The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes

THE HANDBOOK OF NEUROPSYCHIATRIC BIOMARKERS, ENDOPHENOTYPES AND GENES

Volume 1: Neuropsychological Endophenotypes and Biomarkers

Volume 2: Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers

Volume 3: Metabolic and Peripheral Biomarkers

Volume 4: Molecular Genetic and Genomic Markers

Michael S. Ritsner
Editor

The Handbook of Neuropsychiatric Biomarkers, Endophenotypes and Genes

Volume 3

Metabolic and Peripheral Biomarkers

Springer

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Foreword

Common genetically influenced neuropsychiatric disorders such as schizophrenia spectrum disorders, major depression, bipolar and anxiety disorders, epilepsy, neurodegenerative and demyelinating disorders, Parkinson and Alzheimer's diseases, alcoholism, substance abuse, and drug dependence are the most debilitating illnesses worldwide. They are characterized by their complexity of causes and by their lack of pathognomonic laboratory diagnostic tests. During the past decade many researchers around the world have explored the neuropsychiatric biomarkers and endophenotypes implicated, not only in order to understand the genetic basis of these disorders but also from diagnostic, prognostic, and pharmacological perspectives. These fields have therefore, witnessed enormous expansion in new findings obtained by neuropsychological, neurophysiological, neuroimaging, neuroanatomical, neurochemical, molecular genetic, genomic and proteomic analyses, which have generated a necessity for syntheses across the main neuropsychiatric disorders. The challenge now is to translate these findings into meaningful etiologic, diagnostic and therapeutic advances.

This four volume collection of Handbooks offers a broad synthesis of current knowledge about biomarker and endophenotype approaches in neuropsychiatry. Since many of the contributors are internationally known experts, they not only provide up-to-date state of the art overviews, but also clarify some of the ongoing controversies, future challenges and proposing new insights for future researches. The contents of the volumes have been carefully planned, organized, and edited in close collaboration with the chapter authors. Of course, despite all the assistance provided by contributors and others, I alone remain responsible for the content of these Handbooks including any errors or omissions, which may remain.

The Handbook is organized into four interconnected volumes covering five major sections.

Volume 1 "Neuropsychological Endophenotypes and Biomarkers" contains 17 chapters composed of two parts emphasizing schizophrenia as a prototype. The first section serves as an introduction and overview of methodological issues of the biomarker and endophenotype approaches in neuropsychiatry and some technological advances. Chapters review definitions, perspectives, and issues that provide a conceptual base for the rest of the collection. The second section comprises chapters in

which the authors present and discuss the neuropsychological, neurocognitive and neurophysiological candidate biomarkers and endophenotypes.

Volume 2 "Neuroanatomical and Neuroimaging Endophenotypes and Biomarkers", focuses on neuroanatomical and neuroimaging findings obtained for wide spectra of neuropsychiatric disorders.

Volume 3 "Metabolic and Peripheral Biomarkers", explores several specific metabolic and peripheral biomarkers, such as neuroactive steroid biomarkers, cortisol to DHEA molar ratio, mitochondrial complex, biomarkers of excitotoxicity, melatonin, retinoic acid, abnormalities of inositol metabolism in lymphocytes, and others.

Volume 4 "Molecular Genetic and Genomic Markers" contains chapters devoted to searching for novel molecular genetic and genomic markers in less explored areas. This volume includes an Afterword written by Professor Robert H. Belmaker.

Similarly to other publications contributed to by diverse scholars from diverse orientations and academic backgrounds, differences in approaches and opinions, as well as some overlap, are unavoidable. I believe that this collection is probably the first of its kind to go beyond the neuropsychiatric disorders and delve into the neurobiological basis for diagnosis, treatment, and prevention. The take-home message is that principles of the biomarker-endophenotype approach may be applied no matter what kind of neuropsychiatric disorder afflicts our patients.

The Handbook is designed for use by a broad spectrum of readers including neuroscientists, psychiatrists, neurologists, endocrinologists, pharmacologists, psychologists, general practitioners, geriatricians, graduate students, health care providers in the fields of neurology and mental health, and others interested in trends that have crystallized in the last decade, and trends that can be expected to evolve in the coming years. It is hoped that this collection will also be a useful resource for the teaching of psychiatry, neurology, psychology and mental health.

