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ADHD (G KULKARNI, SECTION EDITOR)

Biomarkers for ADHD: the Present and Future Directions

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Abstract

Purpose of Review Attention deficit hyperactivity disorder (ADHD) is one of the most common neurodevelopmental disorders characterized by inattention, impulsivity, diminished executive functions, and hyperactivity. Objective criteria can be used to assess the diagnosis and response of the disease to medications.

Recent Findings Several biomarkers belonging to electrophysiological, genetic, peripheral, and miRNA-based biomarkers have shown promise in studies to be an objective aid to clinical diagnostic criteria for the diagnosis of ADHD.

Summary This review article focuses on summarizing the existing evidence for different biomarkers that have been studied in the past for diagnosing ADHD.

Keywords Biomarker · ADHD · Electrophysiological · Genetic · Neural · Peripheral

Introduction

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder, first described by Sir George F Still, as a condition persisting in children with a problem associated with "moral control" in 1902. This was followed by a neuropsychological study in 1972 that established inattention as a key feature of ADHD [1, 2]. This disorder is characterized by core symptoms of inattention, impulsivity, hyperactivity, and diminished executive functions. It most commonly affects children and adolescents, with 60–80% of these patients having persistence of these symptoms in adulthood [3]. The diagnosis of ADHD emphasizes the presence of symptoms in more than two settings with evidence of a reduction in the quality of social, academic, or occupational functioning after all other psychiatric conditions are ruled out [4].Owing to the subjective nature of the diagnostic criteria, ADHD may be misdiagnosed as any other neurocognitive or neurodevelopmental disorder, thereby causing a delay in diagnosis and treatment [5–7]. This calls for the need of objective markers of the disease that can be used in diagnosis, prognostication, and assessment of response to pharmacological interventions.

A biomarker is defined as "a characteristic that is measured objectively and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacological responses to a therapeutic intervention." [8] The biomarker should have reproducibility, be heterogenous over a large population with a high test-retest reliability, and have high sensitivity and specificity to distinguish those with the disease from those that do not. For ADHD, several biomarkers from the niche of neurophysiology, neurochemistry, neuroimaging, and genetics have been reported in small and moderate studies. This review paper aims to summarize the biomarkers which have been investigated in the past and discusses briefly the challenges with their clinical applications along with future directions.

This article is part of the Topical Collection on *ADHD*

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Electrophysiological Biomarkers

Electroencephalography (EEG) would serve as an ideal biomarker for characterizing neurodevelopmental disorders since it provides us with a direct measure of postsynaptic activity and with a temporal resolution that is greater than functional magnetic resonance imaging (fMRI). It is also more tolerant of the motion artifacts with recordings possible in a more natural

setting for the study of infants and young children [9]. Their noninvasive nature is another advantage that makes EEG-based indices good biomarkers.

Till date, the most robust and stable finding reported in patients with ADHD has been an increase in theta band power (4-7 Hz), notably increased theta relative to beta band power (13-30 Hz) which has been referred to in the literature as "theta to beta" ratio (TBR). First proposed in 1991 by Luber and hypothesized to reflect cortical hyperarousal and slowing [10, 11], TBR quickly gained recognition as a potential electrophysiological marker of ADHD. A meta-analysis by Snyder and Hall in 2006 reported a sensitivity and specificity of 94% for this index in the diagnosis of ADHD [12]. The same group later published an empirical study that reported a specificity of 94%, sensitivity of 87%, and an 89% overall accuracy for ADHD diagnosis [13]. In July of 2013, the US Food and Drug Association (FDA) approved the Neuropsychiatric EEG-Based Assessment Aid Health (FDA,2013), for the assessment of ADHD, which was marketed as "Brain Wave Diagnostic Tool." However, the usage of TBR as a biomarker was questioned by several studies that have rendered this index controversial in its implementation to diagnose ADHD [14–20]. This was also backed by a meta-analysis performed by Arns et al. in 2013 who concluded that increased TBR should not be considered a reliable diagnostic measure for ADHD [21].

