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Individual Risk Detection of Developing Cognitive Decline and Dementia in Adults with Down's Syndrome

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Abstract

Alzheimer's disease (AD) is a neurodegenerative brain alteration and a leading cause of cognitive decline and dementia and incidence and prevalence of AD are increasing in both industrial and rural societies. However, in spite of intensive research during last thirty years no effective medication is available. Neuropathological AD hallmarks are amyloid deposition and neurofibrillary tangles, however, presence of these brian deposits do not completely explain the disease's pathogenesis. Recently Aβ peptide, the proteinaceous precursor of brain amyloid deposits, has been proposed as an anti-microbial factor. Recent investigations have indeed shown that virus and/or bacterial infections influenced the clinical history of AD.

Genotypic, phenotypic, epidemiological and clinical variables have been associated with an increased risk of cognitive decline or dementia as assesed by longitudinal population investigations. For instance, our data suggested that some genetic signatures, as shown by the AD genome wide association studies, might decrease host antimicrobial immune responses and affect progression to clinical dementia in the elderly by increasing susceptibility to herpes virus infections. The aim of this commentary is to briefly show innovative applicative procedures to determine individual risk of dementia and the possibility to modulate cognitive decline/dementia risk by personalized preventive interventions. The approach presented here may have clinical relevance in adult people with Down's syndrome that are considered at elevated risk of developing cognitive decline and senile dementia after their 50'ths of age.

Keywords: Down's syndrome; Cognitive deterioration; Dementia risk chart, Alzheimer's disease; Herpes virus latent infections; Peripheral inflammation

Introduction

Alzheimer's disease (AD) is the leading cause of dementia in the elderly. Prevalence and incidence of this type of dementia is increasing and extensive research has focused on AD pathogenetic mechanisms to find effective preventive procedures and therapeutic drugs. However, no therapy is available. Therefore, focusing upon diverse aspects of the disease in order to discover new therapeutic strategies appears to be relevant for patients. Moreover, new approaches to the disease's pathogenesis may open innovative prevention opportunities for the elderly or other groups of people without manifest cognitive alterations, but with increased risk of developing dementia.

Brain amyloid deposits and intra neuronal neurofibrillary tangles (NFTs) have been suggested as inducers of the disease [1,2]. However, these neuropathological alterations are often also present in the brain of elderly without cognitive alterations or AD pathology [3]. Therefore, it is uncertain whether amyloid or other proteinaceous brain depositions might be causatively linked to AD.

The biological role of the amyloid precursor protein (APP) and its proteolytic derivatives (A-beta peptide) in normal brain is still uncertain [4]. However, recent data showed that A-beta peptide is an anti-microbial factor [5]. A recent study reported that the A-beta peptide showed an *in vitro* anti-virus activity [6]. Therefore, A-beta peptides may play multiple roles in human brain and contribute to anti-microorganism responses.

As we elsewhere discussed, genetic data from four genome wide association (GWA) studies on AD [7-9] suggested that persistent virus infections may be potentially associated with the age related cognitive decline. In fact, this specific genetic signature may predispose to AD by affecting the individual susceptibility to virus infections [7] during the age associated decline of immune competence.

Adults with Down's syndrome (DS) o trisomy of chromosome 21 show an elevated risk of cognitive decline and dementia with advancing age. The over expression of the APP gene on the chromosome 21 may lead to an early amyloid deposition in DS brains and be a susceptibility factor for AD [10].

Middle age people with DS also show increased tangle brain deposition, neuronal loss and neuro-inflammation along with cerebrovascular pathology [10]. All these factors might accelerate brain aging in DS. A dramatic increase in life expectancy, coupled with a significant reduction in early mortality, has led to a substantial increment in the number of DS subjects reaching old age. This demographic picture parallels increased incidence and prevalence of the age related degenerative diseases in persons with DS.

Chronic inflammation is associated with the pathogenesis of most chronic degenerative diseases. In fact, a relevant inflammatory component is always associated with AD, autoimmune diseases, diabetes, atherosclerosis, sarcopenia and cancer. It is of interest that increased levels of circulating inflammatory mediators may be secondary to impaired cytokine response induced by chronic, low-grade stimulation [11] often observed in non trisomic elderly.

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Our longitudinal investigations from elderly have focused upon variables associate with an increased risk of developing age related cognitive decline and dementia. The "Conselice Study on Brain Ageing" performed in Italy from 1999 to 2004, is an example of this type of investigation. Some epidemiological features of this study are summarized in Table 1.

Different and numerous data have been collected from "Conselice Study on Brain Ageing" and clinical, genetic and epidemiological variables with a pivotal role on cognitive decline are presented in Table 2.

