Effects of a Rich Emotionally-Satisfying Childbirth Experience of Mothers on Their Later Parental Attitudes and Behavior in School-Age Children

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This study examined the effects of a rich, emotionally-satisfying childbirth experience (CBE) of mothers on the behavior of school-age children using longitudinal data measured from immediately to 7 years and 6 months after birth. The results of structural equation modeling revealed the following: 1) giving birth in a midwifery center enhances emotional satisfaction with CBE, 2) a rich CBE of mothers was associated with parental warmth, 3) parental warmth during early childhood increased prosocial behavior and reduced behavioral problems in school-age children, and 4) temperamentally difficulty in early childhood were linked to later behavioral problems in school-age children. Thus, a rich CBE and parental warmth were suggested to be factors contributing to the good behavior of school-age children.

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ADHDの診断と治療に求められるバイオマーカーとは：Status quo & Potentialities

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抄録：注意欠如/多動性障害（ADHD）診療に有用なバイオマーカーとして現在，認知機能検査，コンピューターを用いた認知行動検査，脳波検査，fMRI・NIRS等のニューロイメージング検査が臨床場面で活用されている。これらはADHD適応薬の投与前後における病態把握，薬効評価に役立つものである。一方，ADHDの原因遺伝子は未だ不明であり，確定診断や病態評価のために必要な‘真のバイオマーカー’と言うべき分子は同定されていない。現状のバイオマーカーによる病態把握を綿密に行いつつ，患者個人のオーダーメイド治療を発展させるというアプローチとともに，分子生物学的な基盤に立ったバイオマーカーの検出，ニューロイメージングによる病態評価，そして新たな治療法と予防法の開発が今後期待される。そしてADHDの生物学的病態を反映すると思われる胎生～乳児期脳発達に視点を移した研究は，ADHDの具体的・客観的診断治療法開発につながる可能性がある。

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Ⅰ．はじめに——バイオマーカーとは？

病気に役立つバイオマーカー（生物学的検査指標；生物指標物質）として広く使用されているものに「腫瘍マーカー」がある。代表的なものとして血中に含まれるAFP（α–fetoprotein）があり，この物質は胎児の血清中にみられるタンパクの一種で，出生後は消失する。しかし肝細胞がんに高い特異性をもつ[16]ことから，①腫瘍診断の指標となり，かつその後の外科手術・抗がん剤治療といった②治療効果の指標としての性格を備えている。加えて，血中に存在するタンパク質であることから，採血により③簡便にかつ経時的に測定することが可能で，臨床の現場に適した優れたバイオマーカーと言える。つまり，バイオマーカーは，疾患の存在や病勢を反映する客観的指標であり定量性が求められ，現場に普及するためには経済性，利便性も必要となる。生体由来の物質・指標単位としてバイオマーカーは，ゲノミック（遺伝子），メタボロミック（代謝物質），プロテオミック（タンパク），イメージング（パターン，機能計測あるいは画像など）の4つに区分できる。

注意欠如/多動性障害（ADHD）を含む発達障害の診療において，これら①診断指標，②治療効果判定，③簡便性の三大特性を兼ね備えたバイオマーカーは，現在のところ残念ながら存在しない。とくに，ADHDの診療に使用されるバイオマーカーの多くは，診断指標あるいは治療効果判定のいずれかを補助する目的で使用され，簡便性

What types of biomarkers are required for diagnosis and treatment of ADHD?—Status quo & Potentialities.

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に関しても短時間で終わる採血データのようなものは存在しない。上記の四区分で言うならば，様々な指標，様式が医学・心理学・認知心理学領域で紹介され，測定指標は遺伝子から脳機能計測と幅広い。例えば，モノアミン系受容体遺伝子多型のパターンやウェクスラー系知能検査（WISCなど）の下位項目が単独，あるいは複合して検討され，診断指標・治療効果判定に重要な役割を果たしている点も，一般的な疾患アプローチと大きく異なっている。

この背景には，ADHDの根本病態がいまなお不明であること，症状のリストをまとめた症候群としての理解に留まっていることに加えて，科学的な理解が進んでいない「発達期の脳」という生理システムを対象としていること等があげられる。これまで選択されたバイオマーカーは，病態推測にとどまっている点が影響しているであろう。一方で，脳機能の全般的な変性退行を示す疾患「アルツハイマー型認知症（dementia of Alzheimer type：DAT）」の病態過程はamyloidpathyであると説明され，アミロイドベータといった原因物質が特定されている。そのため診断と薬効評価パラダイムがバイオマーカーベースになりつつある。すなわち原因タンパクを実際に計測するためのPETプローブが開発され，イメージング（画像診断）により「診断，治療効果判定」を行うことが可能となりつつある[1]。

今後，ADHDの病態が上記DATのように明確になり，その発生機序に関わる遺伝子群が解明されれば，脳内の特定タンパクの機能を何らかの形でモニタリングすることにより，3つの特徴「診断指標，治療効果判定，簡便性」をもつ優れたバイオマーカーを4つの区分それぞれで見つけだせる可能性は残されている。本稿では現時点でADHDの診療に既に開発・利用されているバイオマーカーを概観し，その有用性と限界について考えてみたい。

Ⅱ．ADHDを診断するバイオマーカー

我が国ではADHD治療薬として徐放性methylphenidate製剤が2007年10月に初めて承認され，atomoxetine製剤は2009年4月に製造販売が承認された。小児期におけるADHDに対してこれら2種類の適応薬を得て，急速に展開しつつあるADHD医療ではあるが，その診断の基本はDSM-IV-TRやICD-10の定める行動的な判断基準にもっぱら従っている。ADHDは不注意，多動，衝動性の行動異常により定義され，その量的異常と経過，様々な場面における困難性の共存によって診断されている。しかし症状の程度を客観的に示す測定方法は確立しておらず，主治医の経験に基づいた主観的判断がなされることが多い。医学的判断を援助するバイオマーカーとして知られるものに，「認知機能検査」「コンピューターを用いた認知行動検査」「ニューロイメージング」等が現在使用されている。以下にそれらを説明していく。

1．認知機能テスト

DSM-IV-TRやICD-10といった診断基準を補助する比較的簡便な検査が医療現場に導入され，これらの検査がADHDを診断する実質的なバイオマーカーとして機能している。具体的には，知能検査（ウェクスラー式知能検査），Wisconsin Card Sorting Test（WCST），Iowa Gambling Task（IGT）などの認知機能検査が利用されている。これらの検査は，基本的にADHDの病態に関する実行系機能と報酬系機能の障害仮説（CSTC：cortico-striato-thalamo-cortical回路の機能低下仮説）に基づき，注意機能をはじめ実行系機能と報酬系機能の評価を目的としている。この仮説は，Sonuga-Barkeらが2003年に発表[20]したもので，これまでの報告からADHD児においては，各種検査で「注意・実行系機能」を反映する項目の点数が低く[9,13]，「報酬系機能」を反映するように実験条件を設定したIGTの項目でADHD児に特徴的な反応が認められることが明らかになっている[2,8]。

2．コンピューターを用いた認知行動検査

ADHDの症状を評価する簡便で客観性が高いものとして持続作業課題（Continuous Performance Test：CPT）があげられる[15]。本特集でも辻

井，山田らが取り上げている（p899–904，905–910）ので参照していただきたい。我々の施設では，「モグラーズ」（のるぷろライトシステムズ）をこれまでよく用いている[5]。この「モグラーズ」は子どもが楽しく遊べるモグラたたきゲームをコンピューターでコントロールしてモニター画面に提示させるものである。画面にサングラスをかけたモグラとかけていないモグラのどちらかが１匹現れては消える仕掛けになっている。通常は，出現頻度を各々50％として，サングラスをかけたモグラが出た時にキースイッチを押すことを被験者に求める課題である。我々の施設では５分間持続してモグラを提示しているが，ADHDの子ども達も喜んで施行できる点が特徴である。

モグラが画面に現れる場所・時間がランダムになるように設定すると，つられて違うタイミングでスイッチを押してしまうという行動を誘発しやすくなる。このモグラーズおよび同様の注意持続課題（たとえば，Test of Variables of Attention：TOVA）を用いた研究において，ADHD児においては健常児に比べ低い正答率，長い反応時間が報告されている。この注意持続課題は薬剤の治療効果をよく反映することも知られ，①診断指標，②治療効果判定の両方を反映できる優れた検査方法である。我々の施設でまた，オドボール課題での視覚性事象関連電位検査における単一波形P300も病態把握に有用であることを報告している[19]。

