COMMENTARY

Biomarkers in psychiatry

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Abstract

Biomarkers are characteristic biological features that can be objectively measured and indicate either normal or diseased processes in the body. Dopaminergic system plays a pivotal role in multidimensional brain functions, such as control and modulation of movement, cognition, memory as well as motivation and emotional behaviour. Reduced glucose utilisation activity in the frontal lobe, altered utilisation activities with tasks, and a reversal of subcortical/cortical relationships have been observed in schizophrenic patients. Any stressful experience (prenatal or maternal traumatic stress or childhood trauma), via a cascade of neurochemical events, alters the microenviromental milieu of the central nervous system, resulting in altered gene and this new gene results in permanent or structural changes which are associated with sensitisation, learning, memory and developing brain differentiation. Brain-derived neurotrophic factor, produced by neurons particularly in the hippocampus and cortex, acts as a neurotrophic factor and is involved in neuroplasticity. Alanine aminotransferase is the more specific measure of alcohol-induced liver injury because it is found predominantly in the liver. Increased concentration of total and hyperphosphorylated tau protein and a reduction of amyloid β peptide Aβ42 have been reported in CSF of Alzheimer's disease patients. Deficits in cognitive flexibility and motor inhibition may represent cognitive endophenotypes for obsessive-compulsive disorder. Low plasma vascular endothelial growth factor is associated with completed suicide. Patients with autism showed decreased activity of glutathione peroxidase in plasma and in erythrocytes compared with the controls. Accurate biomarkers, along with more reliable and valid disease criteria, will help psychiatry achieve greater objectivity in diagnosis.

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Introduction

Biomarkers tell us who is sick, who will get sick, which patients should be treated with what and when, how well does the patient respond to treatment, and when has the patient returned to health. For countless diseases today, biomarkers are providing physicians with valuable information. It is a long-cherished dream of the medical profession to be able to individually tailor diagnosis and treatment for every patient. This dream of personalised medicine could come true with the help of biomarkers.

Definition

It's a measurable indicator of disease or of vulnerability of a disease, that may or may not be causal. The term includes molecular, genetic, immunologic, physiologic signals of events in the biologic systems, that may appear in any of the various steps along the causation pathway of a disorder. According to Biomarkers' Consortium, "Biomarkers are characteristic biological features that can be objectively measured and indicate either normal or diseased processes in the body." The approach integrates animal model gene expression with human genetic linkage associated data as well as, human tissue (postmortem brain, blood) data, to cross validating findings, extract meaning from large datasets, and prioritise candidate genes, pathways, mechanism for subsequent hypothesis driven research.

Drawbacks

Instead of simply focusing on its potential, a closure look at the drawbacks and possible misuses of this new technology is needed.

1. Cost: Extremely expensive; if an individual is positive for a biomarker, additional funds may be needed for post screening support and counselling and treatment for the polygenic inheritance.[1]

2. Unreliability: Multifactorial in origin. There are many unknown genes, one gene may influence another, variable as a function of age, gender, ethnicity and health status.

3. Ethical concerns: Perhaps the biggest concern.

Potentials for biomarker misuse are discrimination, stigma, privacy, insurance screening tool, selective abortion and ill treatment.

What constitutes a good biomarker?

Good biomarkers confirm a difficult diagnosis especially for chronic diseases that require long duration of medications with strong side effects. They identify 'at risk' individual reliably and in a timely manner, so that they can be treated before disease onset or as soon as possible thereafter.

The sample must be as easy to obtain as possible (blood sample, urine, saliva or a drop of blood). Rapid test which delivers results within few minutes is optimal. Detection method must be accurate, easy to carry out as possible and direct or indirect indication of cause of the disease.

Types of markers

Trait marker: The properties of behavioural and biologic processes that play an antecedent, possibly causal role in the pathophysiology of psychiatric disorder. It includes a broader meaning in psychiatry, includes manifestation of altered behaviour and biologic processes that are linked not necessarily to psychosis but to functional abnormality that are at the core of the disorder.

State marker: Status of clinical manifestation in the patient. It varies with the clinical state or phase of the disease. It may appear just before, during or after an episode of illness but not during remission. Typically, but not necessarily, a trait marker is enduring, but a state marker is transient.

Endophenotypes: Objectively measured and biologically anchored heritable traits which co-segregate with clinical illness in pedigrees and is expressed in clinically unaffected family members.

Criteria of trait markers

Any useful trait marker should satisfy at least three criteria—passed down from parents to children through the gene (i.e. heritable), associated with the disease in question on the general population and independent of the state of the disease (it would be present whether the person displayed symptoms of the disease or was asymptomatic).

Based on application, disease related biomarkers are: predictive biomarker (whether there is a threat of disease), diagnostic biomarker (if a disease already exists) and prognostic biomarker (how such a disease might develop in an individual case). Drug related biomarkers indicate whether a drug will be effective in a specific patient and how a patient's body will process it.

