Original Research Article

Thyroid Antibodies, Autoimmunity and Cognitive Decline: Is There a Population-Based Link?

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Abstract

Background: Autoimmunity is considered an uncommon but under-recognised cause of cognitive decline. ***Methods:*** Serum samples from 3,253 randomly selected subjects enrolled in the Hunter Community Study, aged 55–85 years, were assayed for thyrotropin stimulatory hormone, anti-thyroid peroxidase antibodies (TPO-Ab), anti-nuclear antibodies (ANA) and extractable nuclear antigens (ENA). Cognitive function was assessed using the Audio Recorded Cognitive Screen (ARCS) tool. ***Results:*** TPO-Ab were found in 8.4% and ANA in 27.9% of the study population, of whom 3% had positive ENA findings. No relationship was found between the ARCS score and either TPO-Ab (coefficient = 0.133; 95% CI −0.20, 0.82, p = 0.616), ANA at a low (coefficient = 1.01; 95% CI −2.58, 0.55, p = 0.203) or a high titre (coefficient = −0.65; 95% CI −2.59, 1.28, p = 0.508), or ENA antibodies (coefficient = 5.12; 95% CI −0.53, 10.77; p = 0.076). ***Conclusions:*** Autoantibody findings are common in an aging population and are not associated with cognitive decline.

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Introduction

Autoimmunity has been shown to be a key factor in a small subset of patients with cognitive decline and dementia [1–3]. The patients typically present after an insidious onset with rapidly progressive cognitive decline, frequently with a fluctuating course and inflammatory cerebrospinal fluid findings [4–6]. These patients often have autoantibody markers, including anti-cation channel complex antibodies, and respond to immunosuppression [5, 7, 8]. However, autoimmune phenomena are common in the normal adult population, particularly if defined as the presence of antibodies against cellular components. Up to 92% of the population harbour brain-reactive autoantibodies, frequently cross-reactive with the neural tissue of other species [9, 10]. However, only a minority of patients experience disease as a consequence. Anti-thyroid peroxidase antibodies (TPO-Ab) are associated with thyroid disease and are found in patients diagnosed with steroid responsive encephalopathy and thyroiditis (SREAT), and the presence of thyroid autoantibodies forms part of the diagnostic criteria [1, 11]. Anti-nuclear antibodies (ANA) are associated with systemic lupus erythematosus (SLE), a well-recognised cause of neurological and psychiatric disorder, but the diagnosis of SLE relies on both clinical features and autoantibody findings and can be further confirmed through characteristic histological findings in tissues that can be readily biopsied [12, 13]. More recently, a number of well-characterised syndromes associated with specific but rare anti-neuronal autoantibodies, including potassium channel blocking antibodies and N-methyl-D-aspartate receptor antibodies, have been described [14, 15]. The presence of such rare autoantibodies in the context of a characteristic clinical presentation has aided in the recognition of these rare but clinically important syndromes. This paper takes a population approach to address the question of whether the presence of common autoantibodies such as TPO-Ab and ANA is useful in the diagnostic assessment of cognitive decline.

Methods

Population

The Hunter Community Study (HCS) is a cohort of 3,253 subjects aged between 55 and 85 years and drawn at random from the Australian electoral roll. The specifics of their recruitment and their characteristics have been described previously [16]. A large subset of these participants had blood stored at baseline in 2004–2007 and had a concurrent cognitive screen. Depression was assessed using the Centre for Epidemiological Studies Depression (CESD) scale, and psychological distress was assessed with the K10 Kessler Scale. A history of cardiovascular disease (CVD) and thyroid disease was sought by a general health questionnaire as well as a list of medications. The research was approved by the Human Research Ethics Committees of the Hunter New England Local Health District and the University of Newcastle.