3．ニューロイメージング

近年の画像診断技術のめざましい発展にともない，脳の構造を計測できるMRIはADHD児における脳の解剖学的特徴を明らかにするための有力なツールとして注目されている。ADHD児においては大脳基底核や小脳の形態異常（尾状核や淡蒼球，小脳の体積が健常児に比べ小さい）や前頭前野の形態異常も見つかっている。また，ADHDの患者では，ドパミン神経が投射する多くの脳部位（主に前頭皮質や前部帯状回皮質）の形態的，機能的異常が見つかっている[17,21,22]。

Ⅲ．ADHDの治療効果を判定するバイオマーカー

現在，ADHDの治療効果を判定する確立したバイオマーカーは存在しない。しかし，これまでに治療の前後でADHD児が障害をもつとされる脳の前頭葉機能を評価し，治療効果を判定しようとする試みがなされている。

1．fMRI検査

現時点でADHDを対象とした脳機能を測定する手法として秀でているのは，非侵襲的で空間分解能が高いfMRIと言える。ADHDの衝動性といった脳の実行機能を測定するために，Stop-signal課題[12]やGo/No Go課題[14]を使用したところ，fMRIにて前頭前野・帯状回前部・小脳における活動低下が多くの研究で確認されている。しかし，小児へのfMRIの適用はハードウェア，ソフトウェアの点で克服するべき問題は多く，体動が多いADHD児に対しては，撮像法や解析法の一層の進歩が必要であろう。

2．近赤外線スペクトロスコピー（NIRS）による検討

fMRIに比べて比較的簡便な検査法は，脳血流を測定する近赤外線スペクトロスコピー（NIRS）であり，魅力的な評価法である。NIRSを用いて前頭葉認知機能検査を実施した際の血流変化を測定し，ADHDの診断治療用マーカーとしての使用が試みられている。我々の開発した新規Go/No Go課題では，定型発達児群に比べADHD群では，前頭前野の血流が増加せず，ADHD児群では前頭前野の機能不全が存在することが示唆されている[7]。

3．事象関連電位（脳波）による補助的診断の有用性

ADHDにおける認知や注意の障害が事象関連電位で捉えられることがこれまで報告されている。特にStop-signal課題や我々の開発したGo/No Go課題において，ADHD児は健常群に比べ

て頭頂～中心部付近におけるN200の振幅が低下していること，GoからNo Goへのスイッチング機能が低下していることなどが事象関連電位によって示された。すなわちADHDの病態の客観的指標となる可能性が示唆されている[6]。またADHDでは健常群に比べP300の振幅が低下することも報告されている[4]。これらは，methylphenidateなど治療薬の効果を，客観的に表す指標となるであろう。

4．ADHDと睡眠障害に関する研究

最近ADHD児の中核症状（多動・衝動性・不注意）および睡眠覚醒リズムとの関連についての研究も進んでいる。親記入式質問紙票であるThe Children's Sleep Habits Questionnaire（以下CSHQ）を用いて，ADHD児の睡眠を検討した研究がなされている[3]。また体動計であるアクチグラフを使用し行動量を24時間連続記録し，睡眠評価を行った先行研究も存在する[11]。その結果，ADHD児においても睡眠時間の短縮等，多くの問題を含んでいることが明らかになった。また我が国においても，「子どもの睡眠習慣質問紙票日本語版」（The Children's Sleep Habits Questionnaire：CSHQ-J）を用いて，ADHD児の睡眠を検討した研究が進められている[15]。ADHD児の睡眠の問題は，不注意，多動，衝動性といったADHDの中核症状と直接関与するものではないが，学業不振や併存障害である反抗挑戦性障害やうつ病性障害と関連し，QOLと直結する。ADHD児の治療結果の向上を目指す上で，重要な研究テーマと言えよう。

Ⅳ．ADHD診断・治療バイオマーカーの問題点

このように現在利用できるバイオマーカーをまとめた診断キットを作成することは，現時点での病態把握，治療効果の判定をする上で有用である。しかし，病態の本質を理解し，根本的な治療法を開発するためには，診断キット作成の段階から一歩進み，原因遺伝子・タンパク質，くわえてADHD児の大脳病態を誘導しやすい環境因子を明らかにする段階に踏み込む必要があるとも考える。実際，原因遺伝子・関連タンパク質が，本当の意味でのADHDバイオマーカーであり，これまで開発されてきたバイオマーカーは「準」バイオマーカーと言えるのかもしれない。

以下，ADHDの診療に最適なバイオマーカーを構築していく上での考慮すべき点について，2つの視点から考えてみたい。

1．治療開始時期

1つには，適切な治療時期の選択があげられる。ADHDの治療開始時期として一般的に適切と考えられている年齢は，小学校低学年である。この治療開始時期の選択は，就学をきっかけにADHD児の集団行動における問題が顕在化するのに対応した社会的な判断に基づいている。その意味で，これまで開発されてきたバイオマーカーは，病状の把握，治療効果の判定に重要な役割を果たしており，これらのバイオマーカーによって学校における集団生活や学業がなるべくスムーズに進むような行動学習指導，薬剤投与の選択が可能となっている。

しかし，小学校低学年からの治療開始という社会的な判断は，必ずしも生物・医学的に最適な治療開始時期とは言えないかもしれない。すなわち，ADHDの病態の本質が脳の形成過程の異常にあるとすれば，脳の神経基盤が未成熟な胎児期～乳児期にこそ，診断・治療がスタートされるべきかもしれない。しかし，多くの臨床家医師がこの発達初期に治療を行っていない（あるいは行うことがかなわない）根本的な理由は，ADHDの病態理解が不完全で，適切なバイオマーカーが存在していないため，病態評価にもとづいた治療法・新薬の開発が行えないからであろう。したがって，将来ADHDの発症を引き起こす遺伝子あるいはタンパク質が同定できれば，治療開始時期が胎児期～新生児期に大きくシフトする可能性は十分考えられる。さらに踏み込んで述べるならば，現在のADHDに対する治療は残念ながら後手に回っており，ADHDの病態が完成した後に対症療法・対処療法に近い治療ストラテジーを取っている，のかもしれない。

例えば，現在，妊娠母体に対する葉酸投与を行う二分脊椎の予防治療[10]は，将来のADHD治療の一つのイメージを与える。このアプローチには，①脳神経の構築を胎児期から制御し二分脊椎を予防する薬剤である「葉酸」を投与し，②疾患に対する薬剤効果を人口統計学的に疾病率の減少で確認する，という2つのステップが含まれている。特に胎児～新生児期の薬剤効果は，薬剤投与の前後における同一患児の評価を行うことが困難なため，このような公衆衛生学的評価を取り入れることが重要になってくるであろう。

2．治療法確立のためのバイオマーカー

先に述べたように，「アルツハイマー型認知症(DAT)」で取られつつある診断・治療戦略はADHDの領域においても適用可能であり，今後病因遺伝子・タンパク質に基づいたバイオマーカーの発見が，症候群的なアプローチに留まるADHD診療に，新たな展開をもたらしてくれるかもしれない。アルツハイマー病は加齢に伴う変性疾患で，本来は正常な脳の構造・回路が老化に伴い変性してくるという病態であるため，発達初期からの脳構造・回路異常を疑われる発達障害関連疾患と単純に比較することは難しい。しかし，発症時期が老年期から発達初期に移動した脳機能疾患と考えれば，そのバイオマーカーを探るアプローチはアルツハイマー病と基本的に同じである。

一方，アルツハイマー病の研究において原因タンパク質の発見に大きく貢献したのは，大脳病理標本であったことも忘れてはならない。病理標本の検討により，アルツハイマー病ではアミロイドベータという変性タンパク質が高頻度で認められることが明らかになった。老化が進行し最終的に死に至り，死因の検討のために「死後」脳の利用が可能なアルツハイマー病と異なり，ADHD児においては病理標本が実質的に存在せず，実際に脳で起こっている病態を病理学的に確かめることが難しい状況にある。そのためにこそ，ニューロイメージング技術の進展はADHDの病態解明に直接影響する可能性が高い。特に海外で盛んに開発されつつあるMRI用の分子生物学的プローブ[18]は，死後脳の代わりにADHD児の「生きて，活動している脳」の病態を分子病理学的に評価する上で1つの重要な戦略となってくると予想する。先に述べたゲノミックからイメージングまでの統合されたバイオマーカーの創設がポイントになろう。