With much gratitude, I would like to acknowledge the contributors from 16 countries for their excellent cooperation. In particular, I am most grateful to Professor Irving Gottesman for his support of this project. His unending drive and dedication to the field of psychiatric genetics never ceases to amaze me. I wish to acknowledge Professor Robert H. Belmaker, distinguished biological psychiatrist, who was very willing to write the afterword for these volumes. I also wish to take this opportunity to thank my close co-workers and colleagues Drs. Anatoly Gibel, Yael Ratner, Ehud Susser, Stella Lulinski, Rachel Mayan, Professor Vladimir Lerner and Professor Abraham Weizman for their support and cooperation. Finally, I am forever indebted to my wife Galina Ritsner, sons Edward and Yisrael for their understanding, endless patience and encouragement when it was most required.

I sincerely hope that these four interconnected volumes of the Handbook will further knowledge in the complex field of neuropsychiatric disorders.

February, 2009

Michael S. Ritsner
Editor

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Part III
Possible Metabolic and Peripheral Biomarkers

Chapter 28
Peripheral Biomarkers in Dementia and Alzheimer's Disease

Christian Humpel and Josef Marksteiner

Abstract Alzheimer's disease (AD) is a chronic progressive neurodegenerative disease, and is the most prevalent type of dementia. Dementia is usually preceded by a stage of mild cognitive impairment (MCI), with a mean prevalence of about 16%. After Alzheimer's disease, the most common forms of dementia are vascular dementia and Lewy body dementia. Frontotemporal dementia is less common. To date, the most advanced biochemical biomarkers include cerebrospinal fluid levels (CSF) of beta-amyloid(1-42), total tau, and phospho-tau proteins. Decreased levels of beta-amyloid(1-42) and increased levels of tau and phospho-tau are the most reproducible chemical biomarkers for Alzheimer disease. However, laboratories for testing these biomarkers are not readily available, and they also require lumbal puncture. The development and validation of biomarkers for prediction, diagnosis and tracking of progression of dementia and MCI are increasingly important. This chapter reviews the use of CSF biomarkers and of putative blood-related markers.

Keywords Cerebrospinal fluid • blood • plasma • Alzheimer • diagnosis • mild cognitive impairment

Abbreviations AD: Alzheimer's disease; CSF: Cerebrospinal fluid; MCI: Mild cognitive impairment; NGF: Nerve growth factor; PBMC: Peripheral blood mononuclear cells

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Introduction

The life expectancy of humans has increased within the last 100 years from about 40 to about 77 years. As age is the main risk factor for Alzheimer's disease (AD), the number of patients suffering from AD, and mixed forms of dementia will dramatically increase within the next 50 years. It is expected that there will be about 80 million AD patients worldwide in 2050. Looking at these enormously high numbers of presumed AD patients, we have to further establish reliable diagnostic surrogate markers to diagnose and monitor disease progression. It will be essential to delay and counteract symptoms in AD and to start therapeutic treatment as early as possible. A valid and easily accessible diagnostic procedure should be the basis for the treatment.

Diagnosis of Alzheimer's Disease

Progressive impairment in memory and cognition is a key clinical feature of AD. The disorder is morphologically characterized by extracellular beta-amyloid plaque deposition, intraneuronal tau pathology, neuronal cell death, vascular dysfunction and inflammatory processes. Definitive diagnosis of AD requires both a clinical diagnosis of the disease and post mortem detection of beta-amyloid plaques and tau-pathology.[1] A probable diagnosis of AD can be established with a confidence of >90%, based on clinical criteria, including medical history, physical examination, laboratory tests, neuroimaging and neuropsychological evaluation.[2,3] Accurate, early diagnosis of AD is still difficult because early symptoms of the disease are shared by a variety of disorders, including mixed forms of dementia and

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depression, possibly also reflecting common neuropathological features.[2,3]

Mild Cognitive Impairment and Mixed Forms of Dementia

Probable AD can be diagnosed with a high confidence, whereas the diagnosis of mixed forms of dementia, such as vascular dementia, frontotemporal dementia or Lewy Body dementia, is more difficult.[4–15] The transition stage between normal aging and dementia is also referred to as mild cognitive impairment (MCI). MCI is defined as an impairment in one or more cognitive domains (memory) or an overall mild cognitive decline that is greater than would be expected for an individuals age or education but that is insufficient to interfere with social and occupational functioning.[15] In this stage, the validity of diagnosis is more difficult. MCI subtypes may have different outcomes for progression to dementia, and all progressive dementias may have their own predementia states.[16] Vascular MCI, for instance, is thought to result from cerebrovascular disease and is proposed to describe a prodrome of vascular dementia.[17] Patients with Parkinson's disease and MCI may be at higher risk of progressing to dementia than cognitively intact Parkinson's disease patients.[18]