Laboratory Measures

ANA was assessed using HEp-2 ANA slides (Bio-Rad Laboratories, Hercules, Calif., USA); ANAs at a titre of 1/80 were defined as borderline, whereas those with an ANA titre of >1/160 were defined as positive. Extractable nuclear antigens (ENAs) were assessed on those testing ANA positive (titre >1/160) using ELISA screening for the six antigens Sm, RNP, SSA, SSB, SCL-70 and Jo-1 (Immuno Concepts Inc., Sacramento, Calif., USA). ENAs that tested positive in the screen assay in this test were classed as borderline if no defined antigen specificity was identified and as positive if one of the six antibody specificities was identified. TPO-Ab were analysed by ELISA testing (Aesku.Diagnostics, Oakland, Calif., USA). Thyrotropin levels were measured using sandwich chemiluminescent immunoassay on the Dimension Vista System

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(Siemens Healthcare Diagnostics Ltd., Newark, N.J., USA). The coefficients of variations were 0.01 and 0.14% at concentrations of 0.39 and 6.3 mIU/l, respectively.

Cognitive function was assessed using the Audio Recorded Cognitive Screen (ARCS) tool. The ARCS is a novel instrument, which uses an audio device to deliver neuropsychological tests to unsupervised participants who write their responses to the questions in a special booklet for later scoring [17]. The ARCS has been previously shown to be a sensitive and comprehensive method of assessment of cognitive impairment [17, 18]. Five cognitive domains are assessed by the ARCS, and a global, overall score can be obtained. The global and cognitive domain scores are adjusted for age, gender and education level and normalised to a mean of 100 with a standard deviation of 15. An ARCS score of <70 is considered to be abnormal.

Statistics

The cross-sectional association between autoimmune thyroid markers and cognitive scores was examined using linear regression, with ARCS as the outcome. The results were adjusted for known risk factors for cognitive decline including age, gender, self-reported mood disorder and depression, self-reported CVD and self-reported thyroid problems. Given the non-normal distribution of the TPO-Ab titres, this was log-transformed. All analyses were conducted using SAS 9.2 (SAS Institute, Cary, N.C., USA).

Results

A summary of the data, presented in relation to the global ARCS score, is given in table 1. In the primary analysis, log TPO-Ab levels were used as a predictor for the ARCS score in linear regression, adjusting for the confounding variables. Adjustment for the self-reported history of autoimmune disease was attempted, but there was extensive co-linearity with CVD and, as a result, it was not included in the analysis. For this cohort (n = 1,705 with non-missing covariates), there was no evidence that TPO-Ab had a linear effect on ARCS [coefficient = exp (0.133) = 1.143, p = 0.616] after adjusting for CVD status, age, depression and gender (table 2). There was a marginal effect on the ARCS score due to self-reported thyroid problems (coefficient = 2.064, p = 0.09) and a statistically significant effect of self-reported CVD (coefficient = –2.689, p = 0.009).

Subsequent to this analysis, investigations were undertaken to determine the association between TPO-Ab and the global ARCS score among patients with and without self-reported thyroid problems. We investigated the effect of TPO-Ab on ARCS in subjects with and without thyroid problems and included a term for the thyrotropin stimulatory hormone (TSH) category and other confounders. We found no evidence of an independent effect of the TPO-Ab status (coefficient = –0.67, p = 0.831, 95% CI –0.68, 0.55).

This study also investigated the relationship between cognitive impairment, as measured by ARCS, and the presence of two other common autoantibodies, ANA and ENA. The above analysis was repeated separately for the following outcomes: ENA (defined as positive, negative and borderline), ANA (positive, negative and borderline) and a composite antibody score, which was defined as the number of positive findings against ANA, ENA and TPO-Ab (0, 1, 2 or 3). None of these variables showed evidence of an association with ARCS after adjusting for known confounders (see 'score' in table 3). ENA positivity did show marginal evidence of an effect relative to ENA negativity (adjusted coefficient = 5.15, 95% CI –0.50, 10.80), although this was likely due to the multiple comparisons made. We also found no evidence of an effect for any of the antibody measures on ARCS for the subgroup without thyroid problems. The above analysis was repeated using the attentional task subscore of the ARCS as an alternative proxy for a mild confusional state, but the outcome and results were consistent with those for global ARCS.