V．現在のADHDバイオマーカーで分かること――オーダーメイド治療の展開

現在開発されているバイオマーカーは，ADHDとしての病態が形成されてからの脳機能評価を目的としているため，ADHDを根本的に治療するための指標になる可能性は残念ながら少ない。しかし，ADHDの脳機能を正確に把握し，子どもの不注意や多動・衝動性が生じる詳細をより深く評価することができれば，その脳の病態のパターンによって異なる有効な治療法を選択できる。これはいわゆる「オーダーメイド治療」の考え方につながる。患者個人に合わせた治療法効果を，再度ADHDバイオマーカーを用いて客観的に評価することにより，最適な薬の使用量・心理社会的な治療の有効性などを微調整することが可能である。

このような「オーダーメイドあるいはテーラーメイド治療」の考え方は，ADHDを形成する根本的な原因を取り除くことが難しいとしても，徐放性methylphenidate，atomoxetineといった適応薬の今後の効能改善・新薬開発に結びつく可能性がある。また，医学・心理学的な個人差を踏まえた特別支援教育プログラムの開発に科学的な指針を与え，ADHDに悩むこども達・患者さん達に最適な治療を還元できる基礎となると思われ，今後の研究の展開に期待したい。

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Original article

Focal EEG abnormalities might reflect neuropathological characteristics of pervasive developmental disorder and attention-deficit/hyperactivity disorder

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Abstract

Neurophysiological characteristics in electroencephalograms (EEG) were investigated for patients with pervasive developmental disorder (PDD) and for patients with attention-deficit/hyperactivity disorder (AD/HD). This study examined 64 PDD children and 22 AD/HD children with no history of epilepsy or progressive neurological or psychiatric disorder. We used multivariate analysis to compare EEG abnormalities, clinical symptoms, and intelligence levels between PDD and AD/AD patient groups. Paroxysmal discharges at the frontopolar–frontal (Fp–F) brain regions and background EEG abnormalities tended to be detected preferentially in the PDD group, although paroxysmal discharges at central–temporal (C–T) regions tended to be detected preferentially in the AD/HD group. The paroxysmal discharges observed in patients expressing persistence and impulsivity are apparently localized respectively in the Fp–F and C–T regions. A combination of EEG abnormalities, including background EEG abnormalities and paroxysmal discharges at Fp–F and C–T regions, might be useful diagnostic hallmarks to distinguish PDD with AD/HD from AD/HD alone using a logistic regression model. The dysfunction of specific brain areas associated with EEG abnormalities might explain characteristics of clinical symptoms observed in PDD and AD/HD patients.

Keywords: Pervasive developmental disorder; Attention-deficit/hyperactivity disorder; Electroencephalogram abnormality; Paroxysmal discharges

1. Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria, pervasive developmental disorder (PDD) can be discriminated from attention-deficit/hyperactivity disorder (AD/HD). The nosology, which does not accept the existence of dual diagnoses of PDD and AD/HD, assigns priority to the diagnosis of PDD, not AD/HD [1]. Practically, however, clinicians often encounter patients with a spectrum of these two disorders, which could be diagnosed as overlapping PDD and AD/HD rather than as a variant of PDD [2].

Numerous reports have described higher rates of prevalence of epilepsy and electroencephalographic abnormalities in children diagnosed as having PDD or AD/HD than in normal school-aged children. The respective prevalence rates of children with PDD and AD/HD showing EEG abnormalities have been

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reported as 21–86% and 18–30% [3–13]. Whether PDD and AD/HD have distinctive and intrinsic EEG abnormalities remains unknown. This study analyzed and compared the respective relations between EEG abnormalities and either PDD or AD/HD. We then assessed the clinical utility of EEG in the differential diagnosis of these disorders.

2. Patients and methods

This study examined 86 children (12 female and 74 male) with PDD ($n = 64$) or AD/HD ($n = 22$) who had been referred to the Hiratani Clinic for Developmental Disorders of Children during January 2004–December 2008 for evaluation of their development and for diagnosis and treatment of their challenging behaviors. The author (M.H.), a pediatric neurologist at the clinic, checked up and diagnosed all subjects according to DSM-IV criteria. Patients with IQ of 70 or less (Wechsler Intelligence Scale for Children, Third Edition; WISC-III), and those with comorbid epilepsy, progressive neurological or psychiatric disorders were excluded. Informed consent was obtained from the subjects and their guardians. The ethical committee of the University of Fukui approved the project.

Each participant's EEG was recorded for at least 30 min under awake and natural sleep conditions. The 10–20 international electrode placement method was used with a time constant 0.3 and a 100 Hz high-frequency filter. The EEG abnormalities included background EEG abnormalities (slowed rhythmicity or laterality of basic waves) and paroxysmal discharges. "Slowed rhythmicity" was defined as an occipital basic rhythm of which the frequency was at least 1 Hz or slower than that of the age-matched standard basic rhythm, and "laterality of basic waves" was defined as asymmetrical occipital amplitude of not less than 50% [15,16]. Paroxysmal discharges were classified as either "diffuse" or "localized". The localized discharges were divided into three groups according to the respective dominantly affected regions: Fp–F, frontopolar to frontal regions; C–T, central to temporal regions; and P–O, parietal to occipital regions. "Lateralization of paroxysm" was defined as paroxysmal discharges detected only in a unilateral hemisphere. The presence of rolandic spikes (RS), which was one of C–T localized paroxysm, was also examined.

Medical records related to the characteristic symptoms of PDD and AD/HD including delayed language development in early childhood, persistence, impulsivity, temper tantrums, clumsiness, and hypersensitivity were obtained for this study. The intelligence level was assessed using the Wechsler Intelligence Scale for Children, Third Edition (WISC-III).

Statistical analyses were conducted using software (SPSS ver. 13.0 J; SPSS Inc., Tokyo, Japan). Statistical significance was inferred for $p < .05$. Univariate and multivariate associations among various clinical parameters, including symptoms and EEG findings, and the diagnosis were tested using logistic regression analysis. The Press Q statistic was used to evaluate the discriminatory power of the classification matrix produced by a logistic regression model when compared with a chance model.

Data are expressed as the mean ± SD or the median and range. Differences between two groups were analyzed using unpaired *t*-tests, Fisher's exact test, and χ^2-tests.

3. Results

3.1. Clinical characteristics of patients

Subjects enrolled in this study were 8.6 ± 2.2 years old. The EEG and intelligence assessments were examined at similar ages of both PDD and AD/HD groups. Among the clinical symptoms, delayed language development in early childhood, persistence, and hypersensitivity perception were more prevalent in patients with PDD than in those with AD/HD (Table 1). No significant difference was found in the prevalence of impulsivity, temper tantrums, or clumsiness between the PDD and AD/HD groups, or in their IQ values.

3.2. Relation between clinical entities and EEG abnormalities

Background EEG abnormalities were observed more frequently in the PDD patient group than in the AD/HD patient group (22% vs. 9%) (Table 2). The total incidences of paroxysmal discharges were not significantly different between the PDD and AD/HD groups (52% vs. 41%). Paroxysmal discharges with foci at the Fp–F brain region, RS, and diffuse ones tended to be more detected in the PDD group, whereas paroxysmal discharges with foci in C–T and P–O regions tended to be more detected in the AD/HD group. However, univariate analysis showed no statistically significant differences. No significant difference in the laterality of paroxysmal discharges was found between PDD and AD/HD groups. The patients who had been sub-classified into the inattention subtype of AD/HD exhibited no EEG abnormality. No differences among subgroups of PDD were apparent in terms of the prevalence of each EEG abnormality. Fig. 1 presents examples of characteristic EEG abnormalities.

3.3. EEG abnormalities are associated with clinical symptoms but not with intelligence levels

Patients with delayed language development in the early childhood exhibited more background EEG abnormalities (32%, χ^2-tests $p < .01$) than patients with other clinical symptoms (15–21%) (Table 3). Paroxysmal discharges observed in patients expressing persistence or

Table 1
Patient data.

