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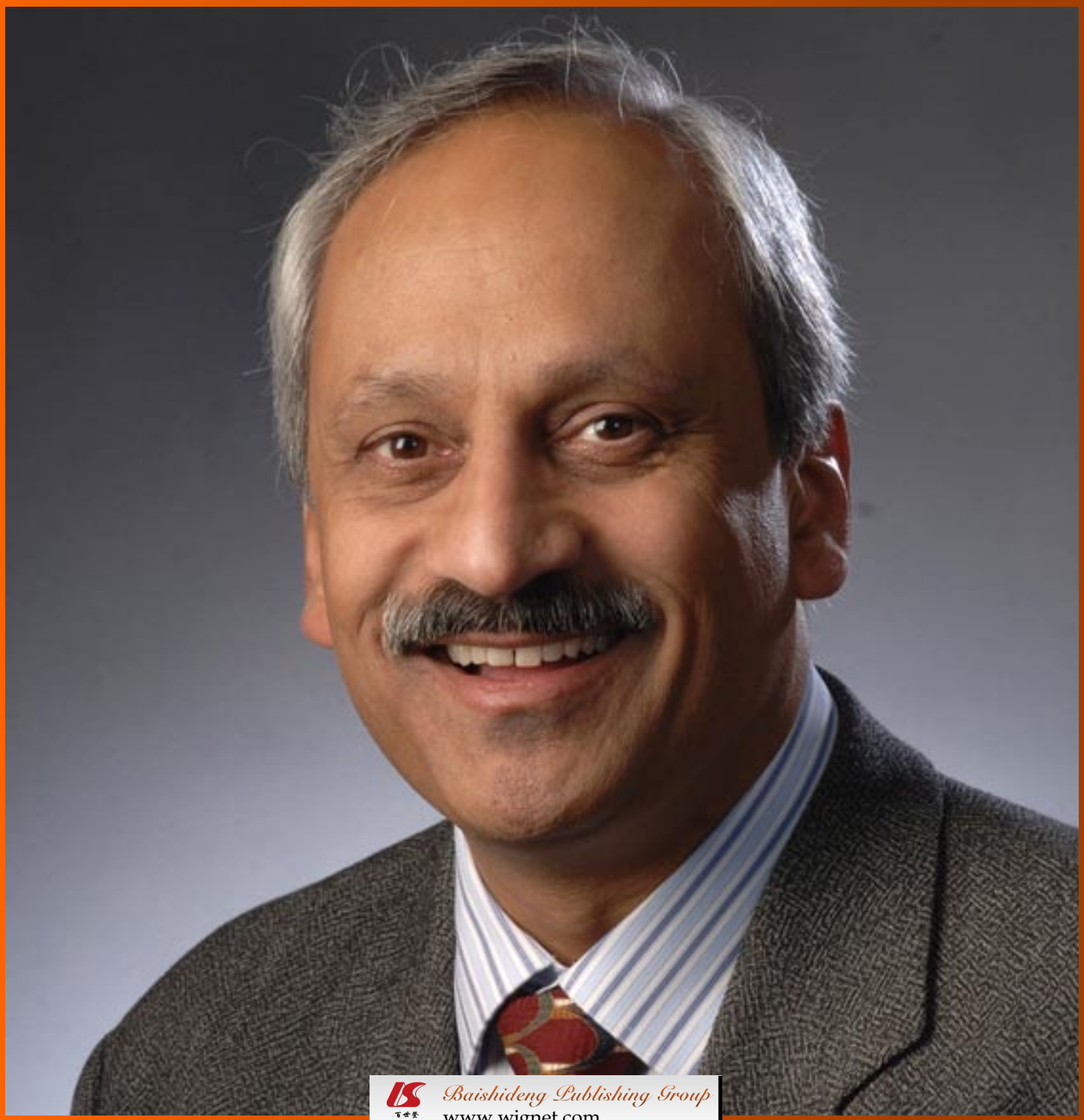

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EDITORIAL

What is the purpose of launching the *World Journal of Psychiatry*?

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Abstract

The first issue of *World Journal of Psychiatry* (*WJP*), whose preparatory work was initiated on May 18, 2011, will be published on December 31, 2011. The *WJP* Editorial Board has now been established and consists of 103 distinguished experts from 32 countries. Our purpose of launching *WJP* is to publish peer-reviewed, high-quality articles *via* an open-access online publishing model, thereby acting as a platform for communication between peers and the wider public, and maximizing the benefits to editorial board members, authors and readers.

Key words: Editorial board members; Authors; Readers; Open-access; Psychiatry

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INTRODUCTION

I am Anantha Shekhar, MD, PhD, a full professor from Indiana Clinical and Translational Sciences Institute, Indiana University School of Medicine (Figure 1) and the Editor-in-Chief of *World Journal of Psychiatry* (*World J Psychiatr*, *WJP*, online ISSN 2220-3206, DOI: 10.5498). I am very pleased to announce that the first issue of *WJP,* on which preparation was initiated on May 18, 2011, is officially published on December 3, 2011. The *WJP* Editorial Board has now been established and consists of 103 distinguished experts from 32 countries. Congratulations to the publisher, members of editorial board of the journal, all the authors and readers for this memorable event!

Thinking about launching a new journal in any area of medicine, when there are scores of journals in every field of science and medicine, one could legitimately ask - why another journal in this field? What is there that is not already being addressed well by existing journals? What will this new journal add? How will this impact the field? Why now? These were the first questions that I asked myself when I was chosen to lead the *WJP* this year. The fact that I have accepted the role must mean that I was

able to answer these objections effectively and believe that there is indeed a need for a new journal of psychiatry that has a global scope and brings a unique international perspective to the field. I hope you, the reader, will agree with me after you read this brief essay.

Research and publishing in psychiatry has been burgeoning over the last 50 years, especially since the development of the Diagnostic and Statistical Manual of Mental Disorders-edition Ⅲ (DSM-Ⅲ) in 1980, which provided for the first time specific guidelines to diagnose and code hundreds of mental health conditions. This was a consensus document, led by US psychiatrists, based on some of the then emerging epidemiological findings, but also notable for its "atheoretical" and descriptive approach. Outside the United States, clinicians have used the International Classification of Mental and Behavioural Disorders-10 (ICD-10) predominantly, but the premise of these two systems is fairly similar. Since the DSMs and ICDs, much has been done to refine the syndromes, their epidemiology, their therapeutics and most recently their genetics. These developments have transformed research in psychiatry into a full-fledged biomedical science with a strong humanistic basis in elucidating pathophysiology. Yet, almost all of the foundational information for this science has come from the data gathered in the developed world, with limited inclusion of the large populations living in the low- and middle-income countries (LMICs) that account for the majority of the world's people. This has significant implications when one thinks about "mental health" issues for humanity beyond the developed world, and we begin to address the increasingly acute needs of the LMIC populations. Alas, there is no systematic approach to develop such a worldwide "big picture" of psychiatry and mental health issues, or a journal dedicated to this mission. I believe that the *WJP* can serve that function and begin to elucidate the many emerging but unexplored aspects of world psychiatry.

To begin with, there are likely to be many differences in the phenomenology of psychiatric disorders between the world's populations at the level of clinical presentation, diagnostic thresholds, disease course, and therapeutic responses, even for the major syndromes where these concepts have been explored in extensive detail in the western world. For example, much has been written about the many different somatic forms of presentation of depression in Eastern cultures compared to the more "psychological" presentations in the West[1,2]. Does this simply mean they are just different clinical manifestations of the same disorder? Do they have the same neurobiological basis but different "mental" constructs? If so, would biological therapies such as "antidepressants" work just as effectively in Chinese cohort of depressed subjects but not "cognitive" therapies? How does this affect the key construct of "depression" in the DSM which requires "sadness" or "hopelessness" as one of the fundamental criteria? Similar questions can be raised for literally anyone of the major DSM diagnostic categories. Thus, a journal dedicated to "World Psychiatry" would be an important venue to systematically publish studies that address these questions.

