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研究と報告

思春期から成人期における広汎性発達障害の行動チェックリスト*

日本自閉症協会版広汎性発達障害評定尺度(PARS)の信頼性・妥当性についての検討

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広汎性発達障害(Pervasive Developmental Disorders：PDD)を評価するために作成された日本自閉症協会検討委員会版広汎性発達障害評定尺度(PDD—Autism Society Japan Rating Scale：PARS)を青年成人に用いて，その信頼性と妥当性を検討した。思春期以降を対象とするPARS思春期成人期尺度は，幼児期・児童期の行動を回顧的に評価する項目群と，現在の行動を評価する項目群から構成され，それぞれスクリーニングと現在の支援ニーズの把握を目的とする。幼児期34項目と現在評価33項目はともに十分な内部一貫性と弁別妥当性を有することが示された。これらより，PARS思春期成人期尺度はPDDのスクリーニング尺度として有用であることが示された。

Key words

Pervasive developmental disorders, Adolescence and adulthood, Screening, Reliability, Validity

はじめに

広汎性発達障害(Pervasive Developmental Disorders；PDD)は，自閉症と自閉症近縁障害からなるDSM/ICD体系における障害群で，相互的対人関係の障害を中心症状とし，種々の程度のコミュニケーション障害と行動や思考の常同性を特徴とする。PDDの下位カテゴリーには，自閉症やアスペルガー症候群，非定型自閉症(DSM-IV[1)]では特定不能の広汎性発達障害，Pervasive Developmental Disorders Not Otherwise Specified；PDD-NOS)などがあるが，厳密なカテゴリー分類は難しいことがある[5,21)]。PDDに共通する重篤で持続的な社会性の障害は，思春期か

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* Reliability and Validity of the Pervasive Developmental Disorder(PDD)—Autism Society Japan Rating Scale(PARS)：A behavior checklist for adolescents and adults with PDDs

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ら成人期に至って顕著な社会不適応を2次的に引き起こし，多くは生涯にわたる一貫した支援が必要である。しかしながら，青年成人におけるPDD，とりわけ高機能(知的障害を伴わない，IQ 70以上)群の診断は困難であり，しばしば統合失調症などの誤診に陥りやすく[10]，わが国では，2005年4月より発達障害者支援法が施行され，法的整備が始まったところである。PDDは幼児期から成人期まであらゆるライフステージと，重度知的障害から正常知能までの幅広い認知発達水準にわたってみられる。しかし，このように多様なPDD全体に対応し得る簡便な評価尺度は，医療，教育，福祉，司法など種々の領域において求められているが，現在のところほとんど存在しない。

PDDの評価尺度には，専門家が直接本人の行動観察を行うものと，親からの情報に基づくものとがある。前者には，自閉症診断観察スケジュール包括版(Autism Diagnostic Observation Schedule-Generic；ADOS-G)[15]や小児自閉症評定尺度(Childhood Autism Rating Scale；CARS)[14,20]などがあるが，いずれも訓練を受けた専門家が実施するように作成されていて，簡便とは言いがたい。後者には，乳幼児期自閉症チェックリスト(Checklist for Autism in Toddlers；CHAT)[2]や修正版CHAT(Modified Checklist for Autism in Toddlers；M-CHAT)[19]のように2歳前後の幼児を対象とするものや，自閉行動チェックリスト(Autism Behavior Checklist；ABC)[12]のように重度の障害児を対象とするもの，高機能自閉症スペクトラム・スクリーニング質問紙(High-Functioning Autism Spectrum Screening Questionnaire；ASSQ)[7]のように高機能PDD児童を対象とするもの，そして自閉症スペクトラム指標(Autism-Spectrum Quotient：AQ)[3,13]のように正常知能の成人を対象とするものなど，対象の年齢や認知発達水準が限定されるものが多い。