Decreased event-related potentials (ERPs) components including the attentional cue and target P300, preparatory contingent negative variation (CNV), and the inhibitory NoGo P300 are considered good markers of ADHD in children and adults [22–26]. A recent study performed a visual stimulus go/no-go task in two groups of age matched adults (75 control vs 75 ADHD) and aimed to investigate the use of ERPs to differentiate adult ADHD patients from nonclinical controls using a classification method originating from machine learning. The study reported that using a tenfold cross-validation approach, the classification accuracy was 91% and showed that ERPs can contribute to the diagnosis of ADHD [27]. A study by Liechti et al. in 2012 showed that the inclusion of ERP markers improved discrimination although they were not diagnostically relevant [28]. These studies show the benefits and power of advanced multivariate methods, which may contribute to the discovery of more reliable electrophysiological biomarkers of ADHD.

miRNA-Based Biomarkers

Genetic factors play a vital role in the causation of ADHD, a disorder that has heritability rates as high as 75–90% [29, 30]. The heritability of the disease is also influenced by epigenetic factors, of which microRNAs (miRNAs) are known to play a key role. They are non-coding RNAs that negatively regulate gene expression in human cells [31] and have emerged as possible biomarkers due to their implicated role in dysregulation of gene expression [32, 33]. It has been predicted that approximately one-third of all the genes in the genome are directly targeted by miRNA, and they play a vital role in the central nervous system where they are involved in neuroplasticity as well as development [34]. Owing to their contribution to the development and functioning of the central nervous system, miRNAs have been implicated in several psychiatric and neurological disorders [35–37].

Earlier in the decade, animal studies have reported that miRNA target gene—Homer 1a is associated with phenotypes of ADHD models [38•, 39–42]. Early human studies, although focused on the domain of genetics and genomics, focused on the role of gene polymorphisms within miRNA and miRNA target sites in ADHD pathogenesis [38•, 39–42].

In human studies, lower levels of miRNA 18a-5p, 22-3p, 106b-5p, 24-3p, and 107 have been observed, whereas miRNA 155a-5p and miRNA let-7d were reported to be higher in individuals with ADHD [43, 44]. In 2010, miRNA let-7d was reported by Wu et al. to be overexpressed in the prefrontal cortex and was reported to target galectin-3, leading to a downregulation of tyrosine hydroxylase which plays a key role in dopamine metabolism as well as ADHD development [45]. A common denominator in all the above-mentioned studies is that the selection of candidate miRNA relied heavily on mechanisms implicated in the etiopathogenesis of the disease rather than screening for genes at a global level. This disadvantage was avoided in a recent study conducted by Wang et al. where they used next-generation technique sequencing (NGS) to create a pooled patient library from controls and ADHD-affected patients and found 13 potential miRNA ADHD biomarkers which were efficient in differentiating ADHD-affected individuals from healthy controls with sensitivity and specificity of 86.8% and 88.9%, respectively [46••]. These 13 miRNAs had not been reported to be involved in the pathophysiology of ADHD previously, which favors the argument of conducting studies that search for implicated miRNA biomarkers globally rather than in a preselected fashion based on previously published literature and etiopathological mechanisms implicated in ADHD.

Genetic Biomarkers

The dopamine transporter gene (DAT1 gene) has been linked to the etiopathogenesis of ADHD with many studies on knockout mice for DAT1 showing deficits in inhibitory behavior and hyperactivity. The same gene has also been mapped near a susceptibility locus for ADHD, i.e., 5p13 [47, 48]. Along with this, methylphenidate and amphetamine, which are drugs used to manage ADHD, are known to bring

