (7.3)	-	4 (6.3)	-	4 (5.3)	-
GPA;	-	-	-	-	-	-	-	-
2a	-	54 (63.5)	36 (65.5)	18 (60.0)	38 (60.3)	16 (72.7)	50 (65.4)	4 (44.4)
2b	-	2 (2.4)	2 (3.6)	-	2 (3.2)	-	2 (2.6)	-
2c	-	1 (1.2)	1 (1.8)	-	1 (1.6)	-	1 (1.3)	-
2d	-	8 (9.4)	5 (9.1)	3 (10.0)	6 (9.5)	2 (9.1)	8 (10.5)	-
MPA;	-	-	-	-	-	-	-	-
3a	-	13 (15.3)	4 (7.3)	9 (30.0)	9 (14.3)	4 (18.2)	8 (10.5)	5 (55.6)
3b	-	3 (3.5)	3 (5.5)	-	3 (4.8)	-	3 (3.9)	-

PR3-ANCA = proteinase 3 anti-neutrophil cytoplasmic antibodies, MPO-ANCA = myeloperoxidase ANCA, PPV=Positive predicted value, NPV = negative predicted value, LR+ = likelihood ratio positive, Q1-Q3 = quartile 1 – quartile 3, EMA = European Medicines Agency.
EGPA = Eosinophilic granulomatosis with polyangiitis, GPA = granulomatosis with polyangiitis, MPA = Microscopic polyangiitis.
‡MPO+ vs. PR3+, $p < 0.01$, † MPO+ vs. PR3+ $p < 0.05$, *P < 0.05, **P < 0.01 positive cases vs. negative.
[a] Missing sample for one individual.
[b] Positivity in ANCA screen and/or ANCA-PR3 test and/or ANCA-MPO test [3]presented according to ref.8.

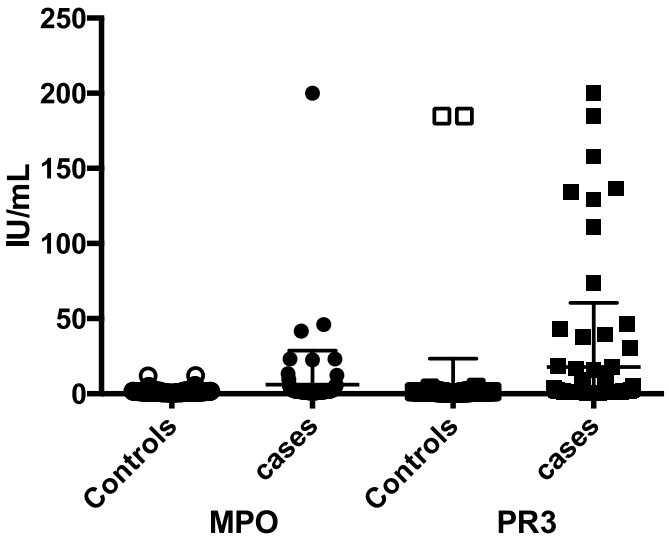

Fig. 3. The levels (IU/mL) of antibodies analysed for PR3-and MPO-ANCA in cases and controls presented with median and interquartile range. Cut-off for positivity was for PR3-and MPO-ANCA set at 7 and 8 IU/mL, respectively. MPO-ANCA (controls; open circle, pre-symptomatic individuals; filled circle) and PR3-ANCA (controls; open square, pre-symptomatic individuals; filled square).

onset, whilst the first appearing MPO-ANCA+ was 4.3 years before symptom onset. The median (Q1-Q3) predating time in women was 6.4 (2.1–8.0) years for PR3-ANCA positivity, and in men 0.3 (0.1–2.1) years, ($p < 0.01$).

Cases positive for PR3-ANCA predating symptom onset were younger than cases negative for PR3-ANCA, mean (SD) 46.7 (19.1) years versus 59.3 (15.0) years, respectively ($p < 0.01$) (Table 1 and Supplementary Table 2). In contrast, individuals with positive MPO-ANCA predating symptom onset were older at symptom onset compared to MPO-ANCA negative (−) cases, 67.0 (15.7) years versus 54.3 (17.0) years ($p < 0.05$) and also compared to PR3-ANCA positive cases ($p < 0.01$) (Table 1). There is a slight non-significant predominance of women in predating MPO-ANCA+ cases.

Twelve individuals had two or three samples before symptom onset of which three converted from negative to positive in the ANCA screen test. The closest time points for conversions between two samples was in one individual from being negative at 2.33 years before symptom onset to positive 2.19 years before onset.

3.2. *Predating ANCA+ and manifestations at symptom onset*

Predating MPO-ANCA+ cases versus negatives had more often manifestations from the respiratory tract, kidney and/or mononeuritis as presenting symptoms (77.8% vs. 28.2%; OR = 8.75, 95%CI 1.67–45.78, $p < 0.05$) and versus PR3-ANCA+ cases (77.8% vs. 30.0%; OR = 8.17 95%CI 1.3–51.40, $p < 0.01$). MPO-ANCA+ had more often pulmonary involvement at symptom onset compared with MPO-ANCA- cases, 55.6% versus 11.8% ($p < 0.001$). Half of the PR3-ANCA+ individuals (50.0%) had ear-nose-throat symptoms at debut and only 22.6% had symptoms of pulmonary, kidney or peripheral nervous system involvements.