Potential biomarkers

Schizophrenia

1. Neurotransmitters
2. Phenotype of schizophrenic psychoses
3. Functional brain systems
4. Chromosomal loci and genetic markers
5. Currently accessible analytical system

Neurotransmitters: Dopaminergic system plays a pivotal role in multidimensional brain functions, such as control and modulation of movement, cognition, memory as well as motivation and emotional behaviour. Prefrontal dysfunction, related to abnormal prefrontal dopamine (DA) signalling, would result in disinhibition of striatal DA activity.[2,3] In contrast to this hypothesis, Kellendonk and colleagues[4] showed that overexpression of D2 receptors (D2Rs) in the striatum of D2 transgenic mice causes irreversible prefrontal deficits in motivation and working memory.

Functional and neurochemical brain imaging studies have suggested that these symptoms might arise from altered prefrontal function documenting the importance of prefrontal DA transmission at D1Rs, the main DA receptor in the neocortex. The literature has, however, at the same time provided evidence for a significant role of frontal D2R in the development of positive symptoms.[5] Imaging studies documented the existence of dysregulation of striatal DA function in schizophrenia, using [18F]DOPA or [11C] DOPA.

In the prefrontal cortex (PFC), D1Rs were found to be up-regulated in patients with schizophrenia, whereas acute DA depletion studies indicated that there was an increased occupancy of D2R by DA at baseline in schizophrenia in comparison with healthy controls.[6] It remains, however, unclear whether the U-curvilinear decrease in prefrontal DA innervations is an acute manifestation of illness or whether it emerges during the course of illness. The hypothesis of a glutamatergic hypofunction was formulated for the first time by Kim and colleagues[7] when they showed markedly reduced cerebrospinal fluid (CSF) glutamate levels in patients with schizophrenic psychoses compared to controls.

Investigation of post-mortem human brain tissue from patients with schizophrenia showed alterations of cortical gamma-amino butyric acid (GABA)-ergic neurons, including decreases in glutamic acid decarboxylase (GAD(67)), reelin, GABA membrane transporter 1 and parvalbumin. Consistent with a presynaptic GABAergic deficit, postsynaptic GABA1 function appears to be upregulated in schizophrenia. Hypermethylation hypothesis of schizophrenia,[8] where over-expression of DNMT1 leads to promoter hypermethylation of selected genes in GABAergic neurons, finally resulting in a downregulation of multiple genes and collectively resulting in a GABAergic neuronal circuit dysfunction. Key components in signal transduction pathways and therefore candidate risk proteins in schizophrenia are: reelin- lower expression, hypermethylation; DISC1 (disrupted-in-schizophrenia 1)- altered hippocampal function (working memory and cognitive deficits); serine/threonine protein kinase; AKT1 (V-akt murine thymoma viral oncogene homolog 1, oncogene AKT1)- decreased expression; GSK3B (glycogen synthase kinase 3 beta); CHRNA7 (a-7 -nicotinic acetylcholine receptor)- genetic linkage analysis to sensory gating deficits (P50) in patients and unaffected relatives.

Increased interleukin 8 (IL-8) levels in the mothers during pregnancy were associated with an increased risk for schizophrenia in the offspring.[9] A well established finding in schizophrenia is the decreased in vitro production of IL-2 and interferon gamma (IFN-gamma), pointing to a blunted production of T-helper-1 (Th1) cytokines.[10] Increased serum IL-6 levels in schizophrenia are found especially in patients with an unfavourable course of the disease. Activation of the Th2 immune response in schizophrenic psychoses encompasses increased production of immunoglobulin E,[11] an increase of IL-10 serum levels,[12] and increased levels of IL-4, the key cytokine for the Th2 immune response, in the CSF of patients with juvenile schizophrenia.[13]

Kendler[14] found evidence for a locus for prominent affective deterioration, poorer outcome, thought disorder and fewer depressive symptoms on 8p22-21. Paunio et al.[15]

found evidence for a locus for verbal learning and memory on 4q21, for visual working memory on 2q36, visual attention on 15q22 and executive function on 9p22.

Eye tracking dysfunction: Extensive studies have shown that eye tracking dysfunction occurs not only in schizophrenia but also in their first degree relatives of probands.[16-19] It may be a trait marker as it is independent of drug treatment and clinical state. Patients with schizophrenia reported to have less accurate smooth pursuit and lower pursuit gain, and to make more frequent saccades than normal control subjects. Holzman et al.[20] have reported that 34 percent of the parents of schizophrenic patients showed eye movement dysfunctions versus ten percent of the parents of manic-depressive patients. The proportion of first-degree family members who show qualitatively abnormal pursuit ranges from 34 percent to 58 percent for schizophrenic patients versus five percent to 13 percent for persons with other psychiatric disorders.

Two patterns of electrodermal activity have been reported in schizophrenic subjects:

1. A hyperresponsive pattern associated with poor outcome in respect of social and occupational functioning.[21]

2. A hyporesponsive or nonresponsive pattern.

The decreased skin conductance orienting response, has been found to characterise 40 percent to 50 percent of schizophrenic patients and five percent to ten percent of normal.

The P300 endogenous brain potential is a large, late, positive potential that reaches a poststimulus peak between 300 to 500 ms. Reduced P300 amplitude has been correlated with schizophrenic patients. P300 abnormalities seem to correlate with attentional deficits in schizophrenic subjects.[22] Abnormalities are more common in children of affected parents who are at high risk of schizophrenia.