The expected conversion rates from MCI to AD have been shown to be 15% (after 1 year), 20% (after 3 years) and 50% (after 5 years). Approximately 42% of MCI patients develop AD, 15% develop other forms of dementia and 41% remain cognitively stable.[8] It is not yet clear, which prognostic capacity biological markers in MCI patients will have to predict the likelihood of conversion from MCI to AD. Vascular dementia is the second most common form of dementia after AD and is further classified as cortical or subcortical dementia. It constitutes a group of syndromes relating to different vascular mechanisms. Autopsy studies have shown the association between AD and vascular lesions.[19]

Biomarkers in CSF

A biological marker or biomarker[10,20] is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention. It serves as an indicator for health and disease or confirms the risk of developing a disease. The biomarker can be primarily related to the disease or can be simply epiphenomenal in nature. The sensitivity and specificity and ease of use are the most important factors that ultimately define the usefulness of a biomarker for diagnosis.

A promising area of research for biochemical diagnosis of AD and mixed forms of dementia is the analysis of cerebrospinal fluid (CSF).[2,5,10,21–30] Three biochemical markers have been well established for CSF to diagnose AD: beta-amyloid(1-42), total-tau and Phospho-tau-181.[7,21–24,27,31–33] We have recently established in our laboratory the detection of these three biomarkers and we can reliably distinguish AD patients from controls and other forms of dementia.[31,32]

Beta-amyloid(1-42)

AD is characterized by extracellular beta-amyloid plaque depositions. Beta-amyloid is cleaved from the large amyloid-precusor protein by different enzymes, called secretases. Processing of the 42-amino acid long peptide correlates with enhanced plaque deposition. However, beta-amyloid accumulation in plaques is insufficient to cause the cell death observed in patients suffering from of AD. It is well established that beta-amyloid(1-42) is so far a prominent CSF biomarker in AD.[5,10,28,30,31,33–38] Analysis of CSF beta-amyloid(1-42) shows a highly significant reduction in AD patients compared to controls (<500 pg/ml) and in patients suffering from mixed forms of dementia including MCI (Table 28.1). It is suggested that these reduced CSF levels of beta-amyloid(1-42) are caused by a reduced clearance of beta-amyloid from brain to blood/CSF and an enhanced aggregation and plaque deposition in the brain. Patients with vascular dementia display significantly higher beta-amyloid(1-42) CSF levels compared to healthy age-matched control subjects and can be differentiated from AD with white matter lesions with a cut off of <750 pg/ml.[13] While there is no change in CSF beta-amyloid(1-40), there is a marked decrease in the ratio of beta-amyloid(1-42)/(1-40), which is useful in diagnosing AD.[31] Beta-amyloid(1-42) CSF levels are also reduced in progressive supranuclear

palsy and corticobasal degeneration.[12] Thus beta-amyloid CSF levels do not discriminate between these diseases and AD. While beta-amyloid(1-42) is decreased in CSF of AD patients, beta-amyloid(1-38) or –(1-40) levels are unchanged, suggesting that ratios of CSF beta-amyloid(1-42) to (1-38) or to (1-40) are not useful.[39]

Total Tau

Tau is a neuronal protein and plays a role in neuronal transport. Dysfunction of tau (called tauopathy) is a key pathological feature in AD and tau is significantly enhanced in CSF in neurodegenerative diseases and AD[34] (Table 28.1). In normal controls total tau CSF levels are increasing by age[36]: <300 pg/ml (21–50 years), <450 pg/ml (51–70 years) and <500 pg/ml (>71 years). A high number of studies has reported that total CSF tau is a valid biomarker for AD and other forms of neurodegeneration.[2,10,21,23,30,31,33,35] Levels of total tau are significantly enhanced in AD patients compared to age-matched control subjects (>600 pg/ml) and in patients suffering from mixed dementia including the MCI group. Interestingly total tau levels are dramatically enhanced in Creutzfeld Jacobs disease (>1,300 pg/ml). Tau levels may also be a prognostic marker with a good predictive validity for conversion from MCI to AD, since high CSF tau was found in 90% MCI cases that later progressed to AD, but not in cases with stable MCI.[21]