While limited systematic work has been done to address the many unanswered phenotypic differences in psychiatric disorders across the world, there have been somewhat greater number of large scale, systematic genetic studies that have been conducted across multiple ethnic groups. These studies consistently show significantly different (sometimes diametrically opposite) effects of genes and or their associations with neuropsychiatric disorders[3,4]. These genetic ethnic differences are further amplified by epigenetic factors such as nutrition, poverty, psychosocial pressures and lack of health services, dramatically altering the prevalence, course, severity or outcomes of psychiatric disorders.

There is also increasing recognition of the socioeconomic effects of mental illnesses across the globe. Recent data suggest that over 11% of the global "disease burden" is of psychiatric in nature. Yet, less than 2% of the global "health care" spending is directed towards mental illnesses[5]. This situation is clearly worsened by the co-occurrence of poverty, poor resource management and unavailable health care. Even more distressingly, there is emerging evidence that mental illness actually perpetuates global poverty. The cycle of poverty does not seem to be as robustly improved by simply by providing financial resources. In contrast, providing mental health services actually has a more robust effect on reversing the poverty cycle. This has major implications for global aid agencies and their strategies for resource distribution. Yet, little research has been done to explore these global economic aspects of mental illnesses[6,7].

SCOPE

WJP aims to report rapidly new theories, methods and techniques for prevention, diagnosis, treatment, rehabilitation and nursing in the field of psychiatry. *WJP* covers topics concerning behavior and behavior mechanisms, psychological phenomena and processes, mental disorders, behavioral disciplines and activities, adjustment disorders, anxiety disorders, delirium, dementia, amnestic disorders, cognitive disorders, dissociative disorders, eating disorders, factitious disorders, impulse control disorders, mental disorders diagnosed in childhood, mood disorders, neurotic disorders, personality disorders, schizophrenia and disorders with psychotic features, sexual and gender disorders, sleep disorders, somatoform disorders, substance-related disorders, and psychiatry-related traditional medicine, and integrated Chinese and Western medicine. The journal also publishes original articles and reviews that report the results of psychiatry-related applied and basic research in fields such as immunology, physiopathology, cell biology, pharmacology, medical genetics, and pharmacology of Chinese herbs.

CONTENTS OF PEER REVIEW

In order to guarantee the quality of articles published in

the journal, *WJP* usually invites three experts to comment on the submitted papers. The contents of peer review include: (1) whether the contents of the manuscript are of great importance and novelty; (2) whether the experiment is complete and described clearly; (3) whether the discussion and conclusion are justified; (4) whether the citations of references are necessary and reasonable; and (5) whether the presentation and use of tables and figures are correct and complete.

COLUMNS

The columns in the issues of *WJP* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in psychiatry; (8) Brief Articles: To briefly report the novel and innovative findings in psychiatry; (9) Case Report: To report a rare or typical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJP*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of psychiatry; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in psychiatry.

CONCLUSION

Finally, the *WJP* will be one of the first psychiatric journals to be published outside the dominant publishing houses of the developed world. It is also an open access, online journal dedicated to rapid publication process that is available to anyone freely. This is a clear sign that the many regions of the world where research and academic publishing was relatively modest in the past are now growing, demanding more responsive, locally grown publication efforts. Yet, with the current electronic publication technology, these journals could now compete in a global information market and be accessible by everyone very easily. This creates new dissemination tools to empower the faculty and researchers employed in a wide range of institutions across many countries where research resources are limited, but where powerful, culturally relevant information is being generated that need to be easily disseminated in peer reviewed academic papers[8]. Thus, I hope the *WJP* will provide a much needed new platform for psychiatric publications that bring out the unique aspects of mental maladies and their therapies across multiple countries, cultures and linguistic boundaries, and give voice to a world-wide chorus of new information that helps us to properly understand the big picture.

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OBSERVATION

Family interventions in schizophrenia: Issues of relevance for Asian countries

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Abstract

A growing body of research evidence has confirmed the efficacy of family-interventions as adjuncts to antipsychotics for the treatment of schizophrenia. Much of the recent evidence for such interventions derives from Asian, principally Chinese, studies. These trials have shown that relatively simple forms of family-interventions have wide ranging benefits, and can be implemented successfully in routine clinical settings. With the accumulation of this evidence in their favour, family-interventions for schizophrenia in Asia are poised to take the next critical step, that of wider implementation and improved accessibility for potential users. However, several issues merit consideration. Family-interventions need to be based on a culturally-informed theory, which incorporates cultural variables of relevance in these countries. While the ideal format for conducting family-interventions is still to be determined, it is quite evident that for such interventions to be useful they need to be simple, inexpensive, needs-based, and tailored to suit the socio-cultural realities of mental health systems in Asian countries. The evidence also suggests that delivery by non-specialist personnel is the best way to ensure that such services reach those who stand to benefit most from these treatments. However, there are several existing challenges to the process of dissemination of family-interventions. The major challenges include the achievement of a critical mass of trained professionals capable of delivering these interventions, and finding innovative solutions to make family-interventions more acceptable to families. If these hurdles are overcome, we could look forward to a genuine collaboration with families, who have always been the mainstay of care for the mentally ill in Asia.

Key words: Asia; Culture; Family interventions; Schizophrenia

Peer reviewer: Ladislav Hosak, MD, PhD, Professor, Development of Psychiatry, University Hospital, Sokolska 581, 500 05 Hradec Kralove, Czech Republic

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INTRODUCTION

Family-based intervention programmes constitute one of the most important advances in the treatment of schizophrenia over the last four decades, or so[1]. Moreover, of all the psychosocial interventions found to be useful in schizophrenia, family treatment is the most extensively studied intervention[2]. Two recent updates of earlier Cochrane reviews on the subject have reiterated some of the findings of earlier research[3,4]. The first, based on a meta-analysis of 53 randomised-controlled trials (RCTs) demonstrated that, compared to routine care, adjunctive family-interventions reduced the frequency of relapse and risk of re-hospitalisation, while encouraging compli-

ance with treatment and improving social functioning[3]. The evidence favouring other positive outcomes such as a decrement in symptoms, reduction of caregiver burden, improvements in caregiver-coping, and cost-effectiveness was, however, either minimal or inconsistent. The second update consisted of a meta-analysis of 44 RCTs, which examined the efficacy of psychoeducation added to routine care[4]. Psychoeducation also led to a significant reduction in relapse and re-admission rates, and appeared to improve compliance with medication, although the extent of improvement was unclear. The findings further suggested the possibility that psychoeducation had a positive effect on the patient's well being and social function. Both reviews again highlighted the fact that despite the robust evidence favouring family interventions, several methodological problems continue to plague the studies constituting the evidence-base. Apart from these methodological concerns, other existing challenges in this area include determining the critical ingredients of successful family-interventions, implementing these treatments in routine clinical settings, and deciding on the modalities for wider dissemination of such treatments[1,5,6].

