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Original article

Autoantibodies are not predictive markers for the development of depressive symptoms in a population-based cohort of older adults

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ABSTRACT

Background: Autoantibodies have been implicated in the etiologic pathway of depressive disorders. Here, we determine the association between the presence of a panel of autoantibodies at baseline and change in depression symptom score over 5-year follow-up in a cohort of healthy elderly Australians.
Methods: Serum samples from 2049 randomly selected subjects enrolled in the Hunter Community Study (HCS) aged 55–85 years were assayed for a range of autoimmune markers (anti-nuclear autoantibodies, extractable nuclear antigen autoantibodies, anti-neutrophil cytoplasmic autoantibodies, thyroid peroxidase autoantibodies, tissue transglutaminase autoantibodies, anti-cardiolipin autoantibodies, rheumatoid factor and cyclic citrullinated peptide autoantibodies) at baseline. Depression symptom score was assessed using the Centre for Epidemiological Study (CES-D) scale at baseline and 5 years later.
Results: Autoantibody prevalence varied amongst our sample with ANA being the most prevalent; positive in 16% and borderline in 36% of study population. No evidence for a relationship was found between change in CES-D score over time and any autoimmune marker. Statins and high cholesterol were significantly associated with change in CES-D score over time in univariate analysis; however, these were probably confounded since they failed to remain significant following multivariable analysis.
Conclusions: Autoantibodies were not associated with change in CES-D score over time. These findings point to an absence of autoimmune mechanisms in the general population or in moderate cases of depression.

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1. Introduction

Emerging evidence suggests an independent role for autoantibodies in the etiologic pathway of depressive disorders. Neuropsychiatric disturbances such as depression are reportedly more prevalent amongst autoimmune sufferers compared to healthy individuals [9,20]. Similarly, depressive sufferers carry an increased risk of developing autoimmune diseases [9]. Collectively, these convergent reports, coupled with overlapping somatic symptoms common to both autoimmune conditions such as Systemic Lupus Erythematosus (SLE) and depression, led to the autoimmune hypothesis of depression [9,20]. Further compelling arguments emerged from studies reporting the utility of thyroid autoantibodies in predicting the occurrence of postpartum

Abbreviations: CES-D, Centre for Epidemiological Study Depression; SLE, Systemic lupus erythematosus; ANA, Anti-nuclear autoantibodies; ENA, Extractable nuclear antigen autoantibodies; Sm, Anti-Smith; RNP, Ribo-nucleoprotein; SS-A, Sjogren's Syndrome A; SS-B, Sjogren's Syndrome B; SCL-70, Topoisomerase-I; JO-1, Autoantibodies against amino acyl-tRNA synthetases; IgG, Immunoglobulin G; IgA, Immunoglobulin A; ANCA, Anti-neutrophil cytoplasmic autoantibodies; TPO-Ab, Thyroid peroxidase autoantibodies; TTG-Ab, Tissue transglutaminase autoantibodies; ACGA, Anti-cardiolipin autoantibodies; RHF, Rheumatoid factor; CCP-Ab, Cyclic citrullinated peptide autoantibodies; hsCRP, High sensitivity C-reactive protein; DNA, Deoxyribonucleic acid; HCS, Hunter community study; LDL, Low-density lipoprotein; TGs, Triglycerides; BMI, Body Mass Index; PAL, Physical activity level; ARFS, Australian Recommended Food Score; FFQ, Food Frequency Questionnaire; DQESv2, Dietary Questionnaire for Epidemiological Studies version 2; AGHE, Australian Guide to Healthy Eating; ELISA, Enzyme-Linked Immunosorbent Assay; GPL, IgG phospholipid units; IU/mL, International unit per millilitre; EU/mL, Enzyme immunoassay units per millilitre; SD, Standard deviation; DAGs, Directed Acyclic Graphs; CNS, Central nervous system.

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depression [17,21,22,30]. Whilst some studies found an excess of depressive symptoms in women who demonstrated thyroid autoantibodies during pregnancy regardless of whether they developed thyroid dysfunction [17,21], others failed to explore whether the occurrence of depressive symptoms was attributable to hypothyroidism rather than the action of autoantibodies [30].

Mouse models of SLE reportedly show behavioural changes that coincide with high autoantibody titres. Moreover, autoantibodies have been noted to evoke depressive-like behaviour following their introduction into healthy mice [13,14,37,41]. Substantial reductions in circulating serum autoantibodies following immunosuppressive therapy and subsequent improved performance on various behavioural tests in mice have also provided compelling evidence to support a direct role for autoantibodies in the development of depressive-like behavioural deficits [33,34,36]. In one such study, reduced dendritic spine density significantly correlated with increased serum levels of anti-nuclear antibodies (ANA) and behavioural dysfunction [35]. Cyclophosphamide treatment resulted in reduced immune marker infiltration of mouse brain, prevented the atrophy and aberrant morphology of pyramidal neurons in the parietal cortex and diminished neurohormonal differences between MRL-lpr mice and congenic MRL/MpJ++ (MRL++) controls (which develop a less severe form of autoimmune disease) [35]. The latter neuropathological changes are the proposed basis for the behavioural deficits observed amongst autoimmune mice, providing insight into the role of immune activation in mental illness [35].