Complex multi-parametric statistical evaluation has been performed to find correlation or association of experimental variables with the clinical end point of the study, e.g. the developing of cognitive decline (CIND 2004), AD (AD 2004), vascular dementia (VD 2004) or presence of no cognitive alteration (Healthy 2004). Thereafter, connectivity maps of relationship among different factors with clinical endpoints by neural network algorithms have been developed. An example of connectivity map of different variables associated with CIND, AD or VD during the four year follow up is shown in (Figure 1).

Chronic Infections and Neurodegeneration

Declining immunity during ageing is often associated with chronic antigen stimulation and peripheral chronic inflammation [12]. Herpes viruses constantly challenge the immune system that, however, is unable to completely eradicate these parasites. Therefore, persistent pathogens such as neurotrophic herpes viruses may activate brain microglia in genetically susceptible elderly and trigger neurodegeneration [7,13]. It is important to note that the central nervous system (CNS) antiviral response has to be balanced with the potential destructivity of immune mediators that may induce neuronal damage [14]. Therefore, a low grade inflammatory response may be a preferential type of immune defense of the brain.

The A-beta peptide has been shown to be a defensive factor of the innate immune system, because of its antimicrobial activity against eight common and clinically relevant microorganisms [5]. Moreover, A-beta peptide shared many of the chemical and biological characteristics of a group of bio-molecules collectively known as "antimicrobial peptides" (AMPs) which are components of the innate immunity [5].

A-beta peptide was protective against *in vitro* infection by the neuro-tropic virus herpes simplex virus 1 (HSV-1) [15] and it was suggested that overproduction of A-beta peptide against latent herpes viruses may partially contribute to amyloid plaque formation [15].

In our previous investigations we suggested that peculiar genetic signatures might predispose to AD, via complex mechanisms, each contributing to affect individual susceptibility to microorganism infection [7].

Therefore, efficient immune responses are necessary to preserve the brain structure and functioning during ageing and brain chronic sub clinical infections may play a pathogenic role in the clinical progression of sporadic AD in the elderly with declining immune efficiency [13].

HSV-1 and AD

A viral pathogenetic component in AD has been already proposed and several studies have shown an association of HSV-1 with the disease [16,17].

Moreover, a recent Sweden longitudinal nested study showed a significant association of HSV-1 infection with AD risk [18], since elevated anti-HSV-1 antibody levels were found in AD patients [18]. A different study from Italy found that increased serum HSV-1 antibody titers correlated with MRI cortical grey matter volume [19].

1999/2000					
Total elderly	**Non participants** [1]	**Final population**	**Prevalent AD dementia**	**Cognitively NC** [2]	**Dementia free**
N=1353	n=337	n=1016	n=60	n=19	n=937
Follow-up 2003/2004					
Reassessed elderly	**Non reassessed** [3]	**Final population**	**Incident AD dementia**	**Cognitively NC**	**Dementia free**
N=937	n=133	n=804	n=109	n=4	n=695

[1]Refusals n=271; Deceased n=59; Not found n=7
[2]NC=Not Classified
[3]Refusals n=74; Deceased n=28; Not Found n=31

Table 1: The elderly population belonging to the "Conselice's Study on Brain Ageing" was investigated at the beginning in 1999/2000 and the followed up in 2003/2004.

Genetic variables (gene variants)
ACT=Alpha-1 Antichymotrypsin, -51 in the promoter region SNP, allele mutation=T
APOE=Apolipoprotein E, 2, 3 and 4 SNP alleles, allele mutation=4
HMG=Hydrossil-Methyl-Glutayl CoA Reductase, -694 SNP, allele mutation=A
IL-1 beta=Interlukin-1 beta, -511 in the promoter region SNP, allele mutation=T
IL-6=Interleukin-6, -674 in the promoter region SNP, allele mutation=C
Phenotypic blood variables
ACT=Plasma Level (ug/ml)
Cholesterol=Plasma Levels (mg/dl)
HDL=Plasma Levels (mg/dl)
Triglycerides=Plasma Levels
CRP=Plasma Levels (mg/ml)
IL-6=Interleukin-6 Plasma Levels (mg/ml)
TNF=Tumor Necrosis Factor-Alpha Plasma Levels (pg/ml)
Other clinical variable
BMI=Body Mass Index

Table 2: Genetic and phenotypic variables used in the statistical analysis to assess dementia risk.