Another striking fact revealed by both these reviews was that although much of the earlier research data originated from European and American studies, over the last few years there has been a phenomenal increase in studies from mainland China and Hong Kong[3,4]. Sensitivity analyses conducted as a part of these meta-analytic reviews revealed that there was no difference between the quality of Chinese and Western studies[3,4]. This suggests that cultural differences are not necessarily an impediment to implementing family-interventions, as has been occasionally found[7]. Rather, culturally-adapted (and simplified) family-interventions are as likely to be successful as the original treatments[2]. In fact, the Chinese studies have shown more robust effects favouring family-intervention[3], and larger effect sizes than studies from Scandinavia or North America[8], although some of these differences could be attributed to suboptimal care received by control groups in these studies[2,9]. Additionally, the Chinese studies have revealed more wide ranging benefits from family-interventions, in terms of positive effects on symptoms, treatment-adherence, social functioning, family burden, relatives' knowledge, attitudes and perception of support, and their sense of self-efficacy[3]. Given this overwhelming support for family interventions, the relative lack of similar trials from other Asian countries is somewhat disappointing. However, it is encouraging to note the recent emergence of RCTs of family-interventions from India[10], Iran[11,12], Pakistan[13], Thailand[14], and Malaysia[15]. With this accumulating evidence of the efficacy of family-interventions in Asian countries, research in this area is poised to take the next big step, that of implementation of such treatments in actual clinical settings, and efforts to make these treatments available for families in need. However, there are several issues that merit consideration at this critical juncture.

NEED FOR STRUCTURED FAMILY-INTERVENTIONS IN FAMILY-CENTRIC ASIAN CULTURES

Unlike the West, Asian families have never been excluded from treatment of the mentally ill; rather, they have always functioned as partners in their care[16,17]. Indeed, Asian families have been the mainstay of care of the mentally ill for a number of different reasons. Some cross-cultural comparisons have suggested that there are significant differences in the social circumstances of Asian patients and their Western counterparts[17,18]. For example, while in the West only about a-third to two-thirds of persons with schizophrenia live with their families (or have regular contact with them), the proportion of patients staying with their families is much higher (over 90%) in countries like India or China[17-19]. Moreover, the close knit composition of Asian families also ensures a somewhat greater involvement of families in all aspects of the care of those with mental illness[18]. This natural preference of families to be involved in the care of their mentally ill kin is further reinforced by the woefully inadequate mental health infrastructure in most of these countries, which virtually compels families to become sole caregivers of the mentally ill[18,19]. These differences have led some authors to question the need for structured family-interventions for Asian patients with schizophrenia and their families. These critics have pointed out that the concept of formal family interventions is a foreign one, based on the notion of expressed emotions (EE), which itself is of doubtful relevance in non-Western cultures. Asian families are already more involved in care, and are generally more tolerant and supportive of the patient, which could account for the better outcome of the disorder observed in this part of the world. Finally, such detractors also contend that structured family interventions are costly, time-consuming and labour-intensive, which makes them unsuitable for Asian countries, where trained personnel and mental-health services are scarce. On the other hand, proponents of the concept argue that although the involvement of families in the patient's care is readily welcomed by professionals, they often fail to appreciate the difficult circumstances in which families get involved in such care. Consequently, professional help and support is less than forthcoming; its absence makes the caregiving experience more burdensome and distressful than it already is. To obviate the negative consequences of caregiving, mental health professionals thus need to forge a genuine collaboration and an equal partnership with families, by providing increased support and help. One way to achieve this objective could be to carry out formal family-interventions, which are culturally congruent, socially appropriate, economical and widely applicable[16-18].

NEED FOR A CULTURALLY-INFORMED CONCEPTUAL FRAMEWORK FOR FAMILY INTERVENTIONS

The construct of EE and its association with relapse has

played a central role in the evolution of family-interventions for schizophrenia. These interventions were originally developed to employ a number of different strategies to reduce high levels of EE, thereby preventing relapses of schizophrenia[20]. Unfortunately, the hypothesis that reduction in EE was the crucial process-variable accounting for the success of family-interventions was not borne out by subsequent research[21,22]. The use of the EE typology to identify families in need of help also proved to have distinct disadvantages in clinical and service settings[23]. Moreover, family-interventions appeared to be equally effective in both high EE and low EE families. This led to the general consensus that such treatments should not be restricted only to high EE families[9,23]. With regard to Asian families, there have always been considerable scepticism about the cross-cultural validity and transfer of the EE model; thus, explanatory theories based on reduction of EE appear to be particularly unsuitable for Asian countries[18,24]. Accordingly, alternative theories, which incorporate other elements of family-interventions as potential variables mediating the positive effects of family-interventions among Asian families, need to be examined. Such process-variables could include stress-reduction, attitudinal change among relatives leading to more adaptive appraisals, and improved coping by relatives. Other cultural processes could also be assessed to determine whether they contribute to the usefulness of family-interventions. For example, recent studies have highlighted the central role of certain cultural variables such as familism and filial obligations in the process of caregiving by families[25]. Although much of this research has been conducted among caregivers of those with dementia, such cultural constructs could well turn out be the critical mechanisms in a culturally-informed theory of family-interventions for schizophrenia.

WHAT SHAPE SHOULD FAMILY INTERVENTIONS TAKE IN ASIAN COUNTRIES?

A variety of family-intervention models and strategies have been developed and empirically tested in the West. Two of the major models are referred to as the behavioural family management model, and the family psychoeducational model[5,6]. The former involves education about the illness, as well as structured training in problem-solving and effective communication skills, whereas the latter places emphasis on developing a therapeutic alliance with the family, providing education and ongoing support, teaching techniques to reduce stress, and identifying and intervening early at times of relapse. These strategies have been used as a part of both group and individual treatment programmes. Another set of strategies, referred to as the family education models, consist of brief educational interventions, either led by professionals or peers, which focus on affected family members rather than patients. A subset of the family education model is the consultation model, in which individual families meet periodically with a professional involved in the patient's treatment, to receive information, advice or support according to their needs[6,26]. Although some forms of family intervention have been studied more often than others, there is no compelling evidence to suggest the superiority of any particular approach over others[3,5,6]. While most of the Asian studies have employed the psychoeducational model of family intervention[10,27], the efficacy of other approaches including behavioural family management[28], family education programmes[11], consultation models[29], and group treatments[30,31], has also been examined, and these strategies have also proved to be useful. Thus, there is still some uncertainty regarding the most appropriate model of family-intervention for Asian countries. Nevertheless, there is considerable consensus about the other essential features of family-interventions. The evidence clearly indicates that relatively simple and inexpensive forms of these interventions, which place emphasis on ongoing contact and medication compliance while offering emotional and practical support, are more likely to succeed in the Asian context[10,18,32]. Finally, family-interventions also have to be tailored to the background and needs of the families, to enhance their acceptability, and positively influence the readiness of families to participate in such interventions[18,23].

ISSUES RELATING TO DELIVERY OF FAMILY INTERVENTIONS IN ASIA

Despite the strong evidence for the efficacy of family-interventions for schizophrenia, the implementation and dissemination of these treatments has been hindered by complex organisational and attitudinal difficulties, even in countries with well-developed mental health services[1,6]. Therefore, this is expected to be an even greater challenge in Asian countries, with their resource limitations and a variety of other social, economic and cultural problems[33]. However, some encouragement can be derived from the fact that many of the Asian trials have been carried out in clinical environments more representative of usual care, both in urban and rural areas[9,27]. Moreover, they have employed relatively simple formats of family-interventions, have often relied on non-specialist professionals for service-delivery, and have turned out to be cost-effective in many instances[10,27,34]. They have thus demonstrated that structured family-interventions can be successfully conducted in "real-world" settings, even when resources for these treatments are limited[10]. Nevertheless, quite a few issues regarding training, supervision, cost and delivery of these services, still need to be resolved, and need to be the focus of future research[10,18,33]. Indeed, most researchers would agree that unless sufficient numbers of trained and motivated personnel are available to work with families, and unless families find these interventions acceptable, it is unlikely that the benefits of family-interventions will reach those families who require it the most[18,33].