about their effects by targeting the DAT1 protein. The most studied variant of DAT1 is variable number tandem repeats (VNTR) of 40 base pairs located at the 3′ untranslated region (3′-UTR) of which 10 repeat (10R) and 9 repeat (9R) alleles are the most common [49]. A recent meta-analysis showed a positive association between 10R allele and ADHD in the pediatric population, although a reverse association is shown to be present for adults [49, 50]. Studies have shown an association between higher commission errors, increased reaction time variability (RTV), and increased impulsive responses in continuous performance test (CPT) and sustained attention to response test (SART) with 10R allele, although there are other studies which show no or opposite association [51, 52]. Some pharmacogenetic studies have also shown increased response to methylphenidate among homozygous 10R, while others have conflicting results [53, 54]. A more recent meta-analysis showed that VNTR polymorphism is not a reliable predictor of MPH treatment success in ADHD patients [55]. A DAT1 VNTR at intron-8 containing 5R and 6R alleles has also been associated with increased susceptibility of ADHD [49]. Other variants such as rs6350 have been reported to be associated with alerting and executive control performance on the attention network test [56]. Another haplotype, 9rs403636(G)/rs463379 (C)/ re393795 (C)/rs37020 (G)), has been reported to be associated with spatial working memory in ADHD [57].

Located on chromosome 11p15.5, the DRD4 gene has a high expression in the anterior cingulate cortex, which is associated with attention and inhibition and thereby also implicated in ADHD [58]. This association is further backed by an earlier study that reported lower mRNA expression levels of DRD4 in ADHD [59]. A highly polymorphic functional VNTR comprising of 11 copies of 48 bp repeat sequences has been studied, and the 7R allele was reported to be associated with ADHD [49, 60]. Other papers have emphasized the association of the 7R allele with processing speed, cognitive impulsiveness, and set-shifting but not with response inhibition [61, 62]. Pharmacogenetic studies have also reported an enhanced response to methylphenidate in 7R carriers even though other studies contradict this finding [53, 54]. Another interesting aspect that was found regarding this issue is that different DRD4 genotypes exhibit different methylphenidate response curves [53, 54]. There have been other variants in the promoter region that have been studied, including the − 521 C/T (rs1800955), 120 base pair duplication (120-bp dup) located in the 5′ untranslated region but showed no association with ADHD [49, 60].

The DRD2 gene is located on chromosome 11q23.1 and is known to be expressed profoundly in brain areas relevant for regulation of mesolimbic pathways and the other regions known to be associated with ADHD [63]. A genome-wide association study reported a nominal association of ADHD susceptibility with this gene [64]. There are three variants that have been studied in association with ADHD—rs2075654, rs10795696, and rs1800497. Higher commission errors have been associated with rs207654 and rs1079596 variants [61], whereas the study trying to find a relation of MPH response with rs1800497 showed no association [65].

The DRD5 gene is located on chromosome 4p15.3 and has been reported to be expressed in high concentration in the hippocampus, a brain area implicated in the pathogenesis of ADHD, and functionally affects synaptic strength in memory formation [66]. Studies have also reported that the 148 bp allele is associated with omission errors, commission errors, RTs, and RTVs [67]. Although no association was found between 148 bp allele and methylphenidate response, the 151 bp allele has been linked to a favorable response [68].

The SLC6A2 codes the norepinephrine transporter and is targeted by one of the medications from the non-stimulant class—atomoxetine—while the NET1 is a gene that is highly expressed in the frontal lobe where it is involved in dopaminergic and noradrenergic reuptake [69]. A genome-wide association study reported a frequently located SNP—rs5569 on exon 9 to have a nominal association with ADHD [70]. Another such study reported two SNPs in the SCL6A2 gene to be associated with methylphenidate response and rs3785143 to be associated with atomoxetine response [71, 72].

Peripheral Biomarkers

One of the most studied protein lines includes the neurotrophins, which are a group of growth factors that are known to play a key role in several psychiatric disorders, including anxiety disorders, major depressive disorder, bipolar disorder, schizophrenia, and autism spectrum disorders [73–79]. The brain-derived neurotrophic factor (BDNF) is found primarily in the central nervous system and is distributed throughout the brain and peripheral blood. Several studies have reported increased circulating levels of BDNF in patients with ADHD and have also shown an association between BDNF gene polymorphisms and ADHD [80–82]. Many studies also reported increased levels of BDNF in patients after being started on treatment with methylphenidate and a decrease in their levels when started on atomoxetine [83, 84]. Animal studies also back the role of BDNF in characteristics that are a key feature of ADHD, including aggression, learning deficiency, and increased locomotion activities [85, 86]. However, there is another set of studies that show no association of BDNF levels with ADHD [87, 88]. Another member of the neurotrophin family is the glial-derived neurotrophic factor (GDNF), which plays a pivotal role in the maintenance and survival of dopaminergic and serotonergic neurons by its actions against oxidative damage and neuroinflammation [89]. Functionally, it is known to be an integral component