Subtype	PDD ($n = 64$) Autistic disorder: 15 Asperger disorder: 32 PDD-NOS: 17	AD/HD ($n = 22$) Inattentive: 5 Hyperactive impulsive: 0 Combined: 17	p-Value
Gender (female/male)	10/54	2/20	n.s.
Age when EEG was recorded	8.7 ± 2.3 years	8.4 ± 1.9 years	n.s.
Age when IQ was assessed	8.6 ± 2.2 years	8.4 ± 2.0 years	n.s.
Clinical presentation			
Delayed language development	23 (36%)	2 (9%)	<.05
Persistence	61 (95%)	4 (18%)	<.01
Impulsivity	44 (69%)	18 (82%)	n.s.
Temper tantrums	46 (72%)	17 (77%)	n.s.
Clumsiness	48 (75%)	12 (55%)	n.s.
Hypersensitivity	42 (66%)	5 (23%)	<.01
WISC-III			
Full-scale IQ	95 ± 14	96 ± 13	n.s.
Verbal IQ	93 ± 15	94 ± 13	n.s.
Performance IQ	99 ± 15	100 ± 15	n.s.

Mean ± SD; PDD, pervasive developmental disorder; AD/HD, attention-deficit/hyperactivity disorder; PDD-NOS, pervasive developmental disorder not otherwise specified; WISC-III, Wechsler Intelligence Scale for Children, Third Edition; n.s., not significant.

Table 2
Relation between EEG abnormalities and clinical entities.

	PDD					AD/HD		
	Autistic disorder	Asperger disorder	PDD-NOS	PDD with AD/HD[a]	Total	Combined type	Inattention type	Total
Number	15	32	17	51	64	17	5	22
Background abnormalities	5 (33%)	7 (22%)	2 (12%)	12 (24%)	14 (22%)	2 (12%)	0	2 (9%)
Paroxysmal discharges	8 (53%)	19 (59%)	6 (35%)	26 (51%)	33 (52%)	9 (53%)	0	9 (41%)
Diffuse	4 (27%)	11 (34%)	5 (29%)	15 (29%)	20 (31%)	4 (24%)	0	4 (18%)
Foci at Fp–F	3 (20%)	10 (31%)	3 (18%)	15 (29%)	16 (25%)	3 (18%)	0	3 (14%)
C–T	3 (20%)	9 (28%)	2 (12%)	12 (24%)	14 (22%)	8 (47%)	0	8 (36%)
P–O	2 (13%)	5 (16%)	3 (18%)	7 (14%)	10 (16%)	5 (29%)	0	5 (23%)
RS	1 (7%)	1 (3%)	1 (6%)	2 (4%)	3 (5%)	0	0	0
Laterality Rt	3 (20%)	9 (28%)	1 (6%)	10 (20%)	13 (20%)	3 (18%)	0	3 (14%)
Lt	1 (7%)	1 (3%)	2 (12%)	4 (8%)	4 (6%)	3 (18%)	0	3 (14%)

PDD, pervasive developmental disorder; AD/HD, attention-deficit/hyperactivity disorder; PDD-NOS, pervasive developmental disorder not otherwise specified; Fp–F, frontopolar–frontal region; C–T, central–temporal region; P–O, parietal–occipital region; RS, rolandic spikes; Rt, right side dominant; Lt, left side dominant.

[a] Cases of PDD fulfilled the diagnostic criteria for AD/HD.

hypersensitivity were most detected in Fp–F brain regions, whereas those observed in patients expressing impulsivity were most in the C–T region. Neither background EEG abnormalities nor the presence of paroxysmal discharges showed a significant correlation with intelligence level, including full scale IQ, performance IQ, and verbal IQ values, irrespective of the clinical entity (Table 4).

3.4. EEG abnormalities according to the age in PDD and AD/HD

Paroxysmal discharges and background abnormalities were detected most frequently in patients aged 6–8, and those aged 9–12, respectively (Table 5). Moreover, significant differences of the positive rate of EEG abnormalities with age were not found between groups (Table 5).

3.5. Usefulness of EEG findings to distinguish PDD and AD/HD

We evaluated the clinical usefulness of EEG findings to distinguish PDD and AD/HD as an auxiliary diagnostic means (Table 6). First, the following variables were analyzed as univariate diagnostic criteria to differentiate PDD from AD/HD: impulsivity, temper tantrums, clumsiness, background EEG abnormalities,

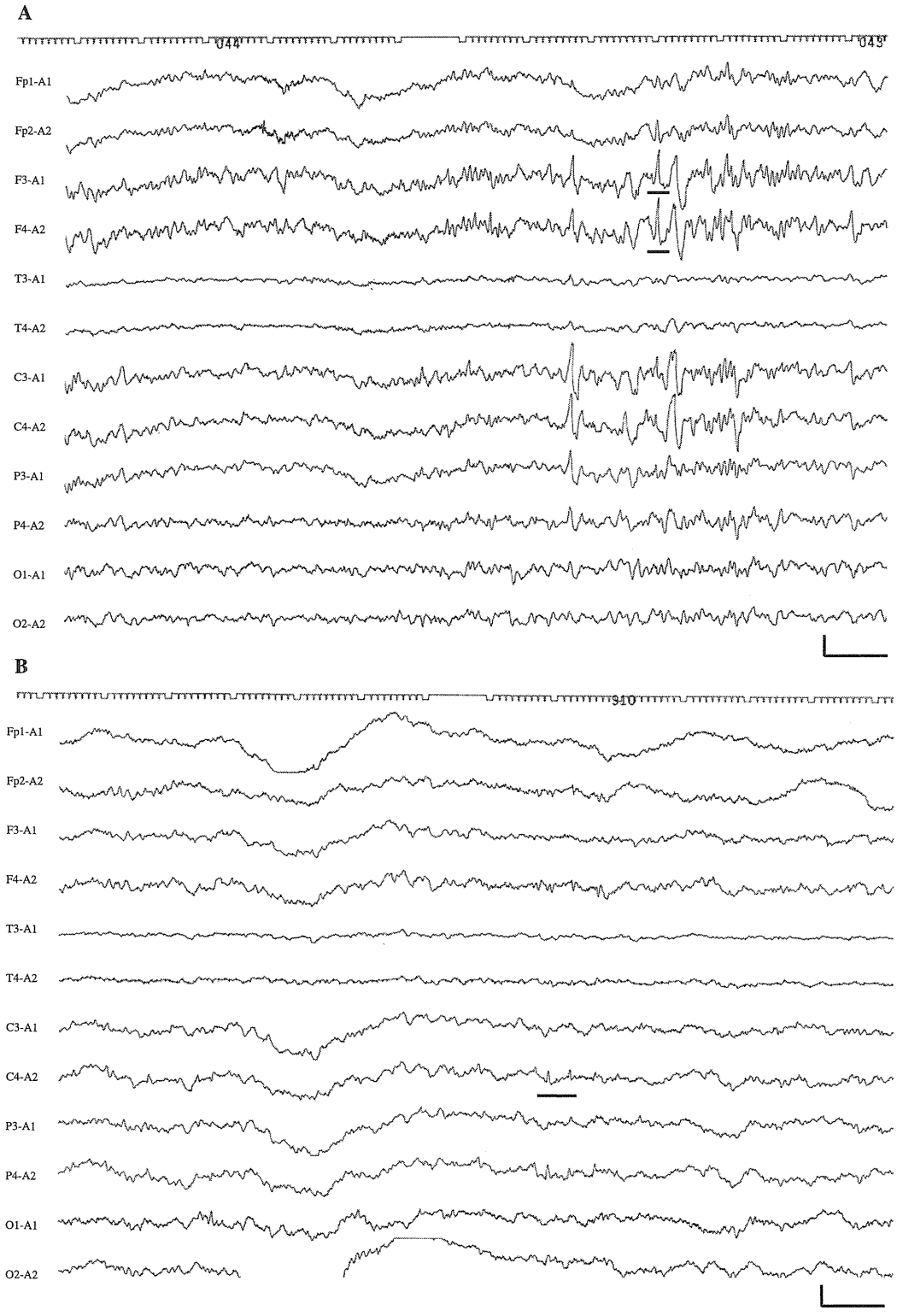

Fig. 1. Examples of characteristic EEG abnormalities. (A) This EEG record during sleep periods of an 8-year-old boy with PDD shows a spike wave on the bilateral frontal region (underline). (B) This EEG record during sleep periods of a 6-year-old boy with AD/HD shows small spike waves on the bilateral central region (underline). Calibration, 50 V, 1 s.

and diffuse, Fp–F, or C–T paroxysmal discharges. Delayed language development and persistence are important criteria for the diagnosis of PDD according to the DSM-IV. Therefore, we excluded these two factors from logistic analysis. Although each criterion alone is not a significant discriminating factor, when

Table 3
Relation between clinical symptoms and EEG abnormalities.