Despite these seemingly formidable potential hurdles,

it would be safe to conclude that the usefulness of family-interventions for schizophrenia among Asian populations has been amply documented. It is for the mental health-care system, and all professionals who are a part of it to use this evidence for the benefit of the suffering patients and their families. It is the responsibility of these professionals to lead the way to a future, in which these interventions could be used to forge a genuine collaboration with patients and families, in order to improve the plight of all those affected by this devastating illness.

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REVIEW

Cerebrospinal fluid and blood biomarkers in Alzheimer's disease

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Abstract

Due to an ever aging society and growing prevalence of Alzheimer's disease (AD), the challenge to meet social and health care system needs will become increasingly difficult. Unfortunately, a definite ante mortem diagnosis is not possible. Thus, an early diagnosis and identification of AD patients is critical for promising, early pharmacological interventions as well as addressing health care needs. The most advanced and most reliable markers are β-amyloid, total tau and phosphorylated tau in cerebrospinal fluid (CSF). In blood, no single biomarker has been identified despite an intense search over the last decade. The most promising approaches consist of a combination of several blood-based markers increasing the reliability, sensitivity and specificity of the AD diagnosis. However, contradictory data make standardized testing methods in longitudinal and multi-center studies extremely difficult. In this review, we summarize a range of the most promising CSF and blood biomarkers for diagnosing AD.

Key words: Alzheimer's disease; Biomarker; Blood; Cerebrospinal fluid; Dementia; Plasma

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ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a progressive neurodegenerative disorder. It is morphologically characterized by deposition of extracellular β-amyloid (Aβ)-containing plaques and intracellular neurofibrillary tangles composed of hyperphosphorylated tau protein[1]. Neuronal loss, hippocampal and cortical atrophy, inflammation, and oxidative damage are further indications of the disease. AD leads to cognitive decline, as well as, memory loss, language problems and deterioration of executive function. Age is the major risk factor for developing AD and it is the most common form of age-related dementia affecting about 35 million people worldwide. This number is estimated to rise to 81.1 million by 2040[2,3]. AD leads to a colossal burden on AD individuals, their families, caregivers and on social and health care systems. This makes it essential to understand disease mechanisms, establish biological markers, and investigate effective therapies. To date, a definitive diagnosis of AD can only be made with both a clinical diagnosis and a post mortem histopathological examination of the brain. A clinical diagnosis of AD is based on medical records, physical and neurological examination, laboratory tests, neuroimaging and neuropsychological evaluation. Diagnosis can be made with an accuracy of over 90%[1,4]. However, neurodegeneration in AD is estimated to start 20 to 30 years before the first clinical symptoms become apparent[5]. Treatment strategies might be most

effective before pathological changes spread throughout the brain. Thus, an early diagnosis with reliable biomarkers is essential to distinguish between AD, mild cognitive impairment (MCI) and other dementia types.

DEFINITION OF A BIOMARKER

A biomarker is generally defined as a measureable substance that can be used as an indicator for ongoing physiological and pathological processes. An ideal biomarker for AD should fulfill the criteria from the consensus report by Growdon *et al*[6] (1998). It should detect AD neuropathology and should be validated by post mortem evaluation. It should have a high diagnostic sensitivity and specificity for the disease, preferably at early or presymptomatic stages. Furthermore, it should be precise, reliable, non-invasive, easy to measure, inexpensive, and adequate for routine screenings. A biomarker should provide an indication of possible drug candidates and should predict clinical outcomes[7].

BIOMARKERS IN AD

There has been an extensive search for AD-specific biomarkers over the past decade. Diagnosis of familial AD can be achieved by DNA sequencing and analysis of known genetic mutations that cause AD. These mutations occur on three genes encoding for amyloid precursor protein (APP), presinilin 1, and presinilin 2[8]. An increased risk of late onset AD is associated with environmental factors and genetic mutations including mutation of the apolipoprotein E epsilon 4 allele. Imaging techniques are relatively non-invasive, however, they are limited by availability and high cost. In addition, the accuracy of these techniques is still under debate[9-11]. Structural imaging, such as computed tomography (CT) and magnetic resonance imaging are mainly used to rule out other pathologies and to detect volumetric changes. Hippocampal atrophy reflects severe neuronal loss and decreased synaptic density, which appears relatively late in disease and makes CT an inappropriate method for the early diagnosis of AD. Single photon emission tomography (SPECT) and positron emission tomography (PET) can reveal metabolic and perfusion changes. Due to disease-specific dyes, PET can be used to detect fibrillar Aβ and tau *in vivo*[12]. Thus, a promising and cost-effective research area for diagnosing AD is the analysis of peripheral biomarkers in cerebrospinal fluid (CSF) and blood[6]. Data from various studies relating biomarker analysis from AD cases *vs* controls are summarized in Table 1.

CEROBROSPINAL FLUID BIOMARKERS

CSF is a promising source of AD biomarkers. CSF is in direct contact with the brain's extracellular space and thus should reflect ongoing biochemical changes occurring in the central nervous system (CNS), providing a potential window for AD-related changes in the brain. There are three well- established candidate biomarkers in CSF which reflect the central AD pathology: total tau (t-tau), phosphorylated tau (p-tau), and the 42-amino acid form of Aβ ($A\beta_{1-42}$).

TAU PROTEIN

Tau is a microtubuli-associated protein, which is mainly located in neuronal axons. It plays an important role in microtubule assembly and stability. Tau is also important for axonal function and axonal transport[13]. There are six isoforms derived from alternative splicing of tau mRNA[14]. Post-translational tau can be modified by several mechanisms including: phosphorylation, glycosylation, ubiquitination, and oxidation[15,16]. Previous studies have shown that t-tau levels in CSF can be measured by ELISA techniques[17]. A strong correlation between age and t-tau in healthy individuals has been determined with a cut off value of > 500 pg/mL (> 70 years)[18]. Increased t-tau levels in CSF of AD patients (> 600 pg/mL) have been reported with an increase of 300% compared to controls. CSF t-tau levels in AD patients have a sensitivity of 90% and specificity of 81% compared to healthy elderly[19-22]. Compared to other dementias, the sensitivity and specificity drops to 50%-60%[20,23]. Similar levels of t-tau have been shown in patients with MCI. MCI converting to AD can be discriminated from stable MCI with 90% sensitivity and 100% specificity, indicating that t-tau is a good predictive marker for incipient AD[24]. In acute conditions, such as stroke, high levels of t-tau have been measured, which correlated with infarct size[25]. The highest increase in t-tau was found in Creutzfeld-Jacobs-disease (CJD) (> 3000 pg/mL)[26]. In addition, elevated concentrations have been reported in vascular dementia (VaD)[27,28], whereas, normal concentrations have been reported in depression, alcoholic dementia, and Parkinson's disease (PD)[27,29,30]. T-tau correlates with general neuronal damage and degeneration in chronic neurodegenerative disorders rather than with AD specific pathology.