3.3. Predating ANCA+ and manifestations at diagnosis

The mean time between first symptoms of disease and diagnosis was 7.1 months (SEM 1.5) for the patients. Stratified for PR3-ANCA positivity versus negativity in predating samples did not show significant differences in time between symptom onset and diagnosis although numerical (5.4 ± 1.2 months vs. 7.7 ± 2 months). Cases being PR3-ANCA+ in predating samples had significantly more often at least one GPA surrogate marker at diagnosis versus MPO-ANCA+ individuals (77.3% vs. 37.5%, $p < 0.05$). At diagnosis, predating MPO-ANCA+ cases had less often ear-nose-throat manifestations ($p = 0.064$) compared with predating MPO-ANCA-cases. Furthermore, after diagnosis all individuals who were MPO-ANCA+ before symptom onset and 90.9% of those with predating PR3-ANCA+ had renal and/or pulmonary manifestations of the disease. Cases with MPO-ANCA+ in predating samples were more often classified as MPA than GPA compared with predating MPO-ANCA- cases (55.6% MPO-ANCA+ vs. 11.8% MPO-ANCA-; $p < 0.01$) (Table 1).

All individuals positive for ANCA screen, and for PR3-or MPO-ANCA in predating samples were positive for ANCA of the same subtype at time of AAV diagnosis.

4. Discussion

In this case-control study on samples collected years before symptom onset of AAV we found increased levels and frequencies of PR3-and MPO-ANCA in the cases vs. controls. The prevalence of PR3-ANCA was much higher than of MPO-ANCA and appeared earlier; strikingly, PR3-ANCA was detected up to 9 years before symptom onset, implying an extended process from breaking of tolerance to autoimmune disease. These results may suggest that PR3-ANCA+ AAV individuals have a more gradual and less aggressive initiation and progress of the disease compared with MPO-ANCA+ cases. Additionally, PR3-ANCA appeared with a longer predating time in women than in men raising hypotheses about different triggering environmental agents associated with AAV in women versus men. Alternatively, this difference may reflect differential immunological processes of breakage of tolerance between men and women in the PR3-ANCA+ subset of AAV.

Interestingly, individuals with predating MPO-ANCA+ were significantly older compared with PR3-ANCA+ and MPO-ANCA- individuals and had a higher proportion of women as previously described [11]. They also exhibited more manifestations at symptom onset from lung, kidneys and the peripheral nervous system versus MPO-ANCA-. The PR3-ANCA+ pre-symptomatic individuals tended to have a higher prevalence of ear-nose-throat involvement at symptom onset compared with MPO-ANCA+, and had to a higher extent at least one surrogate marker for GPA, in line with previous observations [1,12]. Taken together, these results emphasize the distinction of AAV disease subsets, based on the presence of PR3-or MPO-ANCA.

Our findings of presence of PR3-ANCA confirms a previous study on a smaller sample collection, although the frequency of PR3-ANCA in that study was higher, 63% but the predating time was shorter [7]. In our study the predating time point from sampling until symptom onset and time of diagnosis was longer, particularly in individuals negative for ANCA, although all individuals were positive at diagnosis and the time duration from symptom onset until diagnosis was similar. Similar to prior findings in rheumatoid arthritis and systemic lupus erythematosus, we observed a gradual increase in autoantibody positivity closer to onset of symptoms in AAV, applied to both PR3-and MPO-ANCA [13–15]. Awareness of these antibodies even in patients with mild symptoms including ear-nose-throat symptoms increase the potential of an early diagnosis and treatment. Being aware of a diagnostic delay in patients with ANCA vasculitis we carefully reviewed all case records for symptoms and signs of a developing disease. Only about 20% had ear-nose-throat symptoms at diagnosis.

One limitation of the study is that the patients were identified retrospectively and analysed prospectively and consequently they were not consistently followed from disease onset by registrations. A second limitation is that several individuals with AAV that had been identified in the registers had to be excluded from the study, due to missing samples in the biobanks. Further, the collection of samples was not on regular intervals but rather randomly since the samples were from different biobanks with different sampling protocols and the number of cases was limited. Yet, with 85 cases included, this comprises the largest case-control study so far of the pre-symptomatic phase of AAV.

5. Conclusion

We herein present evidence of an initiation of the autoimmune process in AAV several years before appearance of the first symptoms. Furthermore, these results add to the accumulating evidence that PR3-ANCA+ and MPO-ANCA+ AAV are distinct diseases, with substantial differences in pathogenesis and clinical manifestations.

Author contributions

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Study conception and design. Berglin, Mohammad, Dahlqvist, Rantapää-Dahlqvist. Acquisition of data. Berglin, Mohammad, Sjöwall, Johansson, Eriksson, Rantapää-Dahlqvist. Analysis and interpretation of data. Berglin, Mohammad, Dahlqvist, Johansson, Eriksson, Rantapää-Dahlqvist. All listed authors of this manuscript have read and approved this manuscript.

Declaration of competing interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2020.102579.

Disclosure statement

The authors have declared no conflicts of interest.

Statement of ethics approval

The Regional Ethics Committees at Umeå University (No. Dnr 2012-52-31 M, 2012-386-32 M).

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