Diagnosing Dementia

Investigating the use of whole blood proteins as dementia biomarkers

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Introduction

- The number of people suffering with dementia is steadily rising, with 7.7 million new cases each year[1].
- The majority of suffers have **Alzheimer's Disease (AD),** whereas a small proportion will have **Vascular Dementia (VaD)** or **Dementia with Lewy Bodies (DLB).**
- Dementia diagnosis is extremely challenging due to varying symptomology and lack of reliable tests.
- Currently, clinicians use cognitive assessments and brain imaging, both lengthy and time consuming[2].
- Proteins characteristically found in dementia patients have been found to be feasible biomarkers within platelets[3] and other blood components.

Aims

Identify characteristic dementia proteins in whole blood samples and explore their use as biomarkers to discriminate between normal ageing and dementia and differentiate between distinct dementia subtypes.

Methods and Materials

- 202 whole blood samples were taken from clinically evaluated participants; 92 AD, 23 VaD, 17 DLB, 70 Control.
- Samples were screened for a panel of dementia related proteins.
- Novel indirect **Enzyme Linked Immunosorbent Assay (ELISA)** immunoassays, fig 1, were developed for **Amyloid Precursor Protein (APP-N), α- synuclein (ASN) and immunoglobulin G (IgG).**

Indirect ELISA

Step 1: Antigen Coating
Step 2: Primary antibody binding
Step 3: Secondary enzyme linked antibody binding
Step 4: Substrate addition

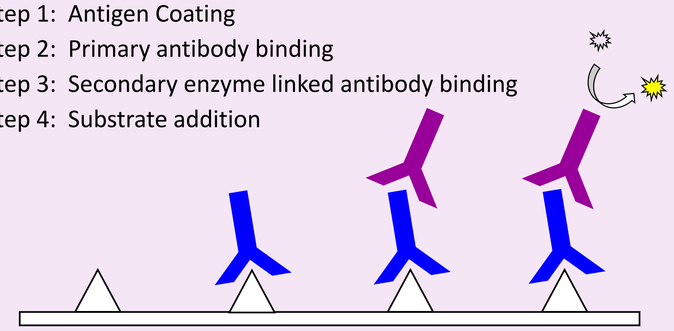

Figure 1: Indirect ELISA protocol.

References
1. Alzheimer's Society.2016. Available from: https://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=412. (Accessed: 2 September 2016)
2. NHS Choices. Tests for diagnosing dementia. 2015. Available from: http://www.nhs.uk/conditions/dementia-guide/pages/dementia-diagnosis-tests.aspx (Accessed: 2 September 2016)
3. Mukaetova-Ladinska E, Abdel-All Z, Dodds S, Andrade J, Alves da Silva J, Kalaria R et al. (2012). 'Platelet immunoglobulin and amyloid precursor protein as potential peripheral biomarkers for Alzheimer's disease: findings from a pilot study.' *Age and Ageing.* 41(3):408-412.

Results

Discriminating between dementia and normal ageing

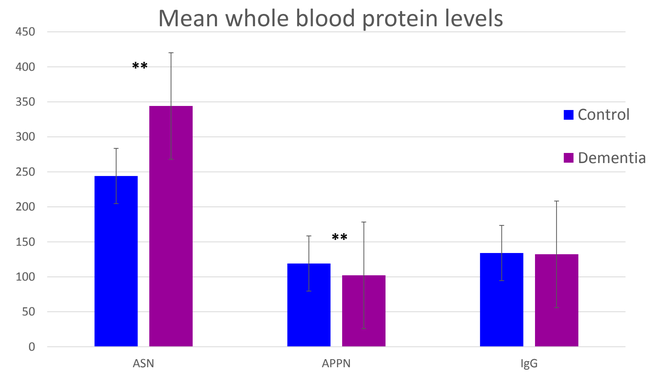

Figure 2: Mean whole blood levels of ASN, APPN and IgG in control (blue) and dementia (purple) groups. As compared to the control group * P < 0.05, ** P ≤ 0.01.