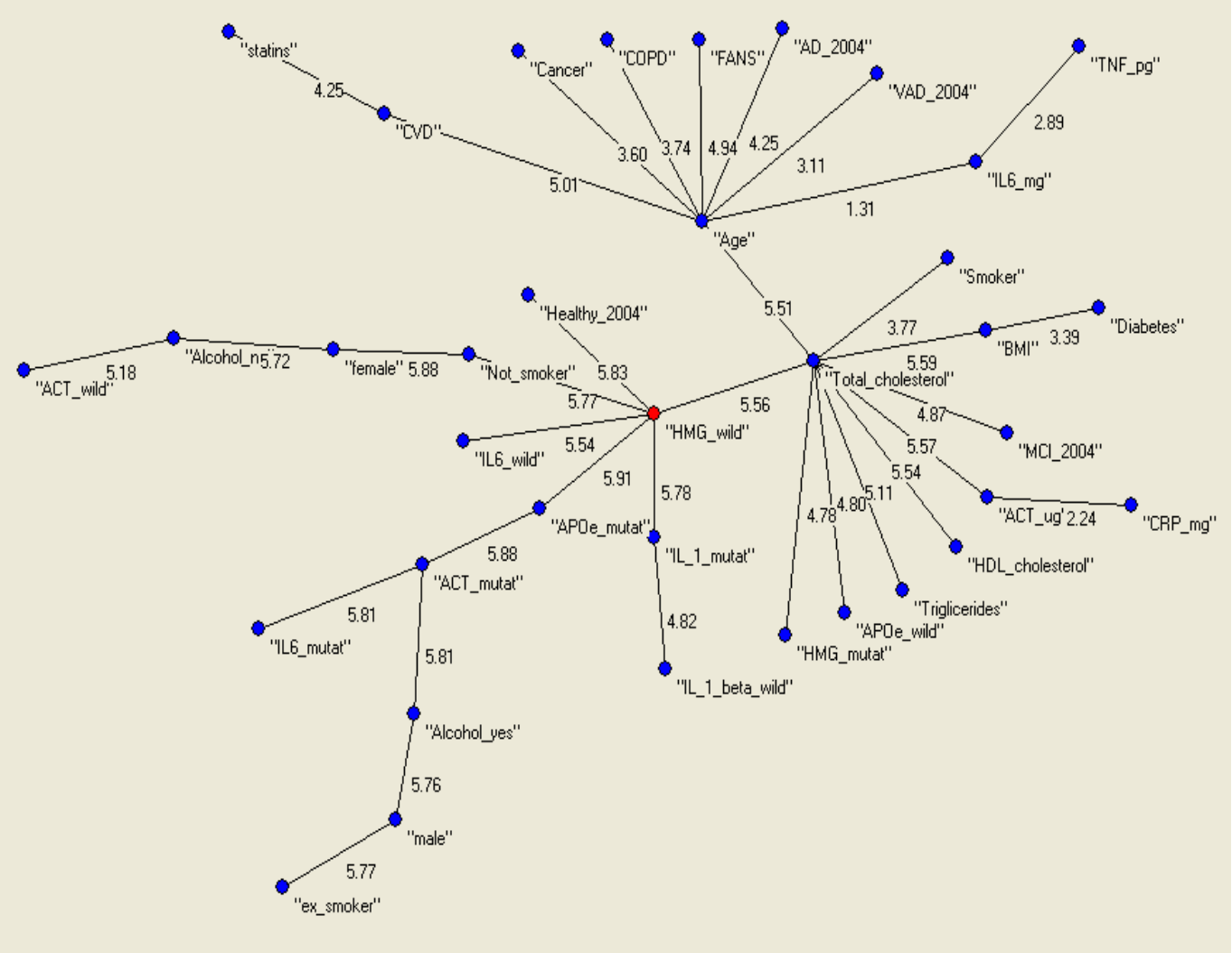

Figure 1: Connectivity map among variables collected during the longitudinal observation from "the Conselice's study on brain ageing" and their relevance with the clinical end points: patients who developed AD (AD 2004), patients who developed vascular dementia (VD 2004), patients who developed mild cognitive impairment (MCI 2004) and people who remained cognitively healthy (Healthy 2004).

Cytomegalovirus (CMV) and AD

CMV is a common parasite of human population and with elevated frequency infects human brain in immune compromised patients or in infants with congenital virus transmission [20]. However, postnatal CMV infection in healthy people is usually asymptomatic and CMV establishes latency in peripheral blood monocytes.

An increased rate of cognitive decline in subjects with elevated CMV antibody titers has been found [21]. Previous investigation showed that CMV was present in brain frontal and temporal cortex from AD patients and controls [22]. A different study showed that brain positivity for CMV was higher in patients with vascular dementia than in controls, suggesting a virus involvement in this type of dementia [23].