of learning and memory-related functions [90]. Although evidence reports that no association exists between ADHD and GDNF levels, a recent study in children reported higher levels of circulating GDNF levels in children with ADHD as compared to controls [91••]. Neurotrophin growth factor (NGF) which is known to play a vital role in learning processes and the executive control of attention [92, 93] has been reported to have a borderline significant association with its polymorphisms and ADHD in a family-based sample [94]. Neurotrophin-3 (NTF3) plays a critical role in dopaminergic neurons, noradrenergic neurons, and glutamatergic neurons in the mesolimbic pathways, locus coeruleus, and hippocampal areas, respectively [95]. Polymorphisms involving NTF3 have been reported to be associated with selective attention deficits in ADHD, with a recent study backing the role of NTF3 in ADHD by endorsing a relationship between the adverse emotional effects of methylphenidate in the pediatric population with ADHD and the NTF3 genotype [96•]. A relatively recent study by Bilgic et al. in 2016 also reported elevated levels of GDNF and NTF3 levels in children with ADHD [97].

A key pathogenic factor that has been implicated in the etiopathogenesis of ADHD is the disturbance of neurotransmitter systems in ADHD [98–102]. Noradrenaline and dopamine deficiency in the prefrontal cortex, putamen, striatum, and limbic regions of the brain were found in patients with ADHD [103–108]. This was followed by a study that reported a two-and-a-half-fold increase in levels of glutamate with relative GABA deficiency in the frontal lobe of ADHD patients [109]. These initial studies were complemented by studies involving disturbances of amino acid and their metabolites, which was first reported by Hoshino et al. in 1985 and reported increased plasma concentration of tryptophan in patients with ADHD [110]. A recent study by Dolina et al. studied pyridoxal phosphate-dependent tryptophan degradation and obtained concentration of compounds formed and metabolized in the pathway of tryptophan degradation and the ratios between these compounds. The group reported low values of 4PA (4-pyridoxic acid)/TRP (tryptophan), IND (indole)/TRP, and IND/KYN (kyneurine) ratios in patients with ADHD, which did not change despite treatment with Ritalin [111••].

A recent study also hypothesized an association between inflammation and its contribution to the etiopathogenesis of ADHD by measuring cytokines and reported increased levels of proinflammatory cytokines and finding cytokine gene polymorphisms in patients with ADHD [112]. A study by Oades et al. reported a high but nonsignificant increase in cytokines, including interleukin 6, interleukin 10, and interferon-gamma [113]. Another study reported increased cytokines with certain symptoms of ADHD, viz., increased interleukin 16 with hyperactivity and interleukin 13 with inattention [114]. This association between inflammation and its role in the pathogenesis of ADHD was strengthened by a study conducted in Turkey by Avcil who reported higher values of neutrophil-lymphocyte ratio (NLR), monocyte lymphocyte ratio (MLR), platelet lymphocyte ratio (PLR), and mean platelet volume (MPV) in patients with ADHD as compared to healthy controls in the study [115].

Conclusion

This review summarizes the biomarkers for ADHD that have been reported in the literature for diagnosis and the response of patients to pharmacological interventions. Although our review article attempted all of the well-studied biomarkers, there might be some that escaped our mention. A common trend noticed in this respect is the fact that with each of these biomarkers, there can be some confounding factors that can lead to elevations or reductions in the level of the biomarker in question. With the onset of the "omic era" and the continuous evolution of machine learning and artificial intelligence, the future of biomarker discovery is promising. The need for a worldwide database that would integrate and store all known patterns of biomarkers that have been assessed in the past would prove to be very useful in the diagnosis of ADHD and its response to drugs.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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