Table 28.1 CSF biomarkers in Alzheimer's disease and dementia

Beta-amyloid(1-42)	Decreased (<500 pg/ml)
Total tau	Increased (>600 pg/ml)
Phospho-tau-181	Increased (>50 pg/ml)
Ratio (phospho-tau-181/beta-amyloid)*100	Increased (>10)
Nerve growth factor	Increased
Monocyte chemoattractant protein-1	Increased/unchanged
Vascular endothelial growth factor	Increased/unchanged
Transforming growth factor-beta	Increased/unchanged
Interleukin-8	Enhanced in MCI and AD
Insulin-like growth factor binding protein-6	Enhanced in AD
Macrophage-Colony stimulating factor	Enhanced in AD
Tumor necrosis-factor-alpha	Enhanced/reduced in MCI/AD/vascular dementia
Neuroserpin	Enhanced in AD
24-OH-cholesterol	Increased/unchanged

Phospho-Tau-181 and "Ratio"

Tau protein is highly hyper-phosphorylated at different sites in AD. In particular, the detection of phospho-tau at the position 181 is specific for AD compared to control subjects.[5,21,26,28,31,40] Phospho-tau-181 is significantly enhanced in AD compared to controls (>50 pg/ml) and in patients suffering from mixed dementia including the MCI group (Table 28.1). However, while phospho-tau-181 levels show relatively high intra-group variability, the ratio between phospho-tau-181 and beta-amyloid(1-42) has a lesser variability. A ratio between phospho-tau-181 and beta-amyloid(1-42) that is higher than 10 specifically differentiates AD from controls. In our hands, ratios of up to 40–90 can be observed in AD patients compared to controls. The analysis of other phosphorylated forms of tau (phospho-tau-199, phospho-tau-231, phospho-tau-235, phospho-tau-396, phospho-tau-404) may offer novel significant improvements to diagnose early AD[15,21] Interestingly, slightly decreased phospho-tau-181 levels may in some cases point to frontotemperal dementia (<15 pg/ml).[31]

Combination of These Three CSF Biomarkers

It is now well established that the combination of all three biomarkers (beta-amyloid(1-42), total tau and phospho-tau-181 or the respective ratio) significantly increase the diagnostic validity for AD (Table 28.1). Combining these three biomarkers yields a sensitivity of 95% and a specificity of 83% for detection of incipient AD in patients with MCI.[8,31] We recommend also to routinely determine total protein levels, which, however, do not influence the diagnostic values.[41]

Other CSF Biomarkers

Despite strong efforts to characterize other potential biomarkers in CSF, up to now no biomarkers with a higher sensitivity and specificity could be identified. From all tested proteins only. Nerve growth factor (NGF) has been found to be increased in CSF of AD patients.[31,42,43] NGF is the most potent trophic factor

supporting survival of cholinergic neurons, which degenerate early in AD, possibly due to defective retrograde transport of NGF to the basal nucleus of Meynert. Interestingly, the increase of NGF is specific for AD and depends on the extent of neurodegeneration as expressed by the ratio of phospho-tau181/beta-amyloid(1-42) (Table 28.1).[4] Although raw NGF data do not reveal a significant difference, the comparison of NGF in AD-patients (phospho-tau181/beta-amyloid(1-42) ratio > 10) with healthy control subjects (ratio phospho-tau181/beta-amyloid(1-42) < 6) reveals a significant difference.[4] This might suggest that NGF accumulates in neurodegeneration of Alzheimer's type possibly only at a certain stage of the disease.

Several other studies measured growth factors and cytokines in CSF, however, the data are very heterogeneous and inconsistent and do not point to a selective biomarker for AD (Table 28.1). Monocyte chomoattractant protein-1 is enhanced in AD patients,[44] however, our recent study[4] showed that monocyte chomoattractant protein-1 levels are age-dependent and could not detect significant difference between AD and age-matched control subjects. Hepatocyte growth factor and vascular endothelial growth factor have been reported to be increased in CSF of AD-patient,[45] however in our study[4] this increase was not statistically significant. In agreement with other studies, brain-derived neurotrophic factor or glial-cell line derived neurotrophic factor levels are very low in CSF of controls but not changed in AD.[4] No changes were seen in fibroblast growth factor-2, monocyte inhibitoring protein-1, tumor necrosis factor-alpha or transforming growth factor-beta, although others reported that transforming growth factor-beta1 or tumor necrosis factor-alpha were enhanced in CSF of AD patients.[4,46,47] Others reported that interleukin-8, macrophage-colony stimulating factor and insulin-like growth factor binding protein-6 were enhanced in CSF of AD patients.[47] Interestingly, recently it was suggested that 24-S-hydroxycholesterol could be a sensitive biomarker for MCI because this marker correlated with CSF total tau.[48] The CSF levels of neuroserpin are significantly enhanced in AD compared to controls.[49] We and others also measured both forms of cholinesterases, acetylcholineesterase and butyrylcholineesterase, in CSF and did not find any differences between controls and AD.[43] In summary, only NGF seems to be consistently enhanced in CSF of severe AD patients, while other growth factors or cytokines do not show consistent changes between controls and AD patients. No other factors could be identified in CSF specific for MCI, vascular dementia or other forms of dementia.