PHOSPHORYLATED TAU PROTEIN

Post-translational modifications, such as phosphorylation, alter the conformation of tau and decrease its affinity to microtubules[31]. Loss of affinity to microtubules results in neuronal cytoskeleton destabilization, dysfunction of axonal transport, and neurotoxicity[32]. Stable tau dimers can form oligomers and further aggregate to neurofibrillary tangles, a hallmark of AD pathology[31]. Phosphorylation of tau takes place at the amino acids serine, threonine and tyrosine. Different phosphorylation epitopes, such as threonine 181, 231 or serine 235, can be detected by different ELISAs[27,33]. The concentration of $p\text{-tau}_{181}$ is increased in AD and yields a sensitivity of 80% and specificity of 92% in discriminating AD from healthy controls[34]. In CJD, a normal to mild increase has been detected in p-tau despite very high levels of t-tau[35]. No changes in the concentration of p-tau in CSF have been found in acute stroke, depression, PD, and other dementias (i.e. VaD, frontotemporal dementia, and Lewy Body

Table 1 Summary of biomarkers in cerebrospinal fluid and blood of Alzheimer's disease cases *vs* controls

Biomarker	CSF	Plasma/serum	Blood cells
Total tau	Increased	-	-
Phosphorylated tau	Increased	-	-
Glycogen synthase kinase-3	-	-	Increased[73,75] Decreased[65]
β-amyloid (Aβ)	Decreased[45,46] No difference[47]	No difference[79-82]	-
$Aβ_{1-40}$	No difference[24]	No difference[83] Increased[84] Decreased[85]	-
$Aβ_{1-42}$	Decreased[24]	Increased[83]	-
$Aβ_{1-42}/Aβ_{1-40}$ ratio	Decreased[48]	No difference[83] Decreased[78,84,86]	-
APP ratio	-	-	Decreased[90-93]
Ubiquitin	Increased[24]	-	No difference[148]
BACE1	Increased[67]	-	-
Cholesterol	-	Decreased[94,95] Increased[96-98]	-
24S-hydroxycholesterol	Increased[102]	No difference[103] Decreased[104]	-
Homocysteine	-	Increased[106,107,109]	-
Epidermal growth factor	-	Decreased[111] Increased[112]	Decreased[93]
Glial cell line-derived growth factor	-	Decreased[111] No difference[112]	-
Nerve growth factor	Increased[63-65]	-	-
Platelet derived growth factor	-	Decreased[111] Increased[112]	No difference[93]
Interleukin-1β	-	Increased[70,113,114] No difference[115]	No difference[93] Decreased[116]
Interleukin-6	-	Increased[70,113,119-121] No difference[114,138]	No difference[117,118]
Interleukin-10	-	Increased[124] No difference[125]	No difference[126]
Tumor necrosis factor alpha	-	Increased[121,128] Decreased[114,129] No difference[115]	-
Monocyte chemotactic protein-1	-	Increased[111] No difference[131,132]	Decreased[133]
Monokine-induced by interferon-gamma	-	Increased[132,134]	Decreased[132]
Macrophage inflammatory protein 1δ	-	Decreased[111] Increased[112]	Increased[132]
Intercellular adhesion molecule-1	-	Increased[137] No difference[141]	No difference[93,138]
Intercellular adhesion molecule-3	-	-	Decreased[138]
Platelet endothelial cell adhesion molecule	-	Increased[137]	-
P-selectin	-	Decreased[138]	Decreased[138] No difference[93]
Vascular cell adhesion molecule -1	-	Increased[140] No difference[141]	No difference[93]
Matrix metalloproteinase-2	Decreased[143]	No difference[144]	Decreased[93]
Matrix metalloproteinase-9	-	Increased and no difference[143-145]	No difference[93]

dementia)[30,34,36,37]. Thus, p-tau reveals a higher specificity than t-tau for diagnosing AD compared to other types of dementias. In addition, MCI patients, who convert to AD, have higher p-tau levels compared to patients with stable MCI. It has also been shown that cognitive decline and tangle pathology in individuals with MCI correlates with CSF p-tau concentrations[38,39]. It seems likely that p-tau is not simply a marker for neuronal degeneration, but rather a more specific marker for AD by reflecting the phosphorylation states of tau and ultimately the formation of neurofibrillary tangles in the brain.

$Aβ_{1-42}$

Aβ is the main component of amyloid plaques seen in AD brains. It is generated from the protolytical processing of APP[40,41]. There are two different pathways for APP metabolism: the physiological pathway regulated by α-secretase (ADAM10) cleavage, and the pathological pathway, where β-secretase (BACE) is the rate-limiting enzyme. BACE cleaves APP and releases a large N-terminal fragment (sAPPβ). The membrane-anchored frag-

ment is cleaved by γ-secretase ultimately leading to Aβ release. Different truncated forms of Aβ exist including $A\beta_{1-38}$, $A\beta_{1-40}$, and $A\beta_{1-42}$, where $A\beta_{1-40}$ is the most abundant[34]. $A\beta_{1-42}$, which aggregate in extracellular plaques, aggregates more rapidly compared to $A\beta_{1-40}$ and forms soluble oligomers and fibrils[42,43]. Quantification of different Aβ forms in CSF can be determined by specific ELISAs[44]. Early studies reported controversial results involving total Aβ measurements in CSF[45-47]. Later, several reports demonstrated no changes in $A\beta_{1-40}$ CSF levels. A moderate to marked decrease in $A\beta_{1-42}$ has been detected in CSF of AD patients compared to healthy elderly with a sensitivity of 90% and specificity of 86%[24]. The ratio of $A\beta_{1-42}/A\beta_{1-40}$ shows an even stronger reduction in AD than $A\beta_{1-42}$ alone[48]. It was believed, that low levels of Aβ in CSF reflect high levels of Aβ plaque formation in the brain[44]. However, low levels of Aβ in CSF have also been reported in disease without Aβ plaque pathology (i.e. CJD, multiple system atrophy and other dementias)[49-51]. There is a strong correlation between low Aβ CSF levels and the number of plaques in specific brain regions of AD patients, such as the hippocampus, which at least partly supports this hypothesis[52]. Unchanged Aβ levels exist in depression and neurological disorders like PD[50]. It has been suggested that Aβ concentration can serve as a good predictor of AD, since reduced levels in CSF have been reported in asymptomatic healthy elderly, who go on to develop AD 1-2 years after follow-up[20]. Recent reports suggest that soluble Aβ oligomers are rather synaptotoxic and causative for AD compared to insoluble, aggregated forms of Aβ[53-55]. No correlation has been found between plaque load and degree of dementia. Some patients with assumed AD show no plaques while cognitive healthy elderly have senile plaques at autopsy[56]. However, one cannot exclude a relationship to preclinical manifestations of AD. It is assumed that the formation of plaques is a downstream event of the generation of more toxic and soluble forms of Aβ[57]. The reduction of $A\beta_{1-42}$ in CSF could result from the formation of oligomers, which are not detected by $A\beta_{1-42}$ ELISA[58]. Fukumoto *et al*[59] (2010) established a novel ELISA system that quantifies $A\beta_{1-42}$ oligomers. They reported an inverse correlation between oligomers in the CSF and severity of dementia. However, measurement of Aβ oligomers in CSF is limited by its low concentrations and must still be validated as an effective biomarker[59].