Attention and information processing: The attentional problems manifested by schizophrenic patients may be sustained focused attention on complex tasks with high processing demands as measured by the visual continuous performance test (CPT). Other potential markers include global and selective verbal memory, nonverbal memory, bilateral and unilateral motor performance, visual and auditory attention, general intelligence, spatial ability, executive function, language, and interhemispheric tactile transfer.[23]Some 40 percent to 50 percent of schizophrenic patients have been reported to show impaired performance on simple versions of the CPT, but not high-risk children.

The most consistent reduction and down-regulation of multiple genes encoding presynaptic proteins in the PFC of schizophrenic patients were observed in transcripts such as N-ethylmaleimide sensitive factor (NSF), synaptosomal-associated protein (SNAP), synaptogyrin-1 and synaptobrevin.[24-26] Targeted and untargeted lipidomics studies are aiding advances in understanding of biochemical pathways in schizophrenia and other brain diseases.[27] In a proteomic approach to the CSF samples, potentially specific changes were observed in a peptide that mapped to the VGF protein and in several peptides that mapped to transthyretin.[28]

Brain imaging procedures

Computed tomography (CT): Many CT studies have described lateral and third ventricular enlargement and reduction in cortical volume in schizophrenic patients. Cerebral asymmetry, cerebellar volume reduction, and brain density changes have also been observed. Imaging studies have suggested a possible association between ventricular enlargement and particular clinical characteristics such as negative symptoms, cognitive impairment, poor outcome, hypofunction of the monoamine system, and a partial neuroleptic response.

Magnetic resonance imaging (MRI): MRI studies have confirmed the CT findings of cerebral ventriculomegaly. Midsagittal, coronal, cerebral, frontal, and cerebellar structures have been found to be smaller in some studies. Corpus callosal area, length, and thickness differences have been reported between schizophrenic and control populations. DeLisi et al.[29] have found bilateral hippocampal/amygdala complex and parahippocampal gyrus area reduction in siblings of schizophrenic patients. Casanova et al.[30] have described corpus callosal anterior and middle segmental shape differences in the schizophrenic half of 12 pairs of discordant monozygotic twins. Andreasen et al.[31], in a study found that decreased cerebral and cranial size was correlated with negative symptoms, although frontal lobe hypoplasia was not. Andreasen et al.[32] reported ventriculomegaly in schizophrenic patients; patients with prominent negative symptoms possessed larger ventricles than those with mixed or positive subtypes.

Positron emission tomography (PET): Reduced glucose utilisation activity in the frontal lobe, altered utilisation activities with tasks, and a reversal of subcortical/cortical relationships have been observed in schizophrenic patients. Decreased glucose consumption in the basal ganglia that can be normalised with neuroleptic treatment can also be seen in schizophrenic patients. In one study, in which [11C]-A/-methylspiperone was used, elevated D2R densities were found in the caudate/putamen of drug-naive first episode schizophrenic subjects.

The G-protein signalling 4 (RGS4) gene, located on chromosome 1q21q22, regulates G-protein-mediated signalling via neurotransmitters such as DA or glutamate, and showed altered expression in the PFC of patients with schizophrenia.[33] G72/G30 on chromosome 13q14q32 has been repeatedly associated with schizophrenia and with weaker evidence with bipolar disorder.[34] AKT1 on chromosome 14q32 locates in a region with weak evidence for linkage, and is mainly supported by pathophysiological considerations.[35] The microdeletion region on chromosome 22q11 contains the genes for catechol-O-methyltransferase (COMT), proline dehydrogenase (PRODH2), and the brain expressed putative palmitoyltransferase (ZDHHC8), implicated in schizophrenia pathogenesis.

Recent markers: Reduced glutathion levels and impaired antioxidant activities in drug naïve first episode schizophrenic patients,[36] hypomethylation of serotonin receptor type-2A gene (HTR2A) at T102C polymorphic site in DNA derived from patients with schizophrenia and bipolar disorder,[37] altered levels of circulating insulin and

other neuroendocrine hormones associated with the onset of schizophrenia.[38] Guest et al.[38] showed that the circulating levels of insulin-related peptides and the secretory granule protein chromogranin A were increased in patients of first episode of schizophrenia. Patients with first-episode schizophrenia have global neurocognitive deficits. Independent first-degree relatives also have deficits in some neurocognitive domains. Neurocognitive performance may be viewed as a biomarker for candidates reflecting genetic liability for schizophrenia.[39]

Depression

Neurodevelopmental factors: Any stressful experience (prenatal or maternal traumatic stress or childhood trauma), via a cascade of neurochemical events, alters the microenviromental milieu of the central nervous system (CNS), resulting in altered gene and this new gene results in permanent or structural changes which are associated with sensitisation, learning, memory and developing brain differentiation. According to Gale and Martyn,[40] impaired neurodevelopment during foetal life may increase susceptibility to depression. Other studies have shown relationship between developmental trauma and depressive disorder.[41] New evidence implicates the PFC in addition to the hippocampus as a site of neuropathology in depression. Three patterns of morphometric cellular changes are noted: cell loss (subgenual PFC), cell atrophy (dorsolateral PFC and orbitofrontal cortex) and increased number of cells (hypothalamus, dorsal raphe nucleus).