PDDに特徴的な行動には，診断的意義のある特異的行動と，診断的意義は少ないがしばしば合併する非特異的行動があり，また年齢や認知発達水準に無関係に存在する行動の他に，幼児期に顕著であるが加齢や認知発達とともに目立たなくなる行動，逆に言語や認知発達に伴って顕著になる行動がある。PDDを疑う青年成人を評価する場合，診断のためには幼児期行動を回顧的に評価することが重要であり，支援のためには現在の特異的行動と非特異的行動の双方を評価する必要がある。自閉症スクリーニング質問紙(Autism Screening Questionnaire；ASQ)[4,6]は，すべての年齢とすべての認知発達水準をカバーするPDDスクリーニング尺度であるが，ほとんどの項目はPDDの主要3領域に関する幼児期の行動を尋ねており，現在の状態像を把握するには不十分である。自閉症診断面接改訂版(Autism Diagnostic Interview-Revised；ADI-R)[16]もすべての年齢と認知発達水準に対応したPDD評価尺度であるが，高度の訓練を経た専門家向けで，長時間を要し実用的ではない。

これらを踏まえて，我々は幼児期から成人期のいずれの年齢段階にも対応可能で，あらゆる認知発達水準のPDD者の行動をとらえ得るPDD評価尺度，日本自閉症協会版広汎性発達障害評定尺度(PDD-Autism Society Japan Rating Scales；PARS)[18]を作成した。PARSの目的は，第一に，熟練した専門家が乏しいわが国において，医療のみならず教育，福祉，司法などのさまざまな領域で臨床家が使用し，専門家による詳細な評価が必要なケースのスクリーニングが可能な尺度を提供することである。第二に，支援ニーズの判定および治療や教育の効果判定に必要な，状態像を総合的に把握する尺度を提供することである。この2つの目的に対応し，PARSで青年成人を評価する場合，診断的価値が高い幼児期行動についての回顧評価と，現在の状態像の把握のために児童期や思春期以降に出現した行動の現在評価の両方を行い，必要に応じて児童期行動の回顧評価も行う。

本論文では，思春期以降の青年および成人を対象に，PARSの信頼性と妥当性を検討したので

報告する。

方法

1．対象

全国5か所の医療・心理・教育機関から紹介された53名のPDD群と42名の非PDD群の計95名の青年および成人が本研究に参加した。PDDの診断は，自閉症について熟練した精神科医により，DSM-IV[1]に基づいて行われ，非PDD群は自閉症について熟練した精神科医によりPDDを除外診断されている。PDD群(男43，女10：平均年齢＝17歳7か月±6歳1か月：範囲＝12～34歳：IQ＜70が11名，IQ≧70が26名，IQ不明が16名)の内訳は自閉症が14人，アスペルガー症候群が28人，PDD・自閉傾向が11人であった。非PDD群(男14，女27，性別不明が1名：平均年齢＝18歳2か月±5歳3か月：範囲＝12～33歳：IQ＜70が8名，IQ≧70が19名，IQ不明が15名)の内訳は統合失調症が11名，適応障害が8名，気分障害が5名，注意欠陥/多動性障害(AD/HD)が4名，精神遅滞が4名，行為障害が3名，強迫性障害3名などであった。両群は年齢と知能水準の分布は似ていたが，PDD群は男性優位に対し，非PDD群は女性優位と性比が異なった。

これとは別に，評価者間信頼性の検討には，12名から成るPDD群(平均年齢＝16歳8か月±3歳10か月：範囲＝12歳6か月～26歳3か月：性比は不明：IQ＜70が4名，IQ≧70が8名)のデータを分析した。

2．PARS

表1に示すPARSは，①対人，②コミュニケーション，③こだわり，④常同行動，⑤困難性，⑥併発症，⑦過敏性，⑧その他(不器用)のPDDに特徴的な8領域57項目から成る。34項目(項目1～34)は幼児期，33項目(項目21～53)は児童期，33項目(項目25～57)は思春期成人期にみられる行動を尋ねており，幼児期から成人期までのすべての年齢段階を通してPDDに特徴的な行動をカバーしている。対象の年齢が思春期から成人期(中学生以降)であれば計57項目に回答する。評定者は情報提供者(多くは養育者)と面接して各項目に該当する行動の有無を尋ね，存在する場合には具体的な説明を聞き，評価マニュアルに基づいてその程度を，なし(0点)，多少目立つ(1点)，目立つ(2点)の3段階で評価する。

3．手続き

PARSの評価者間信頼性の検討のために，2名の専門家(1名は熟練した専門家，もう1名は非熟練の専門家)が同じ対象者に面接し，独立して評価した。複数ペアの専門家からデータが得られたが，対象者数が少なかったため，現在評価の思春期成人期項目の総得点(後に加えられた項目25を除く32項目)の2評価者間の相関係数を算出した。

