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ORIGINAL ARTICLE

A potential diagnostic blood test for attention deficit hyperactivity disorder

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Abstract Diagnosis of attention deficit hyperactivity disorder (ADHD) in children, adolescents, and adults remains controversial. Dramatic growth in the diagnosis of this disorder in both young people and adults has focused criticism on the subjective nature of the diagnostic procedure. A new blood test that measures blood cell membrane potential (expressed as membrane potential ratio [MPR™]) has been recently developed. The current study was performed to explore the potential utility of this blood test in diagnosis of ADHD. Consecutive outpatient children ($n = 89$), adolescents ($n = 18$), and adults ($n = 89$) diagnosed with ADHD, or not ($n = 60$, 17, and 92, respectively), provided sample in which the blood test was performed. ADHD subjects were relatively depolarized with an MPR™ of 0.804 ± 0.0381, compared to non-ADHD subjects, 0.684 ± 0.0260 ($P < 0.05$). The sensitivity is between 0.75 and 0.9, depending on the definition used, and the specificity is 0.75. MPR™ appears to be a viable potential diagnostic tool for ADHD. Larger studies utilizing standardized diagnostic procedures, taking into account medications and comorbidity, and exploring variables such as age and gender are warranted.

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Introduction

The diagnosis of attention deficit hyperactivity disorder (ADHD) appears to be increasing in children in the United States. According to the National Survey of Children's Health (NSCH), which was performed in 2003 and again in 2007, parents' report of children with ADHD increased from 7.8 to 9.5%, an increase of 21.8% over 4 years (Centers for Disease Control 2010). Approximately two-thirds of children with ADHD continue to have impairing symptoms into adulthood (Kooij et al. 2010). Adults tend to continue to have the inattention but lose the hyperactivity (Kessler et al. 2010). Additionally, there are individuals who meet criteria for inattentive ADHD, as adults who do not meet criteria for childhood ADHD (Kessler et al. 2010). But adult ADHD may be underdiagnosed (Knutson and O'Malley 2010). The absence of objective laboratory-based tests for the diagnosis of ADHD makes diagnosis more problematic, particularly in adults (Haavik et al. 2010).

On the other hand, there is an explosion of inappropriate diagnosis of ADHD, particularly on college campuses (Diller 2010). Malingering attentional problems may be easy to do (Sollman et al. 2010; Harrison and Edwards 2010), and malingering may be an increasing problem among college students (Harrison and Edwards 2010), increasing the need for an objective, laboratory-based test.

Diagnosis of ADHD is further complicated by comorbidity (Haavik et al. 2010). As many as 5.4% patients with major depressive disorder and 17.6–18% subjects with bipolar illness have comorbid ADHD (McIntyre et al. 2010; Bernardi et al. 2010). Comorbid ADHD increases

disease burden (e.g., earlier age of onset of mood disorder or increased comorbidities with anxiety disorders) and lowers quality of life (McIntyre et al. 2010). Among children, the problem may be even bigger. For example, as many as 85% of children with bipolar disorder also have ADHD, and up to 22% of children with ADHD have bipolar disorder (Singh et al. 2006), making the distinction difficult.

ADHD appears to be heritable (Bomovalova et al. 2010), with some interesting candidate genes being identified (Domené et al. 2011; Ribasés et al. 2010). However, there is also a significant environmental impact on the expression of ADHD (Swing et al. 2010). Since the genetic variability is likely to be high in ADHD (Neale et al. 2010), the approach most likely to lead to an objective, laboratory-based diagnosis would be one that captures the final common physiologic pathway of the illness.

Recently, Thiruvengadam and Chandrasekaran (2007) reported the results of the initial clinical trial for evaluating the validity of using membrane potential of blood cells, expressed as the membrane potential ratio (MPR™), as a diagnostic tool for bipolar disorder. This initial trial found a sensitivity of 0.78 and a specificity of 0.88 of the MPR™ in diagnosing bipolar I disorder. In the initial study, it appeared that subjects with ADHD could be distinguished from other patients. That observation led to the current exploratory study: Might the MPR™ also identify ADHD? The results of this trial are presented in this paper.

Table 1 Demographics of patient population (Children 8.9 ± SD 2.56; teenagers 16.3 ± 1.85; adults 41.8 ± 12.57 years)

Age group	Gender/ethnicity	ADHD	Bipolar	Negatives
Adult	AF	1	1	3
	AM	0	1	3
	BF	4	8	10
	BM	1	1	6
	HF	4	0	2
	HM	5	0	3
	WF	74	25	65
	WM	44	10	59
Children	AF	0	0	0
	AM	0	0	0
	BF	0	0	1
	BM	1	0	0
	HF	0	0	0
	HM	1	0	0
	WF	1	2	2
	WM	3	1	3
Teens	AF	0	0	0
	AM	0	0	0
	BF	0	0	1
	BM	1	0	0
	HF	0	1	1
	HM	0	0	0
	WF	3	4	3
	WM	9	5	7
	Total	148	59	169