Neurotrophic factors: Brain-derived neurotrophic factor (BDNF), produced by neurons particularly in the hippocampus and cortex, acts as a neurotrophic factor and is involved in neuroplasticity. In postmortem studies of depressed patients with or without antidepressant treatment it was shown that there was abnormalities in the cyclic adenosine monophosphate (cAMP) signaling pathway, and its downstream neurotrophic factor BDNF, which are major targets of antidepressant medication.[42] Studies on human blood levels show BDNF is low in depressed patients.[43] Low BDNF level may play a pivotal role in the pathophysiology of depression and that antidepressants may increase BDNF in depressed patients.[44] BDNF protects against stress-induced neuronal damage, and it might affect neurogenesis in the hippocampus, which is thought to be involved in the pathogenesis of mood disorders.[45]

Fibroblast growth factor (FGF): They are a family of molecules involved in cell growth stimulation, multiple tissue growth, and in growth that takes place in various stages of life. Dysregulation of several FGF system transcripts may occur in frontal cortical regions of brain from human subjects with major depression.[46] The most significant differences were in levels of messenger ribonucleic acid (mRNA) for one of the FGFs called FGF1 and two receptors, FGFR2 and FGFR3.[46]

Serotonin [5-hydroxytryptamine (5-HT)] receptors

5-HT1A receptor: Almost all the studies point to a decreased or unchanged expression of the 5-HT1A receptor. A functional genetic variant of the 5-HT1A receptor, the C(-1019)G promoter polymorphism, has been investigated in major depression. The G(-1019) allele was more frequent in major depression.[47]

5-HT1B receptor: A cofactor of the 5-HT1B receptor, S100A10 (also termed p11) has been suggested to play a role in depression.[48]

5-HT1D receptor: In a single postmortem study, a higher number of 5-HT1D receptors were found in globus pallidus.[49]

5-HT2C receptor: Two out of four studies found an increased frequency of the serine variant, indicating that this variant may be associated with major depression.

Biochemical markers

Lipids: Cholesterol levels were identified as blood markers for depression and anxiety in a normal population in a primary care setting.[50] Recent evidence has suggested an important role for lipids in the aetiology and treatment of depression.[51] Triglyceride lowering alleviates the symptoms of depression. The connection of hypertriglyceridaemia and depression involves insulin resistance, as the ingestion of high glycaemic food releases insulin which immobilises the modulation of essential fatty acid metabolism, negatively impacting the production of prostaglandins, cytokines, hormones, membrane traffic and brain chemistry.[52]

Electrolytes and trace metals: Subnormal levels of zinc are associated with resistant depression.[53] Numerous studies have found long-term chronic low doses of mercury cause mood problems.[54-56] Mercury inhibits enzymatic processes, effects on cytochrome c oxidase, levels of minerals, affects Th1 and Th2, accumulates in pineal gland.

Folic acid: A consistent finder in major depression has been a low plasma and red cell folate, which has been linked to poor response to antidepressant.[57] In a study by Botez et al.,[58] a close association was noted between folate-responsive neuropsychiatric symptoms and changes in 5-HT metabolism in central nervous system (CNS).

Vitamin B6 and B12: Theoretically a low level of vitamin B6 might cause depression as vitamin B6 is a cofactor in the tryptophan 5-HT pathway. A study conducted by Hvas et al.,[59] suggested a low level of plasma pyridoxal phosphate (PLP) is associated with symptoms of depression. Vitamin B12 is required for transmethylation of neuroactive substances (myelin, neurotransmitters), which is impaired in vitamin deficiency (hypomethylation hypothesis).[60]

G-proteins: G-protein b3 subunit appears to be a susceptibility factor for major depression.[61] The C825T polymorphism was associated with seasonal affective disorder.[62] 825T-allele carriers displayed higher levels of depression.[63]

Hypothalamic-pituitary-adrenal axis: The hypothalamic-pituitary-adrenocortical (HPA) axis stimulating properties of higher angiotensin-converting enzyme (ACE) consecutively higher angiotensin and lower substance P concentrations may be crucial factors for the HPA system hyperactivity during major depressive episodes.[64,65] Cortisol hypersecretion, non-suppression or the dexamethasone suppression test (DST) and blunted thyrotropin response to protirelin are extensively studied. The gene encoding corticotropin releasing hormone binding protein is a functional candidate gene

for major depression. Two single nucleotide polymorphisms were associated with the disease.[66]

Neuroimaging markers

PET imaging studies have revealed multiple abnormalities of regional cerebral blood flow (CBF) and glucose metabolism in limbic structures and the PFC in mood disorders. Regional CBF and metabolism are increased in the amygdala, orbital cortex, and medial thalamus, and decreased in the dorsomedial/dorsal anterolateral PFC and anterior cingulate cortex ventral to the genu of the corpus callosum (subgenual PFC).[67,68]

Structural imaging studies have demonstrated reduced gray-matter volumes in areas of the orbital and medial PFC, ventral striatum, and hippocampus, and enlargement of the third ventricle. Depressed subjects with multiple depressive episodes have hippocampal volume reductions, with an association between illness duration and hippocampal volume.[69]

Immunological markers in major depression

Immune cells: Early studies showed an increase of T-helper cells (CD4 cells) and an increased CD4/CD8 ratio in depressive disorders.