OTHER BIOMARKERS IN CSF

An intense search for new probable biomarkers in CSF is ongoing. Several disease-related proteins are under investigation including: ubiquitin, nerve growth factor (NGF) and BACE1. Ubiquitin is involved in protein degradation by tagging target proteins. In AD, paired helical filaments of neurofibrillary tangles are ubiquitinated and increased levels of ubiquitin have been correlated with total tangle formation in the brain[60,61]. Elevated concentrations of free and conjugated ubiquitin in CSF have been detected by a specific ELISA in AD cases[24]. However, to validate ubiquitin as a potential diagnostic marker further studies are needed. NGF maintains cholinergic neurons in the basal forebrain, which have been shown to be primarily affected in AD[62]. Numerous studies have reported higher NGF levels in the brain and CSF in AD patients compared to healthy controls[63-65]. Furthermore, a down-regulation of the NGF receptor has been reported[66]. A dysfunctional neurotrophin system may lead to an accumulation of NGF in the brain and can be detected in the CSF[63]. Measurement of NGF levels in CSF is restricted due to its low concentration and the fact that NGF might accumulate only at a certain stage in AD[64,65]. BACE1 is involved in APP processing of the amyloidogenic pathway in AD and has been discussed as a promising biomarker candidate[34]. Upregulation of BACE1 in the brain and increased BACE activity in CSF have been reported in AD and MCI that progresses to AD suggesting that the upregulation of BACE is an early event in AD pathology[34,67-69]. The advantage of these and other markers is still questionable and further studies are needed to confirm their potential as prognostic or diagnostic biomarkers in AD.

BLOOD BIOMARKERS

Lumbar puncture is an invasive process and the collection of CSF does not seem feasible as a routine procedure. For the growing AD population, the collection of blood, however, by venepuncture is a simple, non-invasive, inexpensive and time-saving method. Thus, a blood-based biomarker would have more potential for routine screenings with repeatable measurements. This type of screening would provide a good chance for early detection, diagnosis and monitoring of the disease, and treatment effects. Peripheral blood has no direct contact with the brain and its delimitation by the blood-brain barrier (BBB) limits the usefulness of markers[70]. However, in humans, CSF is constantly exchanged and cleared *via* the blood[71] suggesting blood could reflect pathological changes in the brain and thus provides a good source of AD biomarkers. In plasma, serum and blood cells (i.e. erythrocytes, leukocytes, platelets) various proteins, lipids and other metabolic products can be examined. Plasma is a highly complex fluid with thousands of proteins available for potential biomarker evaluation. Several candidate biomarkers in blood and blood cells have been introduced, but their lack of sensitivity, specificity, and true relation to brain mechanisms remain unclear. Altogether, the discovery of a single blood-based biomarker in AD has thus far failed and further intense investigations are needed.

TAU

T-tau and p-tau are established markers for diagnosing AD in CSF, while tau levels in blood have not been investigated. Recently, a new sandwich ELISA for $p\text{-tau}_{231P}$

detection in serum was developed. However, reliable data regarding its use for AD diagnosis is still lacking[72]. Studies, instead, have been concentrated on protein kinases and phosphatases, whose alterations are associated with tau pathology. It has been shown that glycogen synthase kinase-3 (GSK3) activity is increased in AD brains. GSK3 contributes to hyperphosphorylation of tau and increased GSK3 levels have been reported in the leukocytes of AD patients. However, these elevated levels were not found in peripheral-blood mononuclear cells of AD patients indicating a high variability in leukocyte subpopulations[73,74]. In addition, increased GSK3 activity has been reported in the platelets of AD and MCI patients compared to controls[75]. Protein phosphatase-2A dephosphorylates tau and a decrease in its activity and expression in AD brains has been reported[76,77]. However, the usefulness of tau-related biomarkers in blood, such as alterations of peripheral kinases and phosphatases, needs further validation.

Aβ PEPTIDES

Peripheral Aβ is not only generated from peripheral tissues and organs, but also from the brain. Aβ is transported over the BBB by RAGE (receptor for advanced glycation end products) and LRP-1 (low-density lipoprotein receptor-related protein-1)[78]. Several assays for $A\beta_{1-40}$, $A\beta_{1-42}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio have been developed. In familial AD cases, total Aβ and $A\beta_{1-42}$ plasma levels are elevated[79]. In sporadic AD, several cross-sectional studies report no significant difference in plasma Aβ concentrations in general compared to controls[79-82]. Unfortunately, longitudinal studies have shown high data variability. Schupf *et al*[83] (2008) reported enhanced levels of $A\beta_{1-42}$, but not $A\beta_{1-40}$ and $A\beta_{1-42}/A\beta_{1-40}$ ratio at baseline. They also showed a decline in $A\beta_{1-42}$ levels over time, which was associated with a higher risk of AD incidence. Another study reported increased $A\beta_{1-40}$ baseline levels and linked it to an increased risk of dementia[84]. In contrast, Sundelöf *et al*[85] (2008) associated lower $A\beta_{1-40}$ levels at baseline with a higher risk for subsequent AD. Multiple studies have associated a higher baseline $A\beta_{1-42}/A\beta_{1-40}$ ratio to a reduced risk of dementia at follow-up or rather a lower ratio of $A\beta_{1-42}/A\beta_{1-40}$ to a higher risk for MCI conversion to AD[84,86,87]. It was found that serum Aβ autoantibodies are decreased, however, another study reported no difference between plasma Aβ autoantibodies in AD and controls[88,89]. Taken together, these results reveal poor consistency between research groups, possibly caused by the influence of medication, by different ELISA techniques, by detection of different Aβ conformations, or by the adherence of Aβ to other proteins, e.g. albumin. In the periphery, platelets express high levels of APP and an altered pattern of APP isoforms (130 - 110 - 106 kDa) has been reported in the platelets of AD patients[90-93]. The APP ratio in MCI and AD, but not in other dementias, is reduced compared to controls with a sensitivity and specificity between 70% and 95%, correlating with AD severity[90-92]. Information about platelet-generated APP and its contribution to AD pathology is still lacking and the potential of the APP ratio as a biomarker is still unclear.

CHOLESTEROL AND 24S-HYDROXYCHOLESTEROL

High cholesterol levels are associated with increased β-secretase activity leading to an enhanced production of pathogenic Aβ from its precursor protein. In AD patients, decreased levels of total cholesterol have been detected[94,95]. However, high serum total cholesterol concentrations are associated with an increased risk of developing AD[96-98]. Controversial results have been reported in patients treated with cholesterol-lowering drugs (statins). Rockwood *et al*[99] (2002) associated cholesterol-lowering drugs with a decreased risk of AD, while other trials did not show any effects[100]. It has been suggested that only mid-life high total cholesterol is a risk factor for AD, however, increased total cholesterol levels at late-life seem to be associated with a reduced risk[95,101]. Cholesterol from damaged neurons is metabolized into 24S-hydroxycholesterol and then transferred across the BBB. Most 24S-hydroxycholesterol in plasma derives from the brain, thus it is believed that plasma levels of 24S-hydroxycholesterol reflect brain cholesterol catabolism, and thereby ongoing neuronal damage. Increased CSF 24S-hydroxycholesterol levels weakly correlate with 24S-hydroxycholesterol plasma levels and plasma levels have been found to be inconsistently increased[102,103]. In addition, it has been reported that plasma concentrations of 24S-hydroxycholesterol are decreased in dementia disorders[104]. Clearly, further studies are needed to investigate the correlation between cholesterol and AD, and the potential of cholesterol and 24S-hydroxycholesterol levels as prospective biomarkers.

HOMOCYSTEINE

Homocysteine (Hcy) is a methionine-derived amino acid. High levels of Hcy are not only a risk factor for vascular disease, but also for cognitive impairment and AD[105]. Elevated plasma Hcy levels and reduced vitamine B 12 and folate levels may indicate VaD and helps distinguish AD cases from healthy controls[106]. High Hcy levels in plasma increase the risk for developing AD by two-fold[107]. It has also been shown that controls who develop AD, have higher plasma Hcy levels compared to controls who convert to MCI[108], and MCI subjects who convert to AD, have higher baseline plasma Hcy levels than stable MCI patients[109].