Presentation Diagnosis	Delayed language development		Persistence		Impulsivity		Temper tantrums		Clumsiness *		Hyper-sensitivity	
	PDD	AD/HD	PDD	AD/HD	PDD	AD/HD	PDD	AD/HD	PDD	AD/HD	PDD	AD/HD
Number	23	2	61	4	44	18	46	17	48	12	42	5
Background abnormalities	8	0	13	0	10	2	9	1	8	1	9	1
Paroxysmal discharges	13	0	32	1	22	8	23	5	23	5	23	3
Diffuse	8	0	19	0	14	4	14	2	14	2	13	3
Foci at Fp–F	3	0	16	0	11	3	8	3	11	2	11	1
C–T	5	0	13	1	10	7	8	4	10	4	8	2
P–O	5	0	9	0	8	4	9	4	7	3	7	1
RS	2	0	2	0	1	0	2	0	3	0	1	0
Laterality Rt	3	0	13	0	11	2	8	3	9	2	9	1
Lt	3	0	4	0	3	3	3	1	4	1	3	0

PDD, pervasive developmental disorder; AD/HD, attention-deficit/hyperactivity disorder; Fp–F, frontopolar–frontal region; C–T, central–temporal region; P–O, parietal–occipital region; RD, rolandic discharge; Rt, right side dominant; Lt, left side dominant. *Two patients' clumsiness was not assessed.

Table 4
Relation between IQ levels and EEG abnormalities.

Diagnosis	VIQ*		PIQ*		FIQ*	
	PDD	ADHD	PDD	ADHD	PDD	ADHD
Number	60	22	60	22	60	22
Background abnormalities	93 ± 12 (13)	98 ± 26 (2)	98 ± 15 (13)	123 ± 9 (2)	95 ± 12 (13)	111 ± 21 (2)
Paroxysmal discharges	92 ± 14 (30)	94 ± 15 (9)	96 ± 16 (30)	99 ± 17 (9)	93 ± 13 (30)	95 ± 15 (9)
Diffuse	91 ± 16 (18)	92 ± 17 (4)	97 ± 18 (18)	103 ± 24 (4)	94 ± 14 (18)	97 ± 20 (4)
Foci at Fp–F	89 ± 12 (16)	90 ± 18 (3)	93 ± 17 (16)	101 ± 11 (3)	90 ± 13 (16)	95 ± 13 (3)
C–T	91 ± 13 (13)	95 ± 16 (8)	93 ± 16 (13)	100 ± 18 (8)	92 ± 11 (13)	97 ± 15 (8)
P–O	89 ± 15 (10)	97 ± 19 (5)	101 ± 13 (10)	110 ± 15 (5)	94 ± 13 (10)	104 ± 14 (5)
RS	96 ± 10 (3)	None	93 ± 12 (3)	None	94 ± 14 (3)	None
Laterality Rt	86 ± 15 (13)	89 ± 16 (3)	95 ± 19 (13)	94 ± 11 (3)	90 ± 15 (13)	91 ± 6 (3)
Lt	90 ± 12 (57)	90 ± 18 (3)	92 ± 8 (57)	106 ± 12 (3)	90 ± 7 (4)	95 ± 15 (3)

VIQ, verbal IQ; PIQ, performance IQ, FIQ, full scale IQ; PDD, pervasive developmental disorder; AD/HD, attention-deficit/hyperactivity disorder; PDD-NOS, pervasive developmental disorder not otherwise specified; Fp–F, frontopolar–frontal region; C–T, central–temporal region; P–O, parietal–occipital region; RD, rolandic discharge; Rt, right side dominant; Lt, left side dominant. *Mean ± SD (cases with EEG abnormalities).

Table 5
Paroxysmal discharges and background abnormalities according to the age in PDD and AD/HD.

	PDD ($n = 64$)		AD/HD ($n = 22$)	
	Paroxysmal discharges	Background abnormalities	Paroxysmal discharges	Background abnormalities
Number (positive rate)	33 (52%)	14 (22%)	9 (41%)	2 (9%)
6–8 years	25/36 (69%)	8/36 (22%)	7/12 (58%)	1/12 (8%)
9–12 years	7/22 (32%)	6/22 (27%)	2/9 (22%)	1/9 (11%)
13–15 years	1/6 (17%)	0/6 (0%)	0/1 (0%)	0/1 (0%)

PDD, pervasive developmental disorder; AD/HD, attention-deficit/hyperactivity disorder.

analyzed with all criteria as confounding factors, the absence of C–T paroxysmal discharges and the presence of Fp–F paroxysmal discharges seems to support the diagnosis of PDD rather than AD/HD. Of note, the presence of Fp–F paroxysmal discharges might affirm the opposite diagnosis depending on co-evaluation of the presence of C–T paroxysmal discharges. Finally, using a stepwise regression method, the final model comprising the presence of background abnormalities and Fp–F paroxysmal discharges was produced. The absence of C–T paroxysmal discharges is apparently useful for the diagnosis of PDD. Cases that were

Table 6
Multivariate analysis of clinical parameters and EEG findings to discriminate PDD from AD/HD.

Clinical parameters	Univariate analysis			Multivariate analysis		
	Un-adjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-Value
Clinical presentation						
Impulsivity	0.49	0.15–1.63	0.25	0.57	0.15–2.21	0.42
Temper tantrums	0.75	0.24–2.34	0.62	0.53	0.13–2.19	0.38
Clumsiness	2.00	0.69–5.76	0.20	2.79	0.84–9.29	0.10
EEG						
Background abnormalities	2.80	0.58–13.46	0.20	4.77	0.74–30.53	0.099
Diffuse paroxysmal discharges	2.05	0.61–6.83	0.25	2.13	0.50–9.08	0.31
Fp–F paroxysmal discharges	0.47	0.12–1.81	0.28	6.27	0.87–45.44	0.069
C–T paroxysmal discharges	0.49	0.17–1.40	0.18	0.13	0.022–0.70	0.018
Regression model based on EEG findings						
Background abnormalities				5.29	0.86–32.55	0.073
Fp–F				5.04	0.92–27.73	0.063
C–T				0.15	0.034–0.68	0.013

OR, odds ratio; 95% CI, 95% confidence intervals; Diffuse, diffuse paroxysms; Fp–F, focal paroxysms at the frontopolar to frontal region; C–T, focal paroxysms at the central to temporal region. Unadjusted and adjusted OR and 95% CI were calculated using logistic regression analysis. Presence and absence of parameters were converted, respectively, to 1 and 0. Diagnoses of PDD and AD/HD were converted, respectively, to 1 and 0.

Table 7
Multivariate analysis of clinical parameters and EEG findings to discriminate PDD with AD/HD from AD/HD.

Clinical parameters	Univariate analysis			Multivariate analysis		
	Un-adjusted OR	95% CI	*p*-Value	Adjusted OR	95% CI	*p*-Value
Clinical presentation						
Impulsivity	0.59	0.17–2.04	0.40	0.74	0.18–3.09	0.68
Temper tantrums	0.64	0.20–2.05	0.46	0.40	0.09–1.76	0.22
Clumsiness	1.95	0.65–5.82	0.23	2.63	0.75–9.26	0.13
EEG						
Background abnormalities	3.08	0.63–15.10	0.17	6.19	0.82–46.51	0.077
Diffuse paroxysmal discharges	1.88	0.54–6.48	0.32	2.24	0.44–11.27	0.33
Fp–F paroxysmal discharges	0.16	0.68–10.27	0.16	9.38	1.09–80.50	0.041
C–T paroxysmal discharges	0.54	0.18–1.59	0.26	0.09	0.01–0.72	0.023
Regression model based on EEG findings						
Background abnormalities				7.54	1.01–42.55	0.049
Fp–F				6.76	1.08–42.55	0.042
C–T				0.12	0.02–0.66	0.015

OR, odds ratio; 95% CI, 95% confidence intervals; Diffuse, diffuse paroxysms; Fp–F, focal paroxysms at the frontopolar to frontal region; C–T, focal paroxysms at the central to temporal region. Unadjusted and adjusted OR and 95% CI were calculated using logistic regression analysis. Presence and absence of parameters were converted, respectively, to 1 and 0. Diagnoses of PDD with AD/HD and AD/HD were converted, respectively, to 1 and 0.

classified correctly by the final regression model were 76.7%. The Press Q statistic was $24.6 > 6.63$, which is the critical value at a significance level of .01, indicating that the predictions were significantly better than could be expected by chance. The logistic regression models showed that VIQ, PIQ, and FIQ were not significant independent criteria (data not shown).