Elderly developing clinical AD during a five year follow up showed increased CMV antibody levels [13]. A different investigation on a longitudinal follow up of 849 participants from USA reported that CMV infection doubled the risk of developing AD [24].

Epstein-Barr virus (EBV) and AD

More than 95% of human beings within the first years of life become infected by EBV. This virus in a minority of immune competent subjects is the cause of acute infectious mononucleosis. Most EBV infections are lifelong asymptomatic and the virus remains latent in B-lymphocytes.

Our recent findings showed that blood positivity for EBV genome was associated with AD and high levels of virus specific antibodies increased the AD risk [13].

Human Herpes virus (HHV)-6 and AD

HHV-6 has been involved in neurological diseases such as seizures, encephalitis, mesial temporal lobe epilepsy and multiple sclerosis [25].

Some investigation reported that HHV-6 positivity was higher in AD than age-matched control brains [22,26]. However, another investigation [27] was not able to confirm these findings.

In a previous work we found an elevated positivity for HHV-6

genome in brains and peripheral blood from AD and increased HHV-6 serum-positivity was more frequent in AD patients [13].

Brain Immunity and AD

Neuro-imaging investigations have shown microglia activation in pre-clinical and clinical AD [28].

A defective regulation of inflammatory responses in AD brains has been recently found; such impairment also correlated with patient cognitive performances [29]. Brain inflammation markers were also found elevated in cerebral spinal fluid (CSF) from preclinical AD [30].

In conclusion, AD brain microglia is activated and releases several factors driving neuro-inflammation.

Therefore, it is likely that during aging infectious agents challenging the CNS prime brain microglia and pathogens inducing peripheral subclinical inflammation causes BBB leaking in some brain districts; these conditions perturbing CNS functioning.

A recent review on this topic suggested that brain infiltrating and IFN-gamma releasing T cells by regulating microglia activation might play a role in AD [31].

The aging immune system in not challenged only by virus infections, since persistent low level bacterial infections may also induce chronic inflammation in old persons. For instance, periodontitis common gum infections have been recently indicated as potential causes of BBB disruption and brain inflammation [32]. Moreover, pathogens responsible for periodontitis were able to infect the brain via trigeminal and/or olfactory nerves [32].

Cognitive functions in patients with early AD treated with interferon beta-1 for twenty eight weeks showed mild clinical improvement [33]. This drug is a known anti-viral agent and the above results supported the notion that persistent virus infections may play a role of in AD.

Down Syndrome (DS) and Chronic Inflammation

Children with DS showed several sign of impaired immunity and activation of peripheral inflammation [34].

Both natural and adaptive immunity show a variable degree of alterations in DS [34] and infections are more frequent in children with the syndrome [35].

Our previous investigations showed that altered signals regulating angiogenesis and vascular activation were detectable in DS plasma [36] along with oxidized low density lipoproteins and peroxide products [37].

More recently APOE 4 genotype frequency has been found increased in subjects with DS [38].

Therefore, the above reported markers point out that DS may be considered a condition of accelerated ageing especially in those individual carrying a specific genetic make-up.

Finally, DS is considered a condition at high risk of developing senile dementia or AD [10].

All the above considerations briefly here summarized suggest that application of a predictive protocol for prevention of cognitive decline in DS may increase the wellness of individual subject and prevent or significantly retard prevalence and incidence of dementia.

Cognitive Decline and Dementia: Multi-factorial risk Evaluation

Dementia is a complex disease and many etiological and pathogenetic factors concur in developing the neurodegeneration leading to cognitive decline and senile dementia, such as AD.

Above we presented several new approaches to identify risk factors associated with dementia and we have developed a risk chart for individual risk assessment of developing cognitive decline and AD.

This preventive approach is particularly suited for persons with increased intrinsic risk of AD such as subjects with positive familiarity for AD, patients with traumatic brain injury, patients with Parkinson's disease and adult persons with Down's syndrome.

This method assesses individual risk and indicates preventive intervention by normalizing the altered risk variables of the risk chart.

Conclusion

- Successful treatment of chronic infections may significantly improve the life quality of the elderly or adults with DS. This approach may also retard the clinical presentation of cognitive decline and dementia.
- Improving individual adaptive immune responses may be another way to retard the clinical manifestation of cognitive decline in the elderly and persons with DS.
- Clinical intervention by assessing AD risk variables and their modification allows personalized prevention protocols with the goal of reducing the risk of age associated cognitive decline and dementia.
- The application of a predictive prevention protocol for cognitive decline in adult DS subjects may increase their quality of life, extend their wellness and prevent or significantly retard prevalence and incidence of dementia.

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