Collectively, these studies suggest a role for autoantibodies as markers of immune dysregulation driving the inflammatory, endocrine and neurotransmitter disturbances often observed in depressive patients [19]. However, most human studies have used cross sectional designs, whereas prospective studies would be stronger for inferring causation. As such, the aims of this study were to capitalize on an existing population-based study of healthy elderly Australians, to examine the association between the presence of autoantibodies at baseline and change in depressive symptom score over 5 years of follow-up.

2. Methods and materials

2.1. Population

Participants were drawn from the existing Hunter Community Study (HCS), a cohort of 3318 elderly Australians, randomly selected from the electoral roll. The specifics of their recruitment and characteristics have previously been described [24]. A large subset of these participants had blood drawn at baseline in 2004–2007 and concurrent neuropsychiatric assessment that was repeated 5 years later. Individuals were excluded from the current analysis if they had evidence of current or prior depression at baseline assessment, as defined by self-reported depression, self-reported use of antidepressant medication or a Centre for Epidemiological Study Depression (CES-D) score greater than 15. Furthermore, participants with immune disorders were also excluded (Appendix A). These exclusions were instituted to investigate the link between autoimmunity and depression in a non-clinical population. Our study sample consisted of 2049 participants, aged 55–85 years, following exclusion of those with a history of past or current depression ($n = 824$) or a diagnosis of one of several chronic diseases ($n = 445$). The research was approved by the Human Research Ethics Committees of the Hunter New England Health District and the University of Newcastle.

2.2. Data collection

At baseline, participants completed a range of questionnaires and a series of clinical measures. Blood samples collected included plasma, serum, whole blood, and DNA that was stored at −80 degrees Celsius in 1-mL aliquots to minimize freeze-thaw cycles. Repeat questionnaires and clinical assessments were carried out 5 years later in order to update exposure and outcome information.

2.2.1. Outcome measure – change in CES-D depressive symptom score over 5-year follow-up

Depressive symptoms were assessed at baseline and follow-up using the CES-D scale. This is a 20-item self-reported measure of depressive symptoms [32], summed to yield a total score between 0 and 60. A higher score is indicative of greater frequency and severity of depressive symptoms. The CES-D scale is a highly reliable measure with an internal consistency of 0.85 in the general population [32]. The criterion validity is well established with other self-report measures, by correlations with clinical ratings of depression, and relationships with other variables, which support its construct validity [5,16].

2.2.2. Confounders

Clinical measures included weight, height, waist-circumference, fasting total cholesterol and blood glucose, low-density lipoproteins (LDLs) and triglycerides (TGs). Morbidity was defined by self-report or using medications treating that condition. Participants wore a pedometer for seven consecutive days during waking hours to enable mean daily steps to be calculated as a measure of physical activity level (PAL). Postal questionnaires were also used to collect information on age, gender, smoking habits and dietary information.

Dietary intake was assessed using the Australian Recommended Food Score (ARFS) [10]. The ARFS was calculated based on national recommendations in the Dietary Guidelines for Australian Adults and the core foods given in the Australian Guide to Healthy Eating (AGHE). Respondents are able to obtain a total of 74 points. As a result of missing data, HCS participants were only able to score a possible total of 67 points. The scoring method is described in Appendix C. A higher score is indicative of greater diet quality.

2.2.3. Laboratory measurements

ANA titre was determined using HEp-2 ANA slides supplied by Kallestad, (Bio-Rad laboratories USA); ANA titres $< 1{:}40$ were defined as negative whilst a titre of 1:80 was defined as borderline, and titres $\geq$ 1:160 were defined as positive. Extractable nuclear antigen antibodies (ENA) were assessed on those testing borderline or positive (titre $\geq$ 1:80) on ANA. Enzyme-Linked Immunosorbent Assay (ELISA) screening was performed for 6 antigens namely: anti-Smith (Sm), ribo-nucleoprotein (RNP), Sjogren's syndrome A and B (SSA and SSB), topoisomerase I (SCL-70) and autoantibodies against amino acyl-tRNA synthetases (Jo-1) (ImmunoConcepts, USA). ENAs that tested positive in the ENA screening were classed as borderline if no defined antigen specificity was identified and positive if one of the six antibody specificities was identified. Measurement of anti-neutrophil cytoplasmic antibodies (ANCA) was performed on commercial formalin-fixed neutrophil slides produced by INOVA (INOVA Diagnostics INC, San Diego, California). Indeterminate and atypical ANCA was classified as borderline whilst those staining with a cytoplasmic fluorescence of classical cytoplasmic or perinuclear pattern of 1:10 or higher dilution were classified as positive. Anti-thyroid peroxidase antibody titres (TPO-Ab) were measured using ELISA testing (Aesku, Germany). Titres $\geq$ 50 units per millilitre (units/mL) were defined as positive. Anti-tissue transglutaminase antibodies (TTG-Ab) were measured using AESKULISA Celicheck immunoglobulin A (IgA) and immunoglobulin G (IgG) TTG ELISA (six point calibrator). Titres $\geq$ 25 units/mL were defined as positive. Anti-cardiolipin antibodies (ACGA) were measured using ELISA produced by Medical Innovations (four-point calibrator curve). ACGA at a titre $\leq$ 5 IgG phospholipid units (GPL) was defined as negative whilst 6–20 was low positive, 21–40 moderate positive and over 40 GPL,

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