Biomarkers in Blood

The routine diagnosis of AD and mixed forms of dementia from CSF has several drawbacks: lumbal puncture and collection of CSF is an invasive treatment with potential side effects. Commercial ELISAs for beta-amyloid, tau and phospho-tau are extremely expensive and screening of patients is often not possible. Follow up analysis of the same patient over years is difficult because of the invasive CSF collection. Thus there is a clear need to search for blood biomarkers to diagnose AD and other forms of dementia.

Biomarkers in Plasma and Serum

Several authors measured the standard CSF biomarkers beta-amyloid and tau in plasma, but the data were all very heterogeneous and not useful for diagnosis. Most studies have shown that plasma beta-amyloid(1-42) and beta-amyloid(1-40) levels are not different in AD and controls.[15] A significant increase of beta-amyloid(1-42) plasma levels have been seen in women with MCI but not in men compared to 72 cognitively normal age-matched subjects.[50] Nevertheless, measurement of beta-amyloid plasma has several drawbacks,[10] because plasma levels for beta-amyloid(1-42) are unstable and influenced by different medications.[31] Recent longitudinal studies showed that high plasma beta-amyloid(1-42) levels are risk factors for developing AD, however, there is agreement that this factor is not sensitive and specific for early diagnosis.[15] A decrease of serum beta-amyloid(42) autoantibodies have been found in AD,[51] however, it was concluded that this parameter alone is not useful as a diagnostic biomarker. Immunoreactivity for the Tau-protein was detected in human plasma but there was no obvious increase in dementia.[52]

Most studies focused on single isolated inflammatory plasma/serum biomarkers in AD, however, so far the heterogeneity was very high and controversial and a single biomarker did not yield any significant

improvement in diagnosing AD. Recently, it has been shown that different cytokines (interleukins-12, -16, -18, transforming growth factor beta1) were significantly enhanced in plasma of AD and vascular dementia patients, confirming the inflammatory process in the disease.[53,54] ELISA-studies showed that ALZAS immunoglobulins are present in plasma of AD patients and preliminary ELISA pilot studies confirmed ALZAS to elicit a specific anti ct-12 autoantibody,[55] suggesting an induced auto-immune reaction. Furthermore oxidative stress markers such as cystatin C were increased in plasma and cathepsin D was decreased in plasma of AD patients.[56] Free copper might correlate to cognitive decline and was higher in the ApoE4 individuals.[57] We recently showed that both cholinesterases, acetylcholineesterase and butyrylcholineesterase, were not changed in plasma of AD and MCI patients. Others found that plasma levels of serotonin may be linked to the pathogenesis and progression of vascular dementia.[58] In summary, the analysis of a single plasma biomarker does not yield any novel information for diagnosing AD.

Despite these different single biomarkers in plasma, a recent promising study showed that the combination of 18 selected biomarkers in plasma may allow the diagnosis of AD.[47] These factors are chemokines, cytokines, growth factors and binding proteins (Table 28.2), involved in inflammation, transmigration of cells, proliferation/differentiation/survival of blood cells and neurons, angiogenetic factors and factors regulating other proteins. These 18 biomarkers were selected from 120 signalling proteins by filter-based arrayed sandwich ELISA and may allow to diagnose MCI with close to 90% accuracy.

Table 28.2 Potential putative biomarkers in plasma[47]

Biomarker	Change	Role in	Chromosome
Angiopoietin-2	↑	Angiogenesis	8
CCL5	↓	Inflammation	17
CCL7	↓	Inflammation	17
CCL15	↓	Inflammation	17
CCL18	↑	Inflammation	17
CXCL8	↑	Inflammation	4
Epidermal growth factor	↓	Proliferation	4
Granulocyte-colony stimulating factor	↓	PDS	17
Glial cell line-derived neurotrophic factor	↓	Survival	5
Intracellular cell adhesion molecule-1	↑	Transmigration	19
Insulin-like growth factor binding protein-6	↑	Control of IGFs	12
Interleukin-1α	↓	Inflammation	2
Interleukin-3	↓	PDS	5
Interleukin-11	↑	Inflammation	19
Macrophage-colony stimulating factor	↓	PDS	1
Platelet-derived growth factor-BB	↓	Mitogenesis	22
Tumor necrosis factor-α	↓	Inflammation	6
TRAIL-R4	↑	Control of TRAIL	8

CCL = chemokine that contains a C–C motif, CXCL = chemokine that contains a C–X–C motif, PDS = proliferation-differentiation-survival, TRAIL-R4 = tumor necrosis factor receptor superfamily, member 10d, decoy with truncated death domain.