Differentiating between dementia subtypes

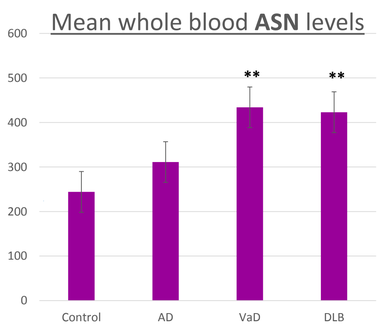

Figure 3a

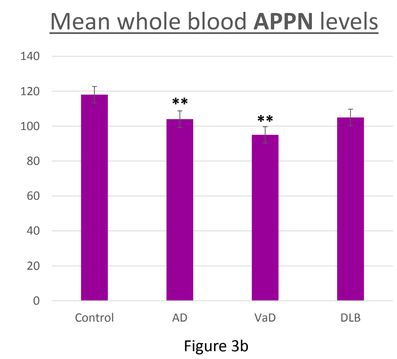

Figure 3b

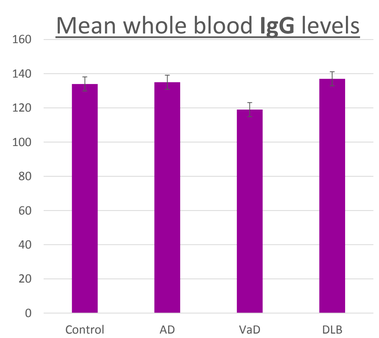

Figure 3c

Figure 3: Mean whole blood ASN, APPN and IgG levels in control and all dementia groups. As compared to control subjects *P< 0.05, ** P≤ 0.01.

Discussion

- No significant difference was observed in IgG levels between control and dementia subjects, fig 2, with little variation amongst dementia subtypes, fig 3c.
- Whole blood ASN levels were 30% greater in dementia patients, fig 3a. A greater increase of 40% and 45% were seen in DLB and VaD groups respectively, fig 3a.
- Whole blood APPN levels showed a 15% decrease in dementia patients, fig 2. A greater decrease of 20% was seen in VaD patients, fig 3b.
- ASN and APPN have the greatest sensitivity when identifying VaD and DLB, fig. 4a and 4b. AD diagnosis is less sensitive but shows greater accuracy in whole blood than platelets[3].

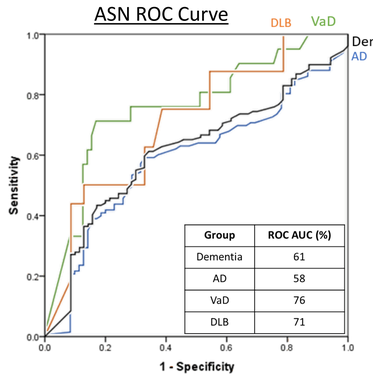

Figure 4a

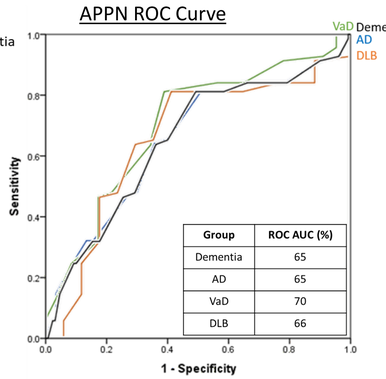

Figure 4b

Figure 4: Receiver operating characteristic (ROC) curves for whole blood ASN and APPN levels in each of the dementia subtypes, including area under the curve (AUC).

Conclusions

- Whole blood IgG levels show little variation and is therefore not an appropriate biomarker.
- Whole blood ASN and APPN levels show encouraging differences between both control and dementia subjects and amongst distinct dementia subtypes. ASN and APPN are feasible peripheral biomarkers.
- Further work is needed to determine whether the ASN and APP changes are a direct consequence of the central brain dementia process.

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