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Table 1. Characteristics of the cognitively normal and impaired groups

| | ARCS | | | | Total | |
| | >70 | | ≤70 | | | |
	n	%	n	%	n	%
TPO-Ab						
Negative	1,426	70.5	270	68.2	1,696	70.1
Detected	174	8.6	29	7.3	203	8.4
Not tested	424	20.9	97	24.5	521	21.5
ANA						
Borderline (detected <1/160)	568	28.1	107	27.0	675	27.9
Negative	735	36.3	133	33.6	868	35.9
Positive (titre ≥1/160)	297	14.7	59	14.9	356	14.7
Not tested	424	20.9	97	24.5	521	21.5
ENA						
Borderline (screen positive only)	12	0.6	4	1.0	16	0.7
Negative	821	40.6	158	39.9	979	40.5
Positive (specific ENA Ab)	28	1.4	4	1.0	32	1.3
Not done (ANA negative)	1,163	57.5	230	58.1	1,393	57.6
Autoimmune disease history						
No	1,723	85.1	321	81.1	2,044	84.5
Yes	301	14.9	75	18.9	376	15.5
CVD history						
No	1,723	85.1	321	81.1	2,044	84.5
Yes	301	14.9	75	18.9	376	15.5
TSH						
Normal	1,478	73.0	270	68.2	1,748	72.2
Abnormal	122	6.0	29	7.3	151	6.2
Not available	424	20.9	97	24.5	521	21.5
Thyroid problems						
No	1,753	86.6	333	84.1	2,086	86.2
Yes	205	10.1	46	11.6	251	10.4
Not available	66	3.3	17	4.3	83	3.4
Depression						
No	1,522	75.2	304	76.8	1,826	75.5
Yes	436	21.5	75	18.9	511	21.1
Not available	66	3.3	17	4.3	83	3.4
Gender						
Male	966	53.1	175	50.0	1,141	52.6
Female	853	46.9	175	50.0	1,028	47.4
Age						
<60	587	29.0	97	24.5	684	28.3
61–65	519	25.6	76	19.2	595	24.6
66–70	386	19.1	80	20.2	466	19.3
71–75	290	14.3	59	14.9	349	14.4
76–80	152	7.5	54	13.6	206	8.5
80+	88	4.3	30	7.6	118	4.9
Not available	2	0.1	0	0.0	2	0.1

Conclusion

Our results indicate that there is no statistically significant relationship between TPO-Ab and ARCS for patients either with or without self-reported thyroid problems, irrespective of the TSH level. We also looked at this relationship adjusting for other autoimmune markers and the relationship was still absent. In this situation, it is important to ensure that it is not a

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Table 2. Results of the linear regression model with ARCS as the outcome

Variable	Coefficient (95% CI) (univariate)	Adjusted coefficient (multivariate)	p value (multivariate)
log TPO-Ab	0.31 (–0.20, 0.82)	0.133	0.616
CVD	–2.67 (–4.43, –0.92)	–2.689	0.009
Thyroid disease	0.26 (–1.81, 2.33)	2.064	0.090
Depression	–1.49 (–3.04, 0.06)	–0.479	0.588
Age (years)			
61–65	6.92 (5.20, 8.63)	6.925	<0.0005
66–70	2.97 (1.13, 4.82)	4.376	<0.0005
71–75	6.24 (4.23, 8.26)	7.207	<0.0005
76–80	–1.68 (–4.09, 0.78)	–1.491	0.303
80+	–3.14 (–6.20, –8.09)	–0.961	0.592
Male	–0.57 (–1.85, 0.70)	0.219	0.769

Table 3. Effect of all three antibody measures on the ARCS score (separately fit in the multiple regression adjusting for age, CVD, thyroid problems, depression and gender)