The following section shortly summarizes the role of the 18 plasma biomarkers for diagnosing AD and MCI.[47] Angiopoietin-2 binds to the endothelial cell specific receptor Tie2 and promotes angiogenesis, sprouting and tube formation and the formation of new blood vessels. CCL5 (also known as RANTES) is chemotactic for monocytes, memory T-cells, eosinophils and basophils and plays an active role in recruiting leukocytes into inflammatory sites. CCL7 (also known as monocyte chemoattractant protein-3) attracts and activates monocytes and regulates the function of macrophages. CCL15 (also known as monocyte inhibitoring protein-1-δ) chemoattracts T cells and monocytes. CCL18 (also known as monocyte inhibitoring protein-4 or PARC) is chemotactic for activated T cells and non-activated lymphocytes. CXCL8 (also known as interleukin-8) mediates the immune reaction, is chemoattractant and recruits neutrophils at sites of inflammation. Epidermal growth factor stimulates the proliferation of various epidermal and epithelial cells, inhibits gastric acid secretion and is involved in wound healing. Granulocyte colony-stimulating factor stimulates the bone marrow to produce granulocytes and stem cells and stimulates survival, proliferation and differentiation and function of mature and neutrophil precursors and white blood cells. Glial cell line-derived neurotrophic factor stimulates the survival of several neurons, such as e.g. dopaminergic neurons or motorneurons. Intracellular adhesion molecule-1 (CD45) is continuously present in low concentrations in the membranes of leukocytes and endothelial cells and plays a role in transmigration of leukocytes through

the blood-brain barrier. Insulin-like growth factor binding protein-6 controls the distribution, function and activity of insulin-like growth factors. Interleukin-1α has a broad range of activities, e.g. stimulation of proliferation and maturation of thymocytes and B-cells, it is involved in immune defense against infections, enhances cell adhesion molecule expression on endothelial cells and induces transmigration of cells. Interleukin-3 is a hematopoietic growth factor that promotes the survival, differentiation and proliferation of megakaryocyte, granulocyte-macrophage, erythroid, eosinophil, basophil and mast cell progenitors and enhances thrombopoiesis, phagocytosis and cellular cytotoxicity and plays a role in immune defense. Interleukin-11 regulates hematopoiesis, stimulates megakaryocytes, stimulates lymphocytes and regulates bone metabolism. It also inhibits production of pro-inflammatory cytokines. Macrophage colony stimulating factor regulates proliferation, differentiation and survival of blood monocytes, tissue macrophages and progenitor cells. Platelet-derived growth factor-BB is mitogenic for cells of mesenchymal origin. Tumor-necrosis factor alpha is secreted by various cells including adipocytes, activated monocytes, macrophages, B cells, T cells and fibroblasts, it induces apoptotic cell death and has also other numerous effects, such as e.g. septic shock, autoimmune disease, rheumatoid arthritis, inflammation and diabetes. Tumor necrosis factor receptor superfamily, member 10d, decoy with truncated death domain (TRAIL-R4) is a receptor with an extracellular TRAIL-binding domain, a transmembrane domain and a truncated cytoplasmic death domain. It does not directly induce apoptosis and inhibits TRAIL-induced apoptosis. However so far no quantitative measurements of these 18 biomarkers have been performed and the results have not been verified by other dementia centers yet.

Biomarker in Blood Cells

Biomarkers in Platelets

In platelets of AD patients an increased level of beta-amyloid was found (Table 28.3), increased activation of beta-secretase and decreased activation of alpha-secretase and a decreased ratio of amyloid-precusor protein (130 kDa/110 kDa).[59] It was suggested that amyloid-precusor protein processing in platelets may be useful for diagnosing AD.[59]