IL-6: Most publications report a marked increase of in vitro IL-6 production or serum IL-6 levels in depressed patients.

IL-2: Data on IL-2 in major depression are mainly restricted to measurements of its soluble receptor in peripheral blood. The blood levels of soluble IL-2 receptor (sIL-2R) were repeatedly found to be increased in major depression patients.[70-2]

Cognitive deficits

Patients with major depression manifest significant impairments in their ability to maintain attention on tasks requiring effortful mental operations i.e. tasks that require selective and sustained attention, or which imply greater sources allocation capacities.[73] Patients with major depression also are particularly impaired on verbal learning and episodic memory tasks.[74,75] Patients with major depression also have widespread executive dysfunctions, including working memory, set-shifting and inhibition processes, even during the euthymic state.[76-78]

Rhythmopathy

Shortened rapid eye movement (REM) latency may serve as a trait marker for depression because it has been found in dysthymia and so called borderline personality disorder, as well as clinically well offspring of adults with major depression.[79] State dependent abnormalities increase phasic REM sleep and poor sleep maintainance.[79]

Biomarkers of alcohol use and abuse[80]

State marker: Biochemical measure that tells clinician something about people's drinking pattern.

Trait marker: Reveal something about a person's inherited risk of abusing alcohol.

Newer state markers: Plasma sialic acid index of apolipoprotein J (SIJ), total serum sialic acid (TSA), 5 hydroxytryptophol (5-HTOL), fatty acid ethyl ester (FAEE), ethyl glucuronide (EtG), acetaldehyde, salsonilol, proteomics.

Gamma glutamyltransferase (GGT): Elevated GGT levels are an early indicator of liver disease; chronic heavy drinkers, especially those who also take certain other drugs, often have increased GGT levels. However, GGT is not a very sensitive marker, showing up in only 30-50 percent of excessive drinkers in the general population.[81] It is not a specific marker of chronic heavy alcohol use, because other digestive diseases, such as pancreatitis and prostate disease, also can raise GGT levels.

Alanine aminotransferase (ALT) is the more specific measure of alcohol-induced liver injury because it is found predominantly in the liver, whereas aspartate aminotransferase (AST) is found in several organs, including the liver, heart, muscle, kidney, and brain. Clinicians often use a patient's ratio of AST to ALT to confirm an impression of heavy alcohol consumption.

Person's volume of red blood cells, also is associated with heavy chronic drinking,[82] as the mean corpuscular volume (MCV) in heavy drinkers tends to exceed the average range. This marker is less useful clinically, however, because the MCV stays high for several months after a person stops drinking.

Beta-hexosaminidase (beta-HEX): An enzyme found to be elevated in heavy drinkers,[83] has been shown in some early studies to be both a sensitive and specific measure of heavy drinking.

Carbohydrate deficient transferrin (CDT) appears to be a highly specific measure of alcohol consumption, showing low rates of false positives.

Researchers became interested in adenylyl cyclase (AC) activity as a potential trait marker when they discovered that AC activity is inherited and the enzyme is less active in the blood platelet cells of abstinent alcoholics than in nonalcoholics.[84] Unfortunately, it appears that marijuana and other drug use also affect AC activity, making it an imprecise marker for alcohol use specifically.[84]

Studies find that people have different levels of GABA and these differences are inherited.[85,86] In addition, studies show that people who are alcohol dependent have lower levels of GABA than do non-alcohol-dependent people. Thus, at least in these preliminary studies, GABA fulfils two of the three requirements of a trait marker for alcoholism.

DA: A recent study[85] found that male alcoholics who had been abstinent for seven years showed a lower level of DA receptor activity compared with nonalcoholic men. Whereas a previous study[87] demonstrated that alcoholics, after a withdrawal period of four to seven days, showed an elevated response to DA, indicating elevated receptor activity.

Studies find that alcoholics have lower levels of beta-endorphin than nonalcoholics, and that children of alcoholics have fewer opioid receptors than children of nonalcoholics. [88-90]

5-HT: The amino acid tryptophan, which influences how

much 5-HT the brain produces, may be decreased in people consuming excess alcohol.[85,91] Research finds natural differences among people in 5-HT transporter activity in blood platelets, and these differences appear to be inherited. In addition, alcoholics who have been abstinent for extended periods of time show higher 5-HT transporter activity than nonalcoholics, as do children of alcoholics compared with children of nonalcoholics.[92]

Alzheimer's disease (AD)

Proposed criteria for effective biomarkers in AD have been described. The ideal biomarker for AD should detect a fundamental feature of neuropathology and be validated in neuropathologically confirmed cases. It should have a diagnostic sensitivity >80 percent for detecting AD and a specificity of >80 percent for distinguishing other dementias; it should be reliable, reproducible, noninvasive, simple to perform, and inexpensive. Recommended steps to establish a biomarker include confirmation by at least two independent studies conducted by qualified investigators with the results published in peer-reviewed journals.[93] It would be especially useful if the biomarker could also capture the beneficial effect of disease-modifying therapy.[94]