As a practical matter, discriminating PDD with AD/HD from AD/HD alone is difficult. We re-evaluated the usefulness of EEG findings to distinguish PDD with AD/HD from AD/HD alone using a logistic regression analysis. As Table 7 shows, similar results were obtained. The presence of background EEG abnormalities, Fp–F, and C–T paroxysmal discharges were identified by statistically significant discriminating factors in the final models. The hit ratio of the final regression model was 74%. The Press Q statistic was 16.78, indicating that the classification results are significantly better than could be expected by chance.

4. Discussion

According to DSM-IV criteria, PDD and AD/HD are classified as distinct clinical entities. However, many cases show difficulty in discriminating PDD with AD/HD from AD/HD alone, according to the clinical symptoms and

developmental history [2]. The usefulness of EEG examination for diagnosis of PDD and AD/HD has remained controversial. Our data show that a combination of EEG findings, including background EEG abnormalities, and paroxysmal discharges at Fp–F and C–T brain regions might be a useful diagnostic hallmark that is useful to distinguish PDD with AD/HD from AD/HD alone, and that focal EEG abnormalities might reflect their neurophysiological characteristics cooperatively.

Patients with PDD or AD/HD are known to present epilepsy and EEG abnormalities in many cases [8–13]. The detected prevalence of EEG abnormalities among patients with PDD or AD/HD varies depending on the study design. Few studies have examined the qualitative differences in the EEG findings between these patient groups. Limitations to interpretation of the results of the previous studies are applicable for the following reasons. First, some studies adopted different diagnostic criteria, such as DSM III-R, or specified none [3,7,9]. Second, the enrolled subjects in the studies differ in age and level of intellectual development. Tuchman et al. reported a significant association between severe language deterioration and EEG abnormalities in a minority of PDD patients [4]. Several studies have demonstrated a correlation between low IQ level and EEG abnormalities [5,6]. Because the patients enrolled in this study were diagnosed with PDD or AD/HD according to the DSM-IV criteria, with neither mental disability (full scale IQ < 70), severe language deterioration, nor epilepsy, we were able to exclude influences of mental disability and epileptic seizures on the subjects' EEG findings. In fact, this study revealed no significant relation between the IQ level and EEG abnormality.

Kawasaki et al. [3] reported that paroxysmal discharges at the frontal brain regions emerged in a patient with PDD during middle childhood and adolescence. Yasuhara et al. [6] demonstrated that 85.9% of children with PDD suffer from epileptic seizure discharges, which more frequently developed from the frontal part (40.5%) and fronto pole (12.5%) than from other brain regions (<11%). Consistent with these findings, paroxysmal discharges at the Fp–F region are apparently detected preferentially in PDD patients and are associated with "persistence", a necessary criterion for the diagnosis of PDD. The presence of paroxysmal discharges at frontal brain regions might support the PDD diagnosis.

The paroxysmal discharges at the P–O region are apparently more associated with "Temper tantrums" than with other clinical symptoms. "Temper tantrums" is a clinical symptom observed in patients with combined type of AD/HD as well as those with PDD. Consequently, unlike the presence of paroxysmal discharges at the Fp–F region, those at the P–O region cannot be regarded as a discriminating factor between PDD and AD/HD by logistic regression analysis.

Holtmann et al. reported that the prevalence of RS in children with AD/HD is significantly higher than that expected from epidemiologic studies and that some AD/HD children with RS tended to exhibit more hyperactive-impulsive symptoms [11,14]. Although RS were not detected in the EEG of AD/HD patients in the present study, the presence of other forms of paroxysmal discharged at C–T regions is more likely to be associated with impulsivity and is apparently a predisposing factor to AD/HD. Dysfunction of C–T brain areas might impair executive functions, leading to impulsive behaviors in AD/HD patients.

Several functional brain imaging studies have revealed a relation between clinical symptoms analyzed in this study and specific brain regions [17–20]. According to these studies, persistence and temper tantrums are related to the frontal lobe, although impulsivity is related to the frontal lobe, basal ganglia, and thalamus [17–19]. A discrepancy exists in the cerebral localization of impulsivity between EEG finding in this study and the results of brain imaging. Additional studies must be undertaken to elucidate the pathophysiological effects of localized paroxysmal discharges on clinical symptoms.

Two main developmental models of developmental disturbance including AD/HD, the maturational lag model [21] and the developmental deviation model [22], have been proposed based on results from electrophysiological studies. In this study, paroxysmal discharges and background abnormalities decreased with age in both groups. Moreover, no significant difference between groups in the positive rate of EEG abnormalities with age was found. Our results are supportive of maturational lag as the neurophysiological theory in PDD and AD/HD, although no long-term longitudinal data of individual subjects exist.

We acknowledge several limitations to our study, mainly attributable to the small sample size of patients from a single clinic and a university hospital. Particularly, patients with inattention type and hyperactive-impulsive type of AD/HD are few. For that reason, characteristics of EEG findings and clinical parameters of the AD/HD group might not be representative of the entire AD/HD population.

In conclusion, we suggest a reevaluation of the diagnosis utility of conventional EEG findings in PDD and AD/HD as independent variables in logistic regression models. Additional studies must be undertaken to elucidate the relation between the foci of paroxysmal discharges and clinical symptoms.

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Switching to aripiprazole in subjects with Pervasive Developmental Disorders showing tolerability issues with risperidone

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ABSTRACT

Background: Subjects with Pervasive Developmental Disorders (PDD) often exhibit behavioral symptoms such as aggressiveness and irritability, which are targets of psychopharmacologic intervention. This retrospective study was designed to examine children and adolescents with PDD experiencing tolerability issues with risperidone treatment, and thereby assess the efficacy and tolerability of switching to aripiprazole.
Methods: This naturalistic study included 23 subjects with PDD (16 males, 7 females, age range 9–24 years, mean age 15.1 ± 3.9 years) diagnosed according to DSM-IV criteria and followed up for 14.9 ± 8.4 weeks after switching to aripiprazole from risperidone. Outcome measures were the Clinical Global Impression-Severity (CGI-S) and CGI Improvement (CGI-I) scales.
Results: The mean CGI-S scores of pre-aripiprazole treatment and post-aripiprazole treatment were, respectively 4.7 ± 1.4 and 4.6 ± 1.3. Mean maintenance dosages of risperidone and aripiprazole were, respectively, 0.7 ± 0.5 mg/day and 2.8 ± 1.3 mg/day. The mean CGI-I score, which shows the difference induced by switching from risperidone to aripiprazole, was 3.4 ± 0.8 for the whole sample, suggesting that the efficacy of risperidone for treating behavioral problems of PDD was maintained by aripiprazole. Some improvement of safety/tolerability issues such as increased appetite, somnolence, hyperprolactinemia, and amenorrhea occurred after switching to aripiprazole.
Conclusion: Results show that switching to aripiprazole might be generally well tolerated and might constitute an alternative treatment for subjects with PDD who experience tolerability issues with risperidone treatment. Additional long-term controlled studies of PDD subjects should be undertaken to evaluate the efficacy and safety of switching to aripiprazole from other antipsychotics.

1. Introduction

Pervasive Developmental Disorder (PDD) is a chronic developmental disorder in which disturbances in the development of the central nervous system impair a person's social, cognitive, and communicative competence (Myers, 2007). In addition, many patients with PDD exhibit behavioral symptoms such as hyperactivity, aggressiveness, irritability, impulsivity, mood disturbance, and self-injurious behavior (Leskovec et al., 2008). Though behavioral therapies are clearly the main interventions for these behavioral symptoms, psychopharmacologic intervention is also often needed from early childhood, which result in longer-term use of psychotropic medications (West et al., 2009). Thereby, it is important to choose generally safe and well-tolerated medications considering the possibility that continuous tolerability issues might have negative impact for the health of child and adolescent subjects with PDD.