Biomarkers in Peripheral Blood Mononuclear Cells and Isolated Monocytes

The detection of parameters in peripheral blood mononuclear cells (PBMC) seems to be promising (Table 28.3). Glycogen synthase kinase-3 was significantly increased in white blood cells in AD compared to healthy subjects.[60] More importantly, glycogen synthase kinase-3 levels were also increased in MCI. Thus, it was concluded that glycogen synthase kinase-3 could be an important parameter for diagnosis of MCI and AD. Similarly, in phytohemmagglutinin-stimulated cultures of PBMC of patients with MCI a dramatically enhanced secretion of interleukin-6 was found compared to controls after 24 h.[61] However AD patients did not differ from controls. Others focused on the inflammatory pathway and found a significant increase in the percentage of monocytes producing different cytokines (interleukins-1β, -6, -12, tumor necrosis factor-α) under basal conditions and after exposure to inflammatory stimuli.[62] They also reported that these cells differentially responded to inflammatory challenges when compared to controls. Higher spontaneous production of interleukin-1 or tumor necrosis factor-alpha by PBMCs are associated with the risk of incident AD.[62]

Protein degradation by the ubiquitin-proteasome system is an essential cellular mechanism that has come into focus of aging research because its activity decreases during the aging process.[64] As cells age the defective activity of the major proteolytic system leads

Table 28.3 Suggested putative biomarkers in blood cells

Platelets	Amyloid-precursor protein ratio 130/110 kDa reduced
PBMC	Glycogen synthase kinase-3 enhanced
	Phytohemmaglutinin-induced interleukin-6 release enhanced
Lymphocytes	Telomere shortening in vascular dementia
Monocytes	Interleukin-1beta, -6,-12, tumor-necrosis-factor-alpha enhanced
Monocytes/fibroblasts	Mutant-like p53 enhanced

to proteasome overload and to the intracellular accumulation of damaged and unfolded protein products. Misfolded proteins often aggregate and accumulate in the cells through life. Insoluble ubiquitinated protein aggregates are present in the pathological hallmarks of AD, particularly neuritic plaques and neurofibrillary tangles. Failure of the ubiquitin-proteasome pathway function has been linked to beta-amyloid toxicity. It is well known that ubiquitin levels are increased many fold in the cerebral cortex of patients with AD and the increase strongly correlates with the degree of neurofibrillary changes in the tissue.[65] Interestingly, in CD45 T-lymphocytes the ubiquitin-proteasome pathway has been shown to be reduced during aging.[66] In addition ubiquitin levels were increased in CSF of AD patients.[67] A dinucleotide deletion in human ubiquitin B messenger RNA leads to formation of polyubiquitin, which has been implicated in neuronal cell death in AD and other neurodegenerative diseases.[63] This issue is of importance and we are recently under way to measure ubiquitin levels in PBMC and lymphocytes.

Cellular senescence is a stress response phenomenon resulting in a permanent withdrawal from the cell cycle and the appearance of distinct morphological and functional changes, such as e.g. telomere shortening.[68] Telomeres are high order structures formed by DNA and a complex array of specialized proteins that cap and stabilize the physical ends of chromosomes.[68] In mammals, telomeric DNA consists of a variable number of nucleotides, which extend over several 1,000 base pairs in length and end in G-rich single stranded overhang.[69] Short telomeres (tandem TTAGGG repeats) induce DNA damage responsive pathways and subsequently induce the permanent cell cycle arrest.[64] Telomere shortening was also found in white blood cells and interestingly short telomere length was associated in peripheral white blood cells in vascular dementia (Table 28.3).[70] We are interested in this issue and started to measure telomerase and telomeres in monocytes of dementia patients. Despite blood cells also other cells became of interest to diagnose AD. Recently it has been reported that fibroblasts from sporadic AD patients specifically express an anomalous and detectable conformational state of the senescent marker p53 (mutant-like p53) that allows to differentiate them from fibroblasts of age-matched non-AD subjects.[71] Interestingly, the same group also showed that mononuclear blood cells from AD patients express a higher amount of mutant-like p53.[72]

Conclusions and Future Directions

In order for a diagnostic biomarker to be useful, certain criteria need to be met. These criteria include the following (see Chapter 1 in this book, Ritsner, Gottesman):

1. The biomarker should reflect some basic pathophysiological processes, and detect a fundamental feature of the disease.
2. The biomarker should be specific for the disease compared with related disorders.
3. The biomarker should not reflect clinical symptomatology and consequences of the disease.
4. The biomarker can be measured repeatedly over time and should be reproducible.
5. The biomarker should be measured in noninvasive and easy-to-perform tests that can be done at the bedside or in the outpatient setting.
6. The biomarker should not cause harm to the individual being assessed.
7. The biomarker should be reliable in many testing environments/labs.
8. The biomarker should be cost effective.