Candidate biomarkers in AD

Increased concentration of total and hyperphosphorylated tau protein and a reduction of amyloid β peptide Aβ42 have been reported in CSF of AD patients,[95] with the combination of the two markers capable of further improving the diagnostic accuracy to a sensitivity and specificity of nearly 90%.[96] The level of CSF total t protein (t-t), which includes both normal and hyperphosphorylated t (P-t), seems to correlate with the number of neurofibrillary tangles (NFTs) in AD postmortem brains. [97] Protein t may be phosphorylated at various sites of phosphorylation (P-t 181, 199, 231, 235, 396, and 404). Among these P-t, three can be correlated with the type of NFT involved: (i) pre-neurofibrillary tangles (P Thr231-t); (ii) intra-neuronal neurofibrillary tangles (P Thr381-t); and (iii) extra-neuronal neurofibrillary tangles (P Ser199-t).[98] All three P-t were elevated in the CSF of AD patients. These three measures have similar sensitivity, although P Thr231-t may have somewhat greater specificity for AD.

Isoprostanes are biomarkers of oxidative stress.[99] Isoprostane levels were found to be markedly elevated in both frontal and temporal cortex of AD brains, but not in the corresponding areas of fronto-temporal lobe degeneration (FTLD) brains and controls.[100,101] CSF F-2 isoprostane levels were found to be significantly increased in AD in comparison with FTLD patients.[102] In addition it appeared that the levels were highly correlated with the severity of the disease.[103]

CSF surrogate markers of brain amyloid deposition have been proposed. Like Amyloid Precursor-Protein (APP), Amyloid Precursor like Protein (APLP) undergoes a metabolic processing by secretases. Higher levels of APLP-1-derived peptides have been identified in CSF of AD patients, both in familiar and in sporadic forms.[104] Lower levels of Sortilin-related receptor (SORL1, also known as SorLA or LR11) have been identified in CSF of AD patients compared with cognitively normal controls and have been proposed as a diagnostic biomarker for AD.[105]

Neuroradiological markers

Visual determination of medial temporal lobe atrophy is a reliable instrument to discriminate AD and mild cognitive impairment (MCI) from normal controls and to predict AD conversion in MCI patients. The evaluation of CBF by single photon emission computed tomography (SPECT) has a well-established sensitivity in identifying AD, showing hypoperfusion of temporoparietal regions and posterior cingulus.[106] PET ligands for AD lesions have been identified, such as [(11)C]PIB (Pittsburgh Compound B) that binds specifically beta-amyloid, and [(18)F]FDDNP (2-(1-{6-[(2-[F-18]fluoroethyl) (methyl) amino]-2-naphthyl} ethylidene)malononitrile) that binds both NFTs and beta-amyloid plaques. Longitudinal studies have established that the pathological changes identified with these molecules may occur in preclinical stages of the disease and may be detected earlier than atrophic changes and hypometabolism recognised by FDG-PET.[107] An increased FDDNP binding was specifically associated with episodic memory impairment, while increased PIB retention was associated with a broader range of cognitive impairment.[108]

Peripheral markers

A longitudinal study has found that high plasma levels of Aβ42 were associated with an increased risk of developing AD in subjects without dementia. Besides, conversion to AD was associated with a decrease of plasma Aβ42 levels and of plasma Aβ42/Aβ40 ratio.[109] Higher level of soluble CD40 (sCD40) is found in plasma of AD patients compared with age-matched controls[110] and is able to predict the risk of conversion to AD in a sample of MCI patients.[111] Moreover, the expression of CD40 cognate ligand, CD40L, is upregulated in AD patients and is associated with an increased cognitive decline over the following two years.[112]

Recently an algorithm based on the values of several serum proteins, many of whom are related to inflammation, demonstrated 80% sensitivity and 91% specificity in discriminating AD from controls. The addition of gender, age, education, and ApoE status to the prediction algorithm increased sensitivity and specificity to 94% and 84%, respectively.[113] Other authors have studied the influence of BDNF, and found that its level is significantly higher in serum of AD and MCI patients, compared with healthy subjects, independently of disease severity, treatment with antidepressant or cholinesterase inhibitors.[114]

PKC intracellular signalling

In cerebral tissues of AD patients, protein kinase C (PKC) protein level, activity, and intracellular translocation are altered compared to control brain tissues.[115] In fibroblasts of AD patients, a reduced PKC activity has been described.[116] Inflammatory stimuli, such as bradykinin (BK), determine in fibroblasts of AD patients a PKC-mediated phosphorylation of extracellular signal-regulated kinases (ERKs) 1/2, which is not detected in fibroblasts of age-matched healthy controls.[117] A phospho-ERK1/phospho-ERK2 index, before and after BK stimulation, has been proposed as AD biomarker, being able to discriminate

not only between AD and healthy subjects, but also between AD and non-AD dementia.[118]