Various psychotropic medications are currently used to treat a range of symptoms associated with PDD, including aggression, repetitive behaviors, low tolerance for frustration, and hyperactivity (McPheeters et al., 2011). Antipsychotics, including risperidone and the conventionally used agent haloperidol, are the most commonly used class of agents for treating patients with PDD (Lemmon et al., 2011; Levy and Hyman, 2005). Several reports have described that risperidone is well tolerated and effective in treating behavioral symptoms associated with PDD in children (McDougle et al., 2005; Shea et al., 2004). Nevertheless, a few PDD patients develop adverse events including extrapyramidal side effects, weight gain, transient sedation, galactorrhea, amenorrhea, and gynecomastia (Barnard et al., 2002; Canitano and Scandurra, 2008).

Abbreviations: DSM, Diagnosis and Statistical Manual of Mental Disorders; CGI, Clinical Global Impression; PDD, Pervasive Developmental Disorders.

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Aripiprazole, an atypical antipsychotic agent, is a potent partial agonist at D2 and 5-HT1A receptors and a potent antagonist at 5-HT2A receptors (Hirose et al., 2004; Jordan et al., 2002). As with other antipsychotics, aripiprazole has been shown to be efficacious and generally well tolerated in children and adolescents with schizophrenia or bipolar mania (Biederman et al., 2005, 2007; Findling et al., 2008a, 2008b). According to the recent two large randomized controlled trials, which were conducted to evaluate the efficacy and safety of aripiprazole in the treatment of maladaptive behaviors in children and adolescents with PDD, aripiprazole was efficacious for irritability and was generally safe and well-tolerated (Marcus et al., 2009; Owen et al., 2009). Furthermore, in contrast to other atypical antipsychotics, aripiprazole is associated with minimal weight gain and has minimal negative influence on metabolic and neuroendocrine parameters (Casey et al., 2003; Naber and Lambert, 2004). Aripiprazole and risperidone have been approved by the U.S. Food and Drug Administration (FDA) for treating pediatric patients with irritability associated with autistic disorder (Prinseton et al., 2009; Titusville, 2009). Hence, switching from risperidone to aripiprazole might be an efficacious option, especially in patients with PDD experiencing insufficient efficacy or tolerability issues with risperidone treatment. However, no report in the relevant literature describes a study assessing the efficacy and tolerability of switching to aripiprazole in children and adolescents with PDD receiving risperidone treatment. We describe our retrospective clinical experience using aripiprazole switched from risperidone in children and adolescents with PDD, who were treated naturalistically in a routine clinical setting.

2. Methods

2.1. Subjects

Our retrospective study was based on a clinical database of 23 outpatients (16 males, 7 females) with PDD, aged between 9 and 24 years (mean age, 15.1 ± 3.9 years), who had been referred to a specialty clinic for children at the Hiratani Child Development Clinic.

Subjects included 16 patients (69.6%) with autistic disorder, 3 patients (13.0%) with Asperger disorder, and 4 patients (17.4%) with pervasive developmental disorders not otherwise specified (PDD-NOS). The diagnosis of PDD was confirmed by a child psychiatrist (author M.H.) based on classifications in the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR; American Psychiatric Association, 2000). Subjects with psychotic disorders or bipolar disorder were excluded. Subjects were also excluded if they had a history of drug or alcohol abuse. In addition, subjects with severe mental retardation for whom a definitive diagnosis of autism could not be made were excluded.

To treat a range of behavioral symptoms associated with PDD, including irritability, aggression, repetitive behaviors and hyperactivity, all subjects had received treatment with risperidone (mean maintenance dosage, 0.7 ± 0.5 mg/day) previously, which was interrupted rapidly and which was simultaneously switched to aripiprazole (mean maintenance dosage, 2.8 ± 1.3 mg/day) because of increased appetite and weight (11 patients), hyperprolactinemia (3 patients), somnolence (2 patients), amenorrhea (1 patient), or long-term safety (6 patients). The dosage of aripiprazole was titrated depending on the clinical outcome and occurrence of adverse effects, but was same as the starting dose during the treatment in most cases. Written informed consent to treatment was obtained from each participant's legal guardian (parents for all children in this report; legally appointed guardians for all adults). Subjects provided assent when able. Twelve subjects (52.1%) continued to receive concomitant psychotropic medications such as carbamazepine, methylphenidate, fluvoxamine, valproate sodium, and zolpidem. Medications except for risperidone and aripiprazole were unchanged during the switching period.

Our naturalistic study was retrospective. The patients could have discontinued medication including aripiprazole at any time when adverse effects occurred. The protocol used for this study was approved by the Institutional Review Board of the University of Fukui.

2.2. Behavioral Rating Scales

Each patient was assessed by the research team for behavioral symptoms before switching to aripiprazole and again after switching to aripiprazole (mean duration of aripiprazole treatment: 14.9 ± 8.4 weeks). The clinical course of the patients was monitored by child psychiatrists of our research team. The child psychiatrists involved in the diagnosis and treatment were highly experienced in managing children and adolescents with PDD. They had been properly trained in the use of the diagnostic instruments. Measures of severity before and after switching to aripiprazole were the following. To assess the severity of behavioral symptoms including irritability, aggression, self-injury, repetitive behaviors and hyperactivity, we used Clinical Global Impression-Severity (CGI-S) (DiLalla and Rogers, 1994): a single item that rates the severity of global symptomatology on a scale from 1 ('normal') to 7 ('extremely ill'). Clinical Global Impression-Improvement (CGI-I) (DiLalla and Rogers, 1994), a single item recorded at the end of the study rating behavior from 1 ('very much improved') to 7 ('very much worsened'), was also applied to compare the severity of global symptomatology before and after switching to aripiprazole. These instruments have been used extensively in psychopharmacological studies of children and adolescents with PDD (Masi et al., 2003; Nicolson et al., 1998; Zuddas et al., 2000).

2.3. Statistical analyses

Results of CGI-S scores are presented as mean ± SD differences. Potential differences between the CGI-S score of baseline (before taking risperidone) and that of risperidone treatment period and aripiprazole treatment period were calculated using Wilcoxon signed-rank tests and were considered significant at $P<.05$.

3. Results

Patient characteristics just before switching to aripiprazole are shown in Table 1. The mean CGI-S score of baseline (before taking risperidone), the endpoint of risperidone treatment period (just before switching to aripiprazole from risperidone), and the endpoint of aripiprazole treatment period (14.9 ± 8.4 weeks after switching to aripiprazole) were, respectively, 5.5 ± 1.2, 4.7 ± 1.4, and 4.6 ± 1.3

Table 1
Patient background.

Subject	n = 23
Age at examination (years)	
Mean ± SD	15.1 ± 3.9
Gender, n	
Male	16
Female	7
Diagnosis, n (%)	
Autistic disorder	16 (69.6)
Asperger disorder	3 (13.0)
PDD-NOS	4 (17.4)
Reason for switching to aripiprazole, n (%)	
Excessive appetite	11 (47.8)
Hyperprolactinemia	3 (13.0)
Somnolence	2 (8.7)
Amenorrhea	1 (4.3)
Long-term safety	6 (26.1)

PDD, pervasive developmental disorders; PDD-NOS, pervasive developmental disorders not otherwise specified.

(Table 2). The mean maintenance dosages of risperidone and aripiprazole were, respectively, 0.7 ± 0.5 mg/day and 2.8 ± 1.3 mg/day (Table 2). According to the CGI-I score, 4 patients (17.3%) were 'much improved' (score of 2). These 4 patients (3 males and 1 female) were all diagnosed with autistic disorder. Female patient was receiving concomitant psychotropic medication (500 mg/day of valprolate and 300 mg/day of carbamazepine), but other three male subjects did not. The symptoms such as excessive appetite, somnolence and irritability were successfully improved in these 4 patients. On the other hand, 6 patients (26.1%) were 'minimally improved' (score of 3), 12 patients (52.1%) were 'unchanged' (score of 4), and 1 (4.3%) had 'worsened' (score of 5). The mean CGI-I score was 3.4 ± 0.8, and differences between the CGI-S score of risperidone treatment phase and aripiprazole treatment phase were not considered significant using Wilcoxon signed-rank tests. These results indicate that aripiprazole was almost as effective as risperidone for treating behavioral problems related to PDD.