その他の分析は，96名から得られた回顧評価の幼児期34項目と現在評価の思春期成人期33項目について行った。この2つの分析を行った理由は，スクリーニング目的には幼児期の回顧評価が，支援ニーズの評価目的には現在評価が必要なためである。児童期33項目は，本研究では分析に含めなかった。

すべての対象について，保護者から，可能な場合は本人からインフォームド・コンセントを得た。

結果

1．評価者間信頼性

項目25を除いた思春期成人期項目総得点について，評価者間のPearsonの積率相関係数は0.85で，1％水準で有意であった。一方，項目ごとの評価者間の一致度(κ)は，項目によるばらつきが大きく，0.70を超えたのは32項目中6項目であった。

2．内部一貫性

思春期成人期33項目についてのCronbachのαは，PDD群，非PDD群，両群でそれぞれ0.86，0.92，0.93，幼児期34項目でそれぞれ0.90，0.86，0.96と，いずれも十分な内部一貫性が示された。削除するとαが0.01を超えて増

表1

以下の項目について，幼児期(就学前)，児童期(小学校時代)，思春期・成人期(それ以降)における，当時の様子をご家族や本人からお聴きいただき，〔0＝なし，1＝多少目立つ，2＝目立つ〕の3段階で，該当欄の数字に○をつけてご記入ください。

＊ 就学前の幼児の方については，幼児期の項目のみを評定してください。
＊ 小学生の方については，幼児期の項目と児童期の項目の両方を評定してください。
＊ 中学1年生以上の方については，すべての項目を評定してください。
＊ ★は，その年代では評価しない項目を示します。

〔0＝なし，1＝多少目立つ，2＝目立つ〕

	幼児期	児童期	思春期
1．視線が合わない	0 1 2	★	★
2．他の子どもに興味がない	0 1 2	★	★
3．名前を呼んでも振り向かない	0 1 2	★	★
4．見せたい物を持ってくることがない	0 1 2	★	★
5．指さしで興味のあるものを伝えない	0 1 2	★	★
6．言葉の遅れがある	0 1 2	★	★
7．会話が続かない	0 1 2	★	★
8．一方通行に自分の言いたいことだけを言う	0 1 2	★	★
9．友達とごっこ遊びをしない	0 1 2	★	★
10．オウム返しの応答が目立つ	0 1 2	★	★
11．CMなどをそのままの言葉で繰り返し言う	0 1 2	★	★
12．感覚遊びに没頭する	0 1 2	★	★
13．道路標識やマーク，数字，文字が大好きである	0 1 2	★	★
14．くるくる回るものを見るのが好きである	0 1 2	★	★
15．物を横目で見たり，極度に目に近づけて見たりする	0 1 2	★	★
16．玩具や瓶などを並べる遊びに没頭する	0 1 2	★	★
17．つま先で歩くことがある	0 1 2	★	★
18．多動で，手を離すとどこに行くかわからない	0 1 2	★	★
19．食べ物でないものを食べたり呑み込んだりする	0 1 2	★	★
20．抱っこされるのを嫌がる	0 1 2	★	★
21．ビデオの特定場面を繰り返し見る	0 1 2	0 1 2	★
22．ページめくりや紙破りなど，物を同じやり方で繰り返しいじる	0 1 2	0 1 2	★
23．全身や身体の一部を，同じパターンで動かし続けることがある	0 1 2	0 1 2	★
24．身体に触れられることを嫌がる	0 1 2	0 1 2	★
25．同じ質問をしつこくする	0 1 2	0 1 2	0 1 2

加する項目はなかった。

3．項目分析と弁別妥当性

表2に示すように，幼児期項目では，項目19を除く全項目で，PDD群が非PDD群より有意に高得点であった。項目19は両群の過半数で「なし」と評価された低頻度行動であった。また表3に示すように，思春期成人期項目では，33項目中24項目でPDD群が非PDD群よりも有意に高得点であった。有意差のなかった9項目中7項目(項目27，29，33，34，48，49，53)は低頻度行動で，項目56と57は両群とも両群の過半数に見いだされた高頻度行動であった。