A conformational modification of p53 protein, associated with an alteration of its transcriptional activity, has been described in skin fibroblasts isolated from AD patients. This protein misfolding, which can be induced in non-AD fibroblasts by low concentrations of Aβ peptide,[119] results in an increased resistance of the cells to p53-mediated apoptosis; therefore, its involvement in the early phases of amyloid deposition has been hypothesised and its possible use as a biomarker of early AD proposed.[120]

There is an increase of membrane CD44 expression in lymphocytes of patients with AD, in comparison with healthy subjects. CD44 is an adhesion molecule involved in the immune response even inside the CNS, and its increase seems to parallel the rise of unfolded p53 in AD lymphocytes.[121]

Another research approach is related to the study of APP metabolism in platelets, based on data showing functional similarities between platelets and neurons. In particular, it has been shown that platelets isolated from AD patients have a different ratio of APP isoforms, with a lower amount of high molecular weight APP, compared to cognitively intact subjects.

Obsessive-compulsive disorder (OCD)

Significant difference in superoxide dismutase (SOD) levels was observed between the OCD and control groups ($p < 0.05$); SOD has a protective role in overcoming oxidative stress; therefore, oxidative stress could have a pathophysiological role in OCD.[122] Sampaio et al.[123] examines the glutamate receptor, ionotropic, kainate 2 (GRIK2) as a candidate gene for OCD susceptibility in a family-based approach. Probands had full DSM-IV (the fourth edition of the Diagnostic and Statistical Manual of Mental Disorders) diagnostic criteria for OCD. The polymorphism at rs1556995 ($P= 0.0027$; permuted P-value = 0.03) was significantly associated with the presence of OCD. Also, the two marker haplotype rs1556995/rs1417182, was significantly associated with OCD ($P= 0.0019$, permuted P-value = 0.01). The presence of the same deficits in the execution of non-verbal memory tasks in OCD patients and unaffected first-degree relatives and suggests the influence of certain genetic and/or familial factors on this cognitive function in OCD and supports the hypothesis that deficits in non-verbal memory tasks could be considered as cognitive markers of the disorder.[124] Hemmings et al.[125] investigated the role of BDNF in OCD and found a significant association in the male subgroup, with the met66 allele implicated as the risk allele in the development of OCD. This allele was also found to be associated with an earlier age at onset of OCD in males. On the other hand, the val66val genotype was associated with more severe OCD in the female population. Study by Samuels et al.[126] suggests that a region on chromosome 14 is linked with compulsive hoarding behaviour in families with OCD. The following three single nucleotide polymorphism markers on the gene for oligodendrocyte lineage transcription factor 2 (OLIG2) were associated with the OCD without Tourette disorder (TD) phenotype: rs762178 , rs1059004 , and rs9653711.[127] Unaffected first-degree relatives and OCD patient probands showed cognitive inflexibility (extradimensional set shifting) and motor impulsivity (stop-signal reaction times).[128] Deficits in cognitive flexibility and motor inhibition may represent cognitive endophenotypes for OCD.[128] Lower whole blood 5-HT concentration, fewer platelet 5-HT transporter (5-HTT)-binding sites, and higher platelet inositol trisphosphate (IP3) content were found in OCD probands and their unaffected parents compared to controls.[129] It supports a familial origin of these disturbances.[129] These alterations may serve as endophenotypic markers in OCD.[129] Marazziti et al.[130] studied the change in platelet markers after treatment with fluvoxamine versus clomipramine and found the reduction in 3H-imipramine (3H-IMI) binding sites in OCD may be related to the severity of the illness and possibly to a positive response to serotonin re-uptake inhibitors, and might be considered as a state-dependent marker, whereas the phenolsulfotransferase (PST) activity would seem to be a trait of the illness. The CD8+ lymphocytes were significantly increased and CD4+ lymphocytes significantly decreased in OCD patient.[131] Family, twin, and segregation studies support the presence of both genetic and environmental susceptibility factors, and the only published genome scan for OCD identified a candidate region on 9p24 at marker D9S288 that met criteria for suggestive significance.[132] Plasma levels of tumour necrosis factor-alpha (TNF-alpha) were significantly lower ($p = 0.001$) in patients with OCD.[133]

Suicide

Falcone et al.[134] support the use of S100B as an adjunctive biomarker to assess suicidal risk in patients with mood disorders or schizophrenia. Low plasma vascular endothelial growth factor (VEGF) is associated with completed suicide.[135] Tryptophan hydroxylase 2 (TPH2) polymorphism was found to be associated with suicide.[136] This genetic marker may be particularly important in understanding risk of multiple suicide attempts.[136] Dwivedi and Pandey[137] suggest that protein kinase A (PKA) and related signalling molecules may serve as important neurobiological factors in suicide. Banki et al.[138] investigated 141 female psychiatric patients, suffering from major depression, schizophrenia, alcohol dependence or adjustment disorder, for their 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA) and cortisol level in the CSF. DSTs were also performed in 111 cases, and thyrotropin-releasing hormone (TRH)/thyroid-stimulating hormone (TSH) tests in 40 subjects. Fifty-two patients were hospitalised following a recent suicide attempt, 18 of which were made using a violent method. The other 34 attempters took tranquilliser or sedative overdoses. CSF 5-HIAA was significantly lower in violent attempters in all four diagnostic categories. CSF HVA was higher in those taking drug overdoses, but only in depression (and less markedly in schizophrenia). CSF cortisol did not differ among either diagnostic or suicidal subgroups. Dexamethasone suppression was more frequently abnormal in suicidal patients than in nonattempters, and this difference was more important where the overall nonsuppression rate was lower. Maximal TSH response to TRH showed an inverse correlation with CSF 5-HIAA, and it was lowest in the nonattempter group.

