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Title of the Thesis: Study Of Genetic Predisposition And Oxidative Stress Risk Factors For Alzheimer's Disease And Vascular Dementia

Research finding

Following were main observations:

Clinical observation:

- Most of the cases were over 60 years (AD: 57/75 and VaD: 39/50). No difference was found in age of onset of disease whether it was AD and VaD.
- High frequency of male was observed in both AD and VaD (Males *vs.* Females in AD: 51 *vs.*24 and in VaD: 37 *vs.* 13).
- IADL scale of AD was significantly (p=0.035) different from VaD cases. No such difference was found in MMSE and BDR score.

Laboratory observations:

BIOCHEMICAL PARAMETERS

- Low serum HDL (p=0.001) and paraoxonase (p=<0.001) level were significantly associated with VaD (p=0.001) when compared to healthy controls.
- In healthy control TC showed positive correlation with TG (r=0.1 & p=<0.001) and LDL (r=0.87 & p=<0.001) while LDL showed negative correlation with HDL (r=-0.25 & p=0.004).

GENETIC FACTORS

- Frequency of allele E4 has been found significantly high in patients (AD: 46.7 % and VaD: 32.0 %) as compared to control subjects (13.3%)

- The frequency of genotype E3E4 was statistically higher in patients (AD: 38.7% and VaD: 28.0 %) as compared to control subjects (11.7%)
- The presence of *ApoE4* allele increased the odds of having disease by 5.68 fold (95% CI: 2.83-11.39) for AD and 3.05 fold (95% CI: 1.38-6.76) for VaD
- *PON1 rs662* allele carrier genotypes (QR+RR) *vs.* QQ (wild homozygous), showed increased the risk of having AD (p=0.044) by 1.8 fold (95%CI: 0.97-3.40) and VaD (p=0.002) by 3.09 fold (95%CI: 1.4-6.9)

CORELATION BETWEEN GENETIC & BIOCHEMICAL PARAMETERS

- RR genotype of *PON1 rs662* polymorphism was associated with increased levels of paraoxonase in AD (p=0.01) and VaD (p=0.05).
- No significant association was found between MM genotype of *PON1 rs85460* polymorphism and biochemical parameters.
- No association was found between *ApoE4* allele and biochemical parameters.

GENE-GENE INTERACTION

- Interactions were observed between *PON1 rs85460 (LM or MM)* and *ApoE4* allele. When both alleles were present together the condition increased the risk of AD by 7.11 folds (p=0.002 and 95%CI: 2.1-24.0) and VaD by 4.92 folds (p=0.015 and 95%CI: 1.36-17.77). This is an example of Epistasis.
- Interactions were observed between *PON1 rs622 (QR or RR)* and *ApoE4* allele. When both alleles were present together the condition increased the risk of AD by 7.56 folds (p=0.00 and 95%CI: 2.9-19.6) and VaD by 6.3 folds (p=0.002 and 95%CI: 2.01-19.69).

Strength of the study

The strength of this study is its inclusion of moderately large number of cases from Indian origin. The study clearly shows the association of *ApoE4* alleles of *ApoE gene* polymorphism with AD and VaD. Statistically significant association of both variant allele and genotype *PON1* rs622 polymorphism was seen with VaD cases. Epistatic interaction between *ApoE* and *PON1 (rs622 and rs85460)* is probably the most interesting finding of our study.