表4は，幼児期項目および思春期成人期項目の総得点をPDD群と非PDD群で，そしてPDD群では知的障害の有無や下位診断別に比較した。幼児期項目と思春期成人期項目はその総得点がPDD群で非PDD群より有意に高かった〔それぞれ$t(70.7)=13.63$，$p<0.001$，Welchの検定：$t(93)=8.37$，$p<0.001$〕。幼児期項目と思春期成人期項目の総得点は両群ともに有意の正相関を示した(PDD群$r=0.59$，$p<0.001$：非PDD群$r=0.32$，$p<0.05$)。

4．カットオフ

表5には，ROC分析(receiver operating characteristic analysis)により，幼児期回顧評価，現在評価のそれぞれについて求めたPARSのカッ

PARS

	〔0＝なし，1＝多少目立つ，2＝目立つ〕 幼児期	児童期	思春期
26. 普段通りの状況や手順が急に変わると，混乱する	0 1 2	0 1 2	0 1 2
27. 生活習慣が乱れ，身辺自立ができなくなる	0 1 2	0 1 2	0 1 2
28. 過去の嫌なことを思い出して，不安定になる	0 1 2	0 1 2	0 1 2
29. 偏食が激しく，食べ物のレパートリーが極端に狭い	0 1 2	0 1 2	0 1 2
30. 特定の音を嫌がる	0 1 2	0 1 2	0 1 2
31. 痛みや熱さなどに鈍感であったり，敏感である	0 1 2	0 1 2	0 1 2
32. 何でもないものをひどく怖がる	0 1 2	0 1 2	0 1 2
33. 急に泣いたり怒ったりする	0 1 2	0 1 2	0 1 2
34. 頭を壁に打ちつける，手を咬むなど，自分が傷つくことをする	0 1 2	0 1 2	0 1 2
35. 年齢相応の友達関係がない	★	0 1 2	0 1 2
36. 周囲に配慮せず自分中心の行動をする	★	0 1 2	0 1 2
37. 人からかかわられた時の対応が場にあっていない	★	0 1 2	0 1 2
38. 要求がある時だけ自分から人にかかわる	★	0 1 2	0 1 2
39. 言われたことを場面に応じて理解するのが難しい	★	0 1 2	0 1 2
40. 難しい言葉を使うが，その意味をよくわかっていない	★	0 1 2	0 1 2
41. 大勢の会話では，誰が誰に話しているのかがわからない	★	0 1 2	0 1 2
42. どのように，なぜ，といった説明ができない	★	0 1 2	0 1 2
43. 抑揚の乏しい不自然な話し方をする	★	0 1 2	0 1 2
44. 人の気持ちや意図がわからない	★	0 1 2	0 1 2
45. 冗談や皮肉がわからず，文字通り受け取る	★	0 1 2	0 1 2
46. 地名や駅名など，特定のテーマに関する知識獲得に没頭する	★	0 1 2	0 1 2
47. よく知っているテレビのシーンを独りで再現する	★	0 1 2	0 1 2
48. 相手が嫌がることをわざと執拗に繰り返す	★	0 1 2	0 1 2
49. 何かにつけ自分が一番でないと気がすまない	★	0 1 2	0 1 2
50. チック症状(瞬き・首振り・汚言など)がある	★	0 1 2	0 1 2
51. 場に不適切なほど，行動が落ち着かない	★	0 1 2	0 1 2
52. 不注意さがひどく，場に応じた行動ができない	★	0 1 2	0 1 2
53. 行動が止まって次の行動に移れなくなったり，固まってしまったりする	★	0 1 2	0 1 2
54. 恥ずかしさを感じていないように思える	★	★	0 1 2
55. 人にだまされやすい	★	★	0 1 2
56. 被害的あるいは猜疑的・攻撃的になりやすい	★	★	0 1 2
57. 気分の波が激しく，落ち込みと興奮を繰り返す	★	★	0 1 2

トオフを示すが，スクリーニングを目的とした場合，幼児期項目のカットオフは10点が最適と判断した。この値は，PDD群の94.3％(感度)を正しくPDDと評価し，非PDD群の92.9％(特異度)を正しく非PDDと評価した。またPARSがPDDと判断した者のうち真にPDDであったのは94.3％(陽性的中率)で，非PDDと判断した者のうち真に非PDDであったのは92.9％(陰性的中率)であった。思春期成人期項目のカットオフを20点とすると，感度81.1％，特異度85.7％，陽性的中率87.8％，陰性的中率78.3％となり，スクリーニングとして最適と判断した。