GROWTH FACTORS

Growth factors support cell survival and play an important role in the regulation of cellular growth in the CNS and periphery. The growth factor NGF is the most

potent factor in counteracting cholinergic cell death[110]. Growth factors have been considered as possible treatments for AD[110]. However, results from plasma growth factor levels have been conflicting. One study reported decreased concentrations of platelet derived growth factor (PDGF), glial cell line-derived growth factor , and epidermal growth factor (EGF), while another study reported increased or unchanged plasma levels in AD patients compared to controls[111,112]. PDGF levels in platelets were similar in AD subjects and controls. However, EGF was decreased in the platelets of AD patients, indicating an enhanced release of platelet EGF into plasma[93].

CYTOKINES AND CHEMOKINES

Previous studies have suggested that chronic inflammation in the brain contributes to AD. However, an adequate reflection of brain cytokine and chemokine levels in peripheral blood is unclear since many of these proteins cannot easily cross the BBB. Several proteins with a putative role in AD pathology have been examined in plasma, serum and blood cells, but the results on protein levels have been highly contradictory. Some examples are given below:

Interleukin (IL)-1β is increased in the plasma and serum of AD patients compared to controls. However, IL-1β was unchanged in other studies, including longitudinal studies[70,113-115]. In platelets, no difference in IL-1β levels between AD, MCI and controls was found[93]. Lipopolysaccharide (LPS)-stimulated peripheral blood mononuclear cells (PBMC) revealed lower IL-1β levels in AD[116]. In contrast, elevated concentrations or no changes in IL-6 have been reported when PBMCs were stimulated with LPS[117,118]. Several studies reported increased IL-6 levels in the serum and plasma of AD patients, while other studies found no differences[113,114,119-122]. Sun *et al*[123] (2003) found a correlation between IL-6 levels in CSF and serum. Higher mean levels of anti-inflammatory IL-10 in patients with dementia have been detected[124]. It has also been reported that serum and LPS-stimulated blood cell IL-10 concentrations were unchanged in AD[125,126]. Studies have demonstrated that tumor necrosis factor α (TNFα) is produced by activated microglia in response to Aβ, but TNFα-levels also increase in serum with age[127]. Results from TNFα measurements in AD patients compared to controls are divergent. Studies show increased, decreased and no changes in serum TNFα levels[114,115,121,128,129]. Paganelli *et al*[129] (2002) showed lower TNFα levels in mild and moderate AD compared to patients with severe AD, pointing to changes in the cytokine profile during the course of the disease. Monocyte chemotactic protein-1 (MCP-1) plays a role in inflammatory processes in the CNS. MCP-1 production can be stimulated by Aβ and are influenced by age[64,130]. In plasma, higher and unchanged MCP-1 levels have been found in AD[111,131,132]. Stimulated PBMCs show decreased levels of MCP-1 in AD compared to controls[133]. Monokine-induced by interferon-γ (MIG) plasma levels are higher in AD *vs* MCI and controls[132,134]. In monocytes, we found lower MIG levels, suggesting an enhanced release from monocytes into the blood[132]. Macrophage inflammatory protein 1δ (MIP-1δ) is expressed by monocytes in the periphery, and reduced plasma MIP-1δ concentrations have been reported[111]. In our study, we found reduced levels of MIP-1δ in monocytes, but enhanced MIP-1δ levels in plasma. These data support similar results obtained by Marksteiner *et al*[112] (2011)[132].

CELL ADHESION MOLECULES

Cell adhesion molecules (CAMs) are involved in the transmigration of monocytes across the BBB and become activated during the inflammatory and neurodegenerative responses[135,136]. In plasma, higher levels of soluble platelet endothelial CAM and intercellular adhesion molecule (ICAM) in AD patients compared to controls have been observed[137]. We found no difference in monocyte and platelet ICAM-1 levels between AD and controls[132,138]. In monocytes, ICAM-3 and P-selectin levels were lower compared to controls[138]. In plasma, P-selectin was also reduced in demented patients, while no changes were found in P-selectin and vascular CAM (VCAM) concentrations in platelets[132,139]. In plasma, VCAM-1 levels increased in AD and VaD[140]. However, another study reported no association between plasma VCAM-1 and ICAM-1 and an increased risk of developing AD[141].

MATRIX METALLOPROTEINASES

Matrix metalloproteinases (MMPs) are involved in cell-cell and cell-extracellular matrix interaction and have been implicated in AD pathophysiology. MMP-2 exhibits α-secretase activity and is responsible for the cleavage of APP[142]. MMP-2 is decreased in platelets in MCI and AD patients, which is in line with reduced MMP-2 CSF levels[93,143]. However, plasma MMP-2 levels are unchanged in AD and MCI patients[144]. Contradictory results have also been published for MMP-9 plasma levels. It has been reported that MMP-9 plasma levels are increased or unchanged in AD patients[143-145]. In platelets, MMP-9 levels were unaltered in AD patients compared with controls[93]. The correlation between MMPs and AD remains unclear. For instance, upregulation of MMP-9 could result from oxidative stress and inflammation, and thus one could hypothesize that the course of the disease varies throughout[146]. In addition, MMPs may play a role in BBB breakdown and cerebrovascular dysfunction in AD and contribute to disease pathology. However, longitudinal studies must be performed in order to validate their potential as reliable biomarkers.

MULTIPLEX APPROACHES

Contradictory results in peripheral protein levels might be due to varying methological techniques and the lack of standardized tests. None of the above-mentioned proteins serves as an exclusive, consistent, and reliable biomarker for early AD diagnosis. Nevertheless, analysis

of markers can further improve our knowledge on the ongoing pathological mechanisms and diagnostic accuracy in AD. Furthermore, these proteins might serve as interesting biomarker candidates for multiple biomarker strategies. Some multiplex approaches are already underway. Ray *et al*[111] (2007) examined the levels of 120 signaling plasma proteins. They identified an 18 plasma protein signature to discriminate AD patients from controls with an accuracy of 90%. They further discriminated MCI converters from stable MCI patients or patients who converted to other dementias. Marksteiner *et al*[112] (2011) examined 16 of these proteins using Searchlight multiplex ELISA and found five elevated plasma proteins with a sensitivity and specificity of 65%-75% and 52%-63%. Other studies examined the same protein in plasma using alternative approaches[71], however, replication of the results from Ray *et al*[111] (2007) in other cohorts was less successful. In our laboratory, we examined the monocytic levels of MIP-1δ and the tumor suppressor protein, p21, in combination with the clinical marker 'Mini-Mental State Examination', providing us with a good tool to differentiate AD patients from healthy controls[132].

CRITERIA FOR VALIDATING NOVEL BIOMARKERS IN AD

Cross-institutional standards must be employed in order to validate a novel biomarker. Sample collection, transport, processing, storage, and analysis interpretation must be optimized for widespread and efficient use[147]. The first step in searching for a successful biomarker is the inclusion of age-matched healthy controls, which include the same sex, comparable education and life-style. It is also important to have a reliable clinical diagnosis that is applicable worldwide and comparable between institutions. Furthermore, the achieved data must be reproducible by other researches and must be published in peer-reviewed journals[6].