AF Asian Female, *AM* Asian Male, *BF* Black Female, *BM* Black Male, *HF* Hispanic Female, *HM* Hispanic Male, *WF* White Female, *WM* White Male

Methods

MPR™ measurement

The methods employed in the current study have been previously reported (Thiruvengadam and Chandrasekaran 2007). Briefly, whole blood cells were incubated in a reference buffer and in a test buffer separately. The reference buffer contained all ions including sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) along with glucose and HEPES. The test buffer contained ethacrynate in addition to these salts, but not K^+. A lipid-soluble fluorescent dye, dihexyloxacarbocyanine iodide [DiOC6(3)], was used for measuring the membrane potentials in a plate reader. The ratio of membrane potential in K^+-free buffer to that in the reference buffer was called membrane potential ratio (MPR™) and was used as the diagnostic parameter. The analyses were performed in a blinded fashion.

Participants

All the patients in this study came from the private practices of clinical psychiatrists with many year of clinical experience located in the greater Baltimore metro area. Patient population included both children and adults (Table 1). Patients were recruited consecutively. Bipolar patients were included as a "positive control" since the MPR™ recognizes bipolar disorder. No patients with comorbid bipolar and ADHD were included in this preliminary study. All subjects or their guardians signed an informed consent, and underage subjects provided assent.

Diagnostic procedure

Clinical diagnoses were assigned after reviewing all available information, including some combination of data from medical records, other assessment tools, clinical interviews with the patient and relatives, and treatment response. The clinical diagnosis was used for our analyses of specificity and sensitivity. Diagnoses followed diagnostic criteria of the Diagnostic and Statistics Manual, 4th edition. Additionally, the World Health Organization's

Adult Self-Report Scale (ASRS) screen was used for ADHD subjects (Barkley 1998; Kessler et al. 2007).

Statistical analysis

ANOVA was used to examine the differences in MPR™ among ADHD, biopolar, and non-ADHD/non-bipolar subjects (Dawson and Trapp 2004). Logistic regression was used to assess the predictive power of the membrane potential ratios for the various diagnoses. A binomial logistic regression model can be used to calculate the probability that the patient is either BPD I or ADHD (Tabachnick and Fidell 2001). Examination of subsamples (e.g., divided by age or sex) was not performed since such samples would not have adequate power for clear statistical evaluation.

Results

The study included 128 children, 35 teenagers, and 213 adults. The ethnicity and gender covered a range prevalent in North America (Table 1). Bipolar I subjects ($n = 59$) were relatively hyperpolarized with an MPR™ of 0.601 ± SD 0.0213, ADHD subjects ($n = 148$) were relatively depolarized with an MPR™ of 0.804 ± 0.0381, compared with non-ADHD/non-bipolar ($n = 169$), 0.684 ± 0.0260. All 3 groups were significantly different from each other ($P < 0.05$) (Fig. 1). Subjects without bipolar I illness or ADHD had diagnoses of schizophrenia, various types of depression and anxiety, or no psychiatric illnesses. The sensitivity of the MPR™ for ADHD, that is its ability to correctly identify subjects with ADHD in the test population, was very high at 0.9, when we used a standardized assessment (the World Health Organization's ADHD screener), but lower, when we used clinical diagnosis following DSM-IV criteria at 0.75. The specificity, or the test's ability to accurately distinguish ADHD from non-ADHD, was reasonable at 0.75. For comparison, the sensitivity and specificity for bipolar I disorder are 0.93 and 0.90, respectively.

Discussion

The current state of clinical diagnosis in psychiatry is in some disarray. Diagnostic stability over time is generally low (Baca-Garcia et al. 2007a, b; Jakobsen et al. 2007). In patient diagnoses and severe psychotic diagnoses tend to be more stable (Baca-Garcia et al. 2007a, b). Bipolar diagnoses tend to remain consistent over a 12-year period in only about 49% of patients (Baca-Garcia et al. 2007a). Subtypes of attentional disorders will change 50% of the

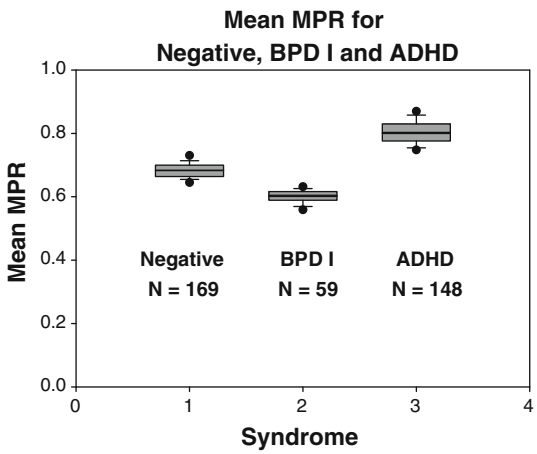

Fig. 1 MPR™ of ADHD and controls. A total of 148 subjects with ADHD and 148 controls patient samples are shown. There were 148 negatives (including schizophrenics, unipolar, obsessive compulsive disorder, and other anxiety disorders), 59 bipolar I, and 148 ADHD samples. Statistical analysis using the ANOVA test shows that the three groups are significantly different from each other with a $P < 0.001$. The data are presented in *box plots*. The *bottom line* of the *rectangular box* represents the 25 percentile of the data population, while the *top line* of the *box* represents the 75 percentile. The *lines inside the box* represent the mean values. Similarly, the *bottom cross line* represents the 5 percentile, and the *top cross line* represents the 95 percentile