5．知的障害の有無と尺度得点との関係

PDD群を，知的障害のない高機能群(n＝26)と知的障害を伴う非高機能群(n＝11)の2群に分けて，幼児期項目と思春期成人期項目の総得点を比較した(表4)。高機能群では，幼児期，思春期成人期項目ともに非高機能群より総得点は低かったが，その差は幼児期項目においてのみ有意だった〔$t(23.2)=2.75$，$p<0.05$，Welchの検定〕。2群で各項目を比較すると，幼児期の7項目(3，6，10，12，15，22，23)は非高機能群が高機能群よりも有意に高得点であった(いずれも$p<0.05$，U検定)。思春期成人期項目では，項目25と項目45で非高機能群が高機能群よりも高得点であ

表2 PDD群と非PDD群における幼児期項目の頻度

項目	PDD群 頻度(相対頻度)			非PDD群 頻度(相対頻度)			Mann-Whitney の U検定
	なし(0)	多少目立つ(1)	目立つ(2)	なし(0)	多少目立つ(1)	目立つ(2)	
1	18 (34%)	16 (30%)	19 (36%)	42(100%)	0 (0%)	0 (0%)	$p<0.001$
2	9 (17%)	13 (25%)	31 (58%)	38 (90%)	4 (10%)	0 (0%)	$p<0.001$
3	26 (49%)	7 (13%)	20 (38%)	40 (95%)	2 (5%)	0 (0%)	$p<0.001$
4	25 (47%)	11 (21%)	17 (32%)	40 (95%)	2 (5%)	0 (0%)	$p<0.001$
5	21 (40%)	10 (19%)	22 (42%)	37 (88%)	4 (10%)	1 (2%)	$p<0.001$
6	12 (23%)	10 (19%)	31 (58%)	33 (79%)	5 (12%)	4 (10%)	$p<0.001$
7	10 (19%)	6 (11%)	37 (70%)	34 (81%)	5 (12%)	3 (7%)	$p<0.001$
8	8 (15%)	12 (23%)	33 (62%)	30 (71%)	11 (26%)	1 (2%)	$p<0.001$
9	5 (9%)	10 (19%)	38 (72%)	37 (88%)	3 (7%)	2 (5%)	$p<0.001$
10	19 (36%)	6 (11%)	28 (53%)	40 (95%)	2 (5%)	0 (0%)	$p<0.001$
11	13 (25%)	9 (17%)	31 (58%)	34 (81%)	5 (12%)	3 (7%)	$p<0.001$
12	26 (49%)	10 (19%)	17 (32%)	37 (88%)	4 (10%)	1 (2%)	$p<0.001$
13	19 (36%)	7 (13%)	27 (51%)	38 (90%)	3 (7%)	1 (2%)	$p<0.001$
14	30 (57%)	15 (28%)	8 (15%)	40 (95%)	2 (5%)	0 (0%)	$p<0.001$
15	33 (62%)	11 (21%)	9 (17%)	41 (98%)	0 (0%)	1 (2%)	$p<0.001$
16	20 (38%)	13 (25%)	20 (38%)	39 (93%)	2 (5%)	1 (2%)	$p<0.001$
17	36 (68%)	8 (15%)	9 (17%)	39 (93%)	2 (5%)	1 (2%)	$p<0.05$
18	15 (28%)	10 (19%)	28 (53%)	35 (83%)	5 (12%)	2 (5%)	$p<0.001$
19	45 (85%)	6 (11%)	2 (4%)	39 (93%)	1 (2%)	2 (5%)	n.s.
20	31 (58%)	6 (11%)	16 (30%)	41 (98%)	0 (0%)	1 (2%)	$p<0.001$
21	21 (40%)	10 (19%)	22 (42%)	38 (90%)	2 (5%)	2 (5%)	$p<0.001$
22	32 (60%)	11 (21%)	10 (19%)	38 (90%)	4 (10%)	0 (0%)	$p<0.01$
23	33 (62%)	10 (19%)	10 (19%)	42(100%)	0 (0%)	0 (0%)	$p<0.001$
24	30 (57%)	9 (17%)	14 (26%)	42(100%)	0 (0%)	0 (0%)	$p<0.001$
25	19 (36%)	10 (19%)	24 (45%)	40 (95%)	1 (2%)	1 (2%)	$p<0.001$
26	16 (30%)	11 (21%)	26 (49%)	36 (86%)	6 (14%)	0 (0%)	$p<0.001$
27	39 (74%)	7 (13%)	7 (13%)	39 (93%)	3 (7%)	0 (0%)	$p<0.05$
28	35 (66%)	9 (17%)	9 (17%)	39 (93%)	3 (7%)	0 (0%)	$p<0.01$
29	23 (43%)	7 (13%)	23 (43%)	36 (86%)	5 (12%)	1 (2%)	$p<0.001$
30	25 (47%)	6 (11%)	22 (42%)	38 (90%)	2 (5%)	2 (5%)	$p<0.001$
31	17 (32%)	13 (25%)	23 (43%)	39 (93%)	3 (7%)	0 (0%)	$p<0.001$
32	26 (49%)	6 (11%)	21 (40%)	41 (98%)	1 (2%)	0 (0%)	$p<0.001$
33	28 (53%)	7 (13%)	18 (34%)	39 (93%)	2 (5%)	1 (2%)	$p<0.001$
34	39 (74%)	6 (11%)	8 (15%)	40 (95%)	1 (2%)	1 (2%)	$p<0.05$