CONCLUSION

$A\beta_{1-42}$, t-tau and p-tau in CSF provide the most reliable, most sensitive and specific biomarkers for AD today. However, the collection of CSF is an invasive procedure, therefore, the development of new methods and identification of blood-based biomarkers are needed. Many biomarkers in blood have been identified, however, no single candidate biomarker demonstrating reliability, sensitivity and specificity for AD has thus far been found. Currently, the most promising approach to diagnosing AD is the combination of multiple markers. However, these multimarker approaches remain in the preclinical phase and further investigation and validation is needed before premortem diagnosis can be achieved.

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Events Calendar 2012

January 19-22, 2012
The 64th Annual National Congress of The Indian Psychiatric Society
Kochi, Kerala, India

January 20-21, 2012
AACAP 2012 Psychopharmacology Update Institute
Child and Adolescent Psychopharmacology: Integrating Current Data into Clinical Practice
Sheraton New York Hotel and Towers, New York, United States

Februrary 08-11, 2012
Thematic Conference of the World Psychiatric Association
Granada

Februrary 09-10, 2012
14th National Conference: Dementias 2012
London, United Kingdom

February 9-12, 2012
New Zealand Association of Psychotherapists Conference 2012
The Face of the Other
Victoria University, Wellington, New Zealand

February 18, 2012
Inaugural RANZCP Symposium on Youth Mental Health
Mantra on Russell, Melbourne, Australia

Februrary 23-24, 2012
Ⅱ Annual Meeting on Therapeutics in Psychiatry
Barcelona, Italy

February 23-24, 2012
Voices VIC 2012 Conference
Voices, Conversations & Transformations – Diverse Approaches to Recovery
Storey Hall, RMIT University, Melbourne, Australia

February 23-25, 2012
American Psychosocial Oncology Society 9th Annual Conference
Miami, FL, United States

February 29, 2012
Conjoint Medical Education Seminar
Hilton on the Park, Melbourne, Australia

March 3-6, 2012
20th European Congress of Psychiatry
Prague, Czech Republic

March 16-19, 2012
2012 American Association for Geriatric Psychiatry Annual Meeting
Washington, DC, United States

March 17, 2012
Body In Mind 2012
AMREP Centre, Alfred Hospital, Melbourne, Australia

March 21-24, 2012
American Neuropsychiatric Association 23rd Annual Meeting
New Orleans, LA, United States

March 21-25, 2012
American Counseling Association 2012 Annual Conference & Exposition
San Francisco, CA, United States

March 23-24, 2012
Psychiatric Society of Virginia 2012 Spring Meeting
Richmond, VA, United States

March 27-31, 2012
5th Annual Psychopharmacology Institute and ISPN Annual Conference - International Society Of Psychiatric-Mental Health Nurses
Atlanta, GA, United States

April 11-14, 2012
33rd Annual Meeting & Scientific Sessions of the Society of Behavioral Medicine
New Orleans, LA, United States

April 12-15, 2012
2012 Anxiety Disorders Association of America Annual Conference
Arlington, VA, United States

April 16-18, 2012
Australian & New Zealand Disaster and Emergency Management Conference
Brisbane Convention Centre, Australia

April 18-21, 2012
45th American Association of Suicidology Annual Conference
Baltimore, MD, United States

April 23-26
Freedom and Recovery: Integrated Mental Health and Addiction Treatment for Service Members
San Diego, CA, United States

May 2-4, 2012
ANZSGM Annual Scientific Meeting 2012
Dementia: Managing Not to Forget
Hilton Hotel, Sydney, Australia

May 5-9, 2012
2012 American Psychiatric Association Annual Meeting
Philadelphia, PA, United State

May 20-24, 2012
RANZCP 2012 Congress
Hobart, Tasmania, Australia

June 14-17, 2012
American Psychiatric Nurses Association 9th Annual Psychopharmacology Institute
Reston, VA, United States

July 6-8, 2012
RANZCP Queensland Branch Weekend Conference
Hyatt Regency Coolum, Australia

July 7-10, 2012
Society For Developmental and Behavioral Pediatrics 2012 Annual Meeting
Phoenix, AZ, United States

July 10-13, 2012
International Congress of the Royal College of Psychiatrists
BT Convention Centre, Liverpool, United Kingdom

August 6-8, 2012
13th International Mental Health Conference
Outrigger Inn, Gold Coast, Australia

September 4-7, 2012
Faculty of Forensic Psychiatry Conference
Hong Kong Academy of Medicine, Hong Kong, China

September 7-11, 2012
International Psychogeriatric Association International Meeting 2012 (Jointly Hosted By the RANZCP Faculty of Psychiatry of Old Age)
Cairns, Queensland, Australia

September 13-16, 2012
American Association For Marriage And Family Therapy Annual Conference 2012
Charlotte, NC, United States

September 27-29, 2012
2nd International Congress on Borderline Personality Disorder and Allied Disorders
Match research, need and demand to treatment and resources
RAI Amsterdam, The Netherlands

October 1-3, 2012
Ranzcp Section of Psychotherapy 2012 Conference
Monash University Centre, Prato, Italy

October 3-5, 2012
RANZCP Faculty of Child and Adolescent Psychiatry Annual Meeting
Novotel Manly Pacific, Sydney, Australia

October 4-7, 2012
64th Institute On Psychiatric Services
New York, NY, United States

October 13-14, 2012
RANZCP Victorian Branch Conference 2012
RACV Healesville Country Club, Australia

October 17-20, 2012
International Convention Of Pan-American Medical Women´s Alliance
Guadalajara, Mexico

October 21-24, 2012
ISQua 29th International Conference
Geneva, Switzerland

November 7-10, 2012
American Psychiatric Nurses Association 26th Annual Conference
Pittsburgh, PA, United States

November 8-11, 2012
International Conference on Clinical Practice in Alzheimer Disease
Budapest, Hungary

November 20-23, 2012
Silent Witnesses: The Place of Coronial System in A Civilised Society (Asia Pacific Coroners' Society)
Amora Hotel, Sydney, Australia

November 22-25, 2012
The 2nd International Multidisciplinary Forum on Palliative Care
Florence, Italy

November 10-12, 2012
CHADD 23rd Annual International Conference on ADHD - Children and Adults with Attention Deficit/Hyperactivity Disorder
Lake Buena Vista, FL, United States

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The columns in the issues of *WJP* will include: (1) Editorial: To introduce and comment on the substantial advance and its importance in the fast-developing areas; (2) Frontier: To review the most representative achievements and comment on the current research status in the important fields, and propose directions for the future research; (3) Topic Highlight: This column consists of three formats, including (A) 10 invited review articles on a hot topic, (B) a commentary on common issues of this hot topic, and (C) a commentary on the 10 individual articles; (4) Observation: To update the development of old and new questions, highlight unsolved problems, and provide strategies on how to solve the questions; (5) Guidelines for Clinical Practice: To provide guidelines for clinical diagnosis and treatment; (6) Review: To systemically review the most representative progress and unsolved problems in the major scientific disciplines, comment on the current research status, and make suggestions on the future work; (7) Original Articles: To originally report the innovative and valuable findings in psychiatry; (8) Brief Articles: To briefly report the novel and innovative findings in psychiatry; (9) Case Report: To report a rare or atypical case; (10) Letters to the Editor: To discuss and make reply to the contributions published in *WJP*, or to introduce and comment on a controversial issue of general interest; (11) Book Reviews: To introduce and comment on quality monographs of psychiatry; and (12) Guidelines: To introduce consensuses and guidelines reached by international and national academic authorities worldwide on the research in psychiatry.

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3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

Organization as author

4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMCID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

Both personal authors and an organization as author

5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

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9 Outreach: Bringing HIV-positive individuals into care. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

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12 **Breedlove GK**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

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14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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