time (Valo and Tannock 2010), but the diagnosis of adult ADHD appears to be stable for at least one year (Sitholey et al. 2010). Clinical diagnoses may resemble outcome of structured diagnostic interviews, but show variability across geographic location (Steiner et al. 1995) and are less concordant in non-psychotic individuals (Shear et al. 2000). The gold standard of consensus diagnosis in the setting of a structured interview (Nurnberger et al. 1994) is too cumbersome to be used in any settings other than well-funded research. Improving diagnosis is an imperative in psychiatry.

Diagnosis of ADHD is difficult due to several factors (McIntosh et al. 2009). Firstly, symptoms required for the diagnosis are frequently present in other psychiatric conditions with which ADHD may be comorbid (McIntyre et al. 2010; Bernardi et al. 2010; Zepf 2009; Barkley et al. 2002). But increased vigilance by the clinician may not be the answer since ADHD is easy to feign (Sollman et al. 2010), and an increasing number of people are doing so (Harrison and Edwards 2010). In the current study, subjects with ADHD were correctly diagnosed in 75–90% of patients with ADHD (75% as defined by DSM-IV and 90% as defined by the World Health Organization's ADHD screener).

It is important to understand that the current study was an exploration of the potential utility of the MPR™ in the diagnosis of ADHD. This study was not meant to determine whether MPR™ is a true diagnostic test for ADHD.

Validation of a diagnostic test requires a much larger study that utilizes standardized "gold standard" diagnostic procedures and control for concomitant medication used. The current study is a necessary initial step to determine whether further investment is warranted.

The current study utilized a mixed outpatient clinical sample to distinguish ADHD subjects from other symptomatic patients. The utilization of an ill control sample was important in this exploratory phase to help define the actual utility of the MPR™ test in a real-world setting. Utilization of this methodology suggests that the MPR™ may be useful for the diagnosis of ADHD. Assuming that the clinical diagnoses are accurate, the sensitivity and specificity of the MPR™ for ADHD were 0.9 and 0.75, respectively.

It is not clear why subjects with ADHD have a relatively depolarized cellular membrane potential on the MPR™. Ionic regulatory dysfunction has not been widely recognized as a biologic abnormality in ADHD. However, recently a family with ADHD-like symptomatology was discovered to have an aberrant sodium/hydrogen counter exchange pump (de Silva et al. 2003). Interestingly, methylphenidate treatment is associated with an increase in brain sodium pump activity in animals (Scherer et al. 2009). This finding may suggest that there is unrecognized ionic dysfunction in ADHD, or that medications may have impacted the results of the current study. Medication type or dosage was not gathered in the current study, so an examination of results as a function of medication cannot be assessed. However, an increase in sodium pump activity would hyperpolarize the membrane potential of cells (El-Mallakh and Wyatt 1995), the opposite of the depolarization observed here.

There are clear limitations to the current study. The first among these is the use of clinical diagnoses, rather than a standardized research diagnosis. As previously noted, clinical diagnoses can be problematic with over- and under-diagnoses, and inconsistency of diagnosis over time (Baca-Garcia et al. 2007a). However, the high sensitivity and specificity of the MPR™ test in a clinical population is notable. Nonetheless, prior to widespread application, the MPR™ test must be tested in a population defined by the gold standard consensus diagnosis and supporting psychological testing. Additionally, many of the subjects were treated with medications. Medications may alter the membrane potential of cells and contribute to the relative depolarization of the MPR™. Thus, future studies must focus on the possible effects of medications on the MPR™. Finally, in this study, patients with comorbid ADHD and bipolar illness were not studied, given that the MPR™ for the two frequently comorbid disorders is in the opposite direction, examination of subjects with coexisting bipolar and ADHD is required.

Conclusions

Despite these limitations, the MPR™ test offers significant promise as a potential diagnostic blood test for ADHD. In this exploratory trial, sensitivity and specificity of 0.9 and 0.75, respectively, compare favorably with other tests used to diagnose complex diseases such as antinuclear antigen for systemic lupus erythematosus or prostate specific antigen for prostate carcinoma (Thiruvengadam and Chandrasekaran 2007). Future work with this blood test is required to determine its true clinical utility. Future experiments will require utilization of an objective standardized diagnostic procedure, cross-validation with psychological testing, examining the effect of medications, and examining the effect of comorbid psychiatric conditions.

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Conflict of interest Dr. Woodruff is medical director for PsychNostics, Dr. Thiruvengadam holds the patent for the TMP™ and is president of PsychNostics. Dr. El-Mallakh does not have a relevant conflict of interest to report.

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