Variable	Adjusted coefficient (95% CI)	p value
log TPO-Ab	0.13 (–0.39, 0.65)	0.616
ENA (negative referent)		
Borderline	0.36 (–7.19, 7.91)	0.925
Positive	5.15 (–0.50, 10.80)	0.074
ANA (negative referent)		
Borderline	–1.01 (–2.58, 0.55)	0.203
Positive	–0.65 (–2.59, 1.28)	0.508
Score	0.19 (–1.05, 1.44)	0.760

lack of power that leads to a false-negative result. Given our sample size, the number of participants with an abnormal TPO-Ab titre, a power of 80% and a p value of 0.05, we had sufficient power to detect a difference of 2.9 points (out of 100) between the TPO-positive and -negative groups. Hence, we can conclude that our negative result is robust. Alternatively, if there is an association between TPO-Ab and cognition, it is very small in magnitude and clinically immaterial. The presence of TPO-Ab alone does not increase the risk, at a population level, for cognitive impairment.

SREAT is an important diagnosis as it is a potentially reversible cause of cognitive impairment [1, 2, 8, 19]. However, the diagnosis is largely a clinical one, and the role of thyroid autoimmunity in this syndrome's pathogenesis remains unclear. Fluctuations in the TPO-Ab titre have not been associated with clinical changes in the encephalopathy [5, 20], and a reliable association between the response to immune-based therapy and TPO-Ab has not been found [5, 8, 21, 22]. The clinical context is key in making a diagnosis of SREAT, though the presentation can be variable and patients with SREAT are frequently misdiagnosed at presentation with alternative diagnoses including viral encephalitis and degenerative dementia [21].

It has been suggested that autoimmune disease increases the risk of delirium and dementia [3, 5, 23, 24]. A second element of this study was to assess whether the presence of autoreactivity, as defined by the presence of TPO-Ab, ANA, or ENA, increases the risk of cognitive decline. Neither TPO-Ab nor ANA nor ENA was associated with an impaired ARCS

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score either alone or as a composite assessment of an autoimmune score. The result implies that like TPO-Ab, ANA is common in the population and not predictive of cognitive decline. It also suggests that the presence of multiple common autoantibodies is not a risk factor for dementia.

There are limitations to the study. SREAT is an unusual diagnosis, so despite the large sample size, we could fail to find an association between TPO-Ab and cognitive decline. However, this would not detract from the central finding of the study, namely that the detection of an autoantibody that is common in the community, such as ANA or TPO-Ab, does not increase the risk for cognitive decline and should be interpreted in the clinical context. In cerebral SLE, the diagnosis of systemic disease can be strengthened by a biopsy of an easily accessible and potentially involved tissue such as kidney, muscle or skin, so one can be confident that the diagnosis of SLE at least is secure. However, our results suggest that the finding of a positive ANA in isolation would have limited independent diagnostic utility for the diagnosis of cerebral lupus in an aging cohort. The same point can be made in the diagnosis of SREAT, where the clinical presentation is key to the diagnosis, and the presence of TPO-Ab forms part of the syndrome diagnosis [19]. Another potential weakness in the analysis is that serial cognitive analysis was not performed to assess for serial changes in cognition over time. However, if there were a significant effect on the speed of cognitive decline due to the presence of autoimmunity, this should have been evident in the age cohort analyses, unless the effect size was small.

The finding of associations between CVD, age and the ARCS score is consistent with previous findings and reflects the validity of ARCS as a tool for the measurement of cognition [25, 26]. Age, as expected, was associated with a low ARCS score, particularly when the age was >75. Interestingly, co-linearity between self-reported CVD and self-reported autoimmune disease was also noted, consistent with the reported increased incidence of CVD in patients with autoimmune disorders including SLE [27, 28]. This finding suggests that any association between autoimmunity and cognition would need to carefully consider the role of CVD in that association.

In conclusion, the data demonstrate that autoantibody findings are common in an aging cohort and do not increase the risk of cognitive decline, as measured by ARCS.

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