Taken together, up-to-date only the analysis of beta-amyloid(1-42), total tau and phospho-tau-181 in CSF allows reliable, sensitive and specific diagnosis of AD in body fluids. Other forms of dementia cannot be diagnosed with these biomarkers so far and other CSF biomarkers do not add any novel information. Unfortunately, the use of CSF biomarkers is limited because of the invasive collection. Thus, the discovery of peripheral blood biomarkers has several advantages over CSF biomarkers.

So far a single peripheral blood "super-biomarker" for diagnosis of dementia has yet not been found, and possibly will not exist. It seems very likely that only the combination of several biomarkers will be successful: (1) either several biomarkers in plasma, as reported e.g. by Ray et al.[47] using 18 signaling proteins, or and more likely (2) the combination of some plasma biomarkers and some blood-cell-derived biomarkers, such as e.g. the differences in monocyte phenotype or different expression of proteins or DNA changes (such as e.g. telomere shortening) in PBMC. So far, some biomarkers are of interest, not yet fully established international, but some reflect the basic pathophysiological process of the disease (e.g. amyloid-precursor protein

changes, inflammation, cerebrovascular damage, etc.). However, these biomarkers do not yet allow to diagnose different forms of dementia with high sensitivity and specificity. The major advantage of peripheral blood biomarkers is that blood can be easily collected from patients, allowing repeated measurements over time and screening of many patients, also of younger individuals. Such screening over years may allow to identify an "age-related biomarker", which may be stable over years and might change at the beginning of the disease. In addition, all methods (e.g. ELISA or Western Blots) are well established in several laboratories, allowing good reproducibility of the assays. However, the procedures of detection, blood handling, transport and stability of proteins needs to be tested and international standards need to be defined. Unfortunately, the analysis of several combined biomarkers will dramatically increase the costs for laboratory analysis. In conclusion early, fast and cheap diagnosis from body fluids will become extremely important in the future to diagnose different forms of dementia and to measure therapy improvements.

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Chapter 29
S100B as a Potential Neurochemical Biomarker in a Variety of Neurological, Neuropsychiatric and Neurosurgical Disorders

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Abstract S100B is a calcium-binding protein found in Schwann cells in the peripheral nervous system, and in astrocytes in the central nervous system. It has multiple functions including the inhibition of protein phosphorylation through interacting with kinase substrates, regulating enzyme activity and interacting with cytoskeletal elements. It is also involved in calcium homeostasis, and is believed to have a role in cytosolic calcium buffering.

In recent years it has been shown that S100B is elevated and released into the circulation in a wide variety of neuropathologic states. As such it has generated a great deal of interest as a surrogate biomarker for injury to the CNS. It has been shown to be raised in many organic brain disorders such as traumatic brain injury, subarachnoid haemorrhage, stroke, epilepsy, multiple sclerosis, Parkinson's disease and hydrocephalus. In addition to this there is now clinical and laboratory evidence that it is raised in neuropsychiatric disorders such as schizophrenia, depression, bipolar disorder, anxiety, post-traumatic stress disorder and neuropsychiatric systemic lupus erythematosus.

S100B has great potential to become a specific neurological screening tool that is predictive of outcome and reactive to treatments.

Keywords S100B • biomarker • neurochemistry • neuropathology • brain injuries

Abbreviations FTD: Fronto-temporal dementia; LDH: Lactate dehydrogenase; MCAO: Middle cerebral artery occlusion; NPSLE: Neuropsychiatric systemic lupuserythematosus; SAH: Sub-arachnoid haemorrhage; TBI: Traumatic brain injury

Introduction

Chemical Biomarkers

A biomarker can be defined as a measurable indicator of a specific biological state.[1] It can be relevant to the stage of a disease process, the presence of disease or the risk of contracting a disease. A biomarker can take many forms, most commonly they are plasma measurements of specific proteins or molecules. Effective biomarkers can have a great variety of clinical uses. They can be used as screening tools or to diagnose and monitor disease activity. There is also great potential for biomarkers to guide molecularly-targeted rational therapies and to monitor response to treatments.[2]

Chemical biomarkers can be measured in the plasma or other fluids more proximal to the site of disease. Proximal fluids such as cerebrospinal fluid (CSF) can act as sinks for proteins or molecules secreted or leaked from diseased tissue and can provide a more accurate indication of disease activity. Measurements of protein levels are made more easily from plasma however, indeed laboratory assays to measure over 100 different proteins are currently used in routine clinical practice.[3] For a potential biomarker to be clinically useful it must be sensitive, specific, accurate and reliable. It must also provide a high predictive value.

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