No changes were apparent in blood examinations, including CBC and liver enzymes, or in ECG assessments. Extrapyramidal symptoms were not observed during short-term treatment period. At the time of data collection of CGI-S and CGI-I scales, 23 patients were receiving aripiprazole treatment. However, because of insomnia, one patient discontinued taking aripiprazole during the follow-up and reverted to risperidone treatment again. In contrast, somnolence was improved in 2 subjects who complained of daytime sleepiness. Although no significant change in weight was apparent during short-term treatment period, excessive appetite was improved in 7 of 11 subjects who showed increased appetite and obesity during risperidone treatment. Three male subjects who were taking risperidone 1.2 mg/day, 0.4 mg/day, and 0.6 mg/day, respectively showed increased serum prolactin concentrations of 34.7 ng/ml, 29.5 ng/ml, and 23.7 ng/ml. The serum prolactin levels decreased to 4.8 ng/ml, 13.5 ng/ml, and 1.1 ng/ml respectively after switching to 4 mg/day, 2 mg/day, and 2.3 mg/day of aripiprazole.

In addition, amenorrhea was improved in a female subject after switching to aripiprazole (2 mg/day) from risperidone (0.5 mg/day), although data of her serum prolactin concentrations were not available.

4. Discussion

This open-label, retrospective study is the first reported trial to assess the effectiveness and tolerability of switching to aripiprazole from risperidone in subjects with PDD. According to the CGI-I scores, relatively low dosage of aripiprazole (2.8 ± 1.3 mg/day) in comparison with those used in other studies (Marcus et al., 2009, 2011; Masi et al., 2009), was as effective as risperidone for treating behavioral problems in most PDD subjects: 78.2% of the subjects were considered 'minimally improved' or 'unchanged'. Our results suggest that low dosage of aripiprazole might be useful for treating behavioral problems of PDD subjects, though the role of dosage remains questionable when treating behavioral symptoms of PDD with aripiprazole. For example, in a flexible-dose study in which subjects with autistic disorder were randomized to receive aripiprazole (2–15 mg/day, titrated to clinical effect, with doses of 5, 10, 15 mg/day) or placebo, aripiprazole produced significant improvement compared to the placebo at all dosages. Interestingly, significant improvement was still observed in the first week of treatment, during which all subjects were receiving aripiprazole 2 mg/day (Owen et al., 2009), which is consistent with our results.

Aripiprazole was generally well tolerated in this short-term treatment. Only one subject discontinued aripiprazole because of insomnia. No subject experienced severe adverse events, including extrapyramidal symptoms. The low frequency of adverse effects might result from the lower dosage of aripiprazole used in this study compared with those used in other studies. Although the lack of systematic data of age- and sex-adjusted BMI is one of the limitations in this short-term study, improvement of excessive appetite was reported in 7 (63.6%) of 11 subjects who had shown increased appetite and obesity before switching to aripiprazole. This result suggests that switching to aripiprazole from risperidone might be an effective treatment for subjects with PDD showing increased appetite and obesity. However, because weight gain and increased appetite are also frequently reported adverse effects associated with aripiprazole treatment in PDD subjects, clinicians should be apprised of the potential for weight gain when treating children and adolescents with aripiprazole (Marcus et al., 2011; Owen et al., 2009). Additionally, weight gain was associated with longer term treatment and higher dosage of aripiprazole (Rugino and Janvier, 2005). Therefore, to investigate the influence of switching to aripiprazole on change in body composition more accurately, careful monitoring for age- and sex-adjusted BMI should be done in subjects with PDD, especially those receiving higher doses of aripiprazole for longer treatment periods.

Decreased serum prolactin levels with aripiprazole treatment, as confirmed in three male subjects in the present study, were observed in a previous study as well (Findling et al., 2008a). Aripiprazole has been shown to be useful in the treatment of antipsychotic-induced hyperprolactinemia because of its potent (high-affinity) partial agonist property at dopamine D2 receptors (Chen et al., 2010; Ishitobi et al., 2010). On the other hand, risperidone treatment was associated with two-fold to four-fold mean increases in serum prolactin in children with autism, because of its' full antagonist property at dopamine D2 receptors (Anderson et al., 2007). Although some uncertainty remains with respect to the clinical implications of elevated serum prolactin level in children and adolescents compared to adult subjects, and few guidelines exist in relation to monitoring prolactin levels in children and adolescents receiving risperidone, prolonged and substantial elevations in serum prolactin level are clearly associated with adverse events. Children and adolescents with PDD who are treated with risperidone should be monitored at least for clinical symptoms of hyperprolactinemia. Clinicians should provide appropriate alternatives including switching to aripiprazole if clinical signs of elevated prolactin are detected during risperidone treatment.

The efficacy and tolerability findings in this study should be interpreted with careful consideration of several limitations such as the open-label and retrospective design, lack of placebo control group and the small number of subjects. Additional limitations should also be considered. First, this study permitted the use of concomitant psychotropic medication. At their last visit, 52.1% of subjects were receiving concomitant medication, most frequently an antiepileptic (50.0%) or a psychostimulant (33.3%). Although it is important to recognize the influence of concomitant medication when interpreting the efficacy and tolerability findings, the use of concomitant medication is more likely to provide useful information for daily clinical practice. Further studies, which

Table 2
Medication history and clinical assessment.

	Mean ± SD
Maintenance dose (mg/day)	
Risperidone	0.7 ± 0.5
Aripiprazole	2.8 ± 1.3
CGI-S	
Baseline (before taking risperidone)	5.5 ± 1.2
endpoint of risperidone treatment	4.7 ± 1.4*
endpoint of aripiprazole treatment	4.6 ± 1.3*
CGI-I (comparison between risperidone treatment phase and aripiprazole treatment phase)	3.4 ± 0.8
Duration of treatment (weeks), Mean ± SD	
Risperidone	145.8 ± 96.2
Aripiprazole	14.9 ± 8.4

CGI-S; Clinical Global Impression Severity, CGI-I; Clinical Global Impression Improvement,
*P<0.05, versus baseline (Wilcoxon signed-rank tests).

assess the efficacy and tolerability of switching from risperidone monotherapy to aripiprazole monotherapy, are needed.

Second, one must consider the short study period and the lack of a fixed end-point as limits to conclusions related to the longer-term efficacy or safety of switching to aripiprazole in this population. Along with a longer-term prospective study evaluating the efficacy of aripiprazole, it is necessary to assess systematic safety evaluations, based on reports of adverse events, vital signs, ECG findings, weight, and laboratory assessments, in addition to structured assessment of extrapyramidal symptoms. Third, because low-dosage aripiprazole was used in this population, a minimally effective dosage or a maximally tolerated dosage of aripiprazole was not identified. Therefore, to establish the drug switching algorithm, further studies investigating the dose-dependent effects of aripiprazole switched from risperidone are needed. In addition, further studies are also needed to investigate whether lowering the risperidone dosage would have similar effect as switching to aripiprazole or not. Fourth, because the studied population was diverse, mainly included subjects with autistic disorder, the generalizability of these results to PDD of other type is unknown. Fifth, although diagnoses were made by trained child and adolescent psychiatrists using DSM-IV-TR criteria, additional diagnostic instrument such as Autism Diagnostic Interview-Revised (Lord et al., 1994) should also be administered. Additionally, we have used only CGI-S and CGI-I, which are not specific measures for improvement, as outcome measures. We should also have used some other behavioral rating scale including the Aberrant Behavior Checklist- Irritability subscale, which has frequently been used in previous studies (Marcus et al., 2009; Owen et al., 2009), to assess clinical changes precisely. Finally, because this study was not a systematic comparison study, judgments related to the relative efficacy and tolerability of aripiprazole compared with other antipsychotic agents including risperidone cannot be made.

5. Conclusion

These findings of this retrospective study suggest that switching to aripiprazole was generally well tolerated and that it might be an effective treatment option for subjects with PDD experiencing insufficient efficacy or tolerability issues with risperidone treatment. Additional long-term controlled studies are warranted to evaluate the efficacy and safety of switching to aripiprazole from other antipsychotics in PDD subjects.

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