Autism

Recent studies have demonstrated that transforming growth factor (TGF)-β1, macrophage chemoattractant protein (MCP)-1, IL-6, IL-8, IL-10, TNF-α and IFN-γ are increased in the frontal cortices of autistic brains. MCP-1, IL-6, IL-8, IFN-γ and TNF-α were found to be significantly increased in the CSF of autistic children. A specific pattern of immune dysregulation that includes elevated T- lymphocyte production of TNF-α and IFN-γ and reduced levels of IL-10 was recently described in colonic, upper and lower small intestine mucosal samples, as well as plasma samples in children with autism and gastrointestinal (GI) symptoms. [139]

Neopterin levels were significantly decreased in the autistic group compared to control blood or urine with oxidative pretreatment. When no oxidative pretreatment was used, urinary neopterin measures were significantly increased in the autistic children. Zoroglu et al.[140] have reported increased thobarbituric acid reactive substances (TBARS) in erythrocytes of patients with autism as compared to normal controls. Malonyldialdehyde (MDA) levels, referred as TBARS, can be measured from the method described by Wasowicz et al. method.[141]

Patients with autism showed decreased activity of glutathione peroxidase (GSHPx) in plasma and in erythrocytes compared with the controls. Reduced levels of total glutathione and lower redox ratio of glutathione reductase (GSH) to oxidised glutathione (GSSG) in plasma and decreased catalase and superoxide dismutase (SOD) activity was also observed.

Sogut et al.[142] have reported increased nitric oxide (NO) levels in erythrocytes of patients with autism and have suggested that nitric oxide synthase (NOS) may be activated in autism. Increased xanthine oxidase (XO) activity has been reported in the erythrocytes of patients with autism. Levels of ceruloplasmin and transferrin are reduced in the serum of children with autism as compared to their unaffected siblings.[143]

The most frequently reported pathology in these studies is a reduction in the normal number of Purkinje neurons, which has been reported when the cerebellum was, observed.[144] Post-mortem studies revealed Purkinje cell loss in the cerebellum and atrophy of the cerebellar folia in autism.[145] The neuroglial activation was particularly prominent in the granular cell layer and white matter of the cerebellum.[146] Amygdala abnormalities consisted of small neuronal size and increased cell packing density predominantly in the cortical, medial, and central nuclei of the amygdala.[147] Relatively small and densely packed neurons were also observed in hippocampal fields CA1–CA4, the subiculum, entorhinal cortex, mammillary bodies, medial septal nucleus, and anterior cingulate gyrus of all the autistic brains.[147] Abnormalities in the ventricles, in particular enlargement of the left temporal horn are particularly found in autistic children.

Autism can represent the main clinical presentation of a mitochondrial disease[148] since mitochondrial disorders often result in CNS dysfunction, leading to developmental regression, learning disability, and various behavioural disturbances. In several studies of individuals with autism, an increased level of ammonia has been reported. Lactic acidosis has frequently been found in association with autism.[149] Lactic acidosis may be secondary to pyruvate dehydrogenase deficiency or mitochondrial respiratory chain defects including co-enzyme Q and cytochrome oxidase deficiency.

Mucosal abnormalities noted in the ileum included granularity, loss of vascular pattern, and patchy erythema (nonspecific colitis). Abnormalities of 5HT metabolism include 5HT transporter, TPH2, tryptophan 2, 3 diooxygenase, 5HT receptor sensitivity and altered 5HT levels as a function of age were observed. The variable response to selective serotonin re-uptake inhibitors (SSRI) medications and atypical antipsychotic medications suggests a role for 5HT in at least some children with autism. Approximately 50% of subjects with autism exhibited significantly elevated levels of HVA in CSF.[150] Glutamate, the primary excitatory neurotransmitter, is elevated in plasma and CSF in many children with autism. Increased expression of the glutamate transporter and polymorphisms in genes encoding metabotropic and ionotropic glutamate receptors are also reported in children with autism. Metabolites of GABA, the primary inhibitory neurotransmitter, may be reduced in many children with autism.[151] Reduced GABA transmission has been associated with hyperkinesis, impaired sleep, seizures, mental retardation, impaired motor coordination, and hyperactivity, which are symptoms commonly observed in autism.

Conclusion

The mere existence of biomarkers in psychiatric illness does not mean we should ignore the cultural, psychosocial, and existential components of our patients' problems, or attribute their psychopathology to biochemical factors alone. Nonetheless, accurate biomarkers, along with more reliable and valid disease criteria, will help psychiatry achieve greater objectivity in diagnosis. Even more promising, biomarkers may soon help us diagnose psychiatric disorders in their earliest stages, potentially enhancing the care of our patients.

Further Reading

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