ったが，項目56では逆に高機能群のほうが高得点であった(いずれも$p<0.05$，U検定)。幼児期項目，思春期成人期項目のカットオフをそれぞれ10点，20点とすると，非高機能群の全員が両カットオフを超えた。一方，高機能群の26名中23名(88%)は幼児期項目のカットオフを超えたが，思春期成人期カットオフを超えたのは18名(69%)で，この18名は幼児期カットオフも超えた。

6. PDD群の下位診断と尺度得点との関係

表4に示すように，幼児期項目総得点を自閉症，アスペルガー症候群，その他のPDDの3群で比較すると有意差があり〔$F(2,50)=6.12$, $p<0.01$〕，多重比較(TukeyのHSD法)の結果，自閉症がアスペルガー症候群より有意に高得点であった($p<0.01$)。思春期成人期項目評定では下位診断による有意な差はなかった。自閉症の全員が幼児期，思春期成人期ともにカットオフを超えた。アスペルガー症候群では，28名中25名(89%)が幼児期項目のカットオフを超え，そのうち21名(75%)が思春期成人期のカットオフも超えた。その他のPDDの11名全員が幼児期項目のカットオフを超え，そのうち8名(73%)が幼児

表3　PDD群と非PDD群における思春期成人期項目の頻度

項目	PDD群 頻度(相対頻度)			非PDD群 頻度(相対頻度)			Mann-Whitney の U検定
	なし(0)	多少目立つ(1)	目立つ(2)	なし(0)	多少目立つ(1)	目立つ(2)	
25	10 (19%)	14 (26%)	29 (55%)	33 (79%)	9 (21%)	0 (0%)	$p<0.001$
26	19 (36%)	25 (47%)	9 (17%)	27 (64%)	13 (31%)	2 (5%)	$p<0.05$
27	39 (74%)	6 (11%)	8 (15%)	28 (67%)	8 (19%)	6 (14%)	n.s.
28	18 (34%)	18 (34%)	17 (32%)	26 (62%)	10 (24%)	6 (14%)	$p<0.05$
29	38 (72%)	11 (21%)	4 (8%)	33 (79%)	7 (17%)	2 (5%)	n.s.
30	22 (42%)	13 (25%)	18 (34%)	35 (83%)	5 (12%)	2 (5%)	$p<0.001$
31	19 (36%)	17 (32%)	17 (32%)	33 (79%)	8 (19%)	1 (2%)	$p<0.001$
32	32 (58%)	9 (16%)	14 (25%)	34 (81%)	6 (14%)	2 (5%)	$p<0.05$
33	31 (58%)	9 (17%)	13 (25%)	27 (64%)	10 (24%)	5 (12%)	n.s.
34	34 (64%)	16 (30%)	3 (6%)	29 (69%)	11 (26%)	2 (5%)	n.s.
35	6 (11%)	10 (19%)	37 (70%)	25 (60%)	11 (26%)	6 (14%)	$p<0.001$
36	8 (15%)	24 (45%)	21 (40%)	28 (67%)	10 (24%)	4 (10%)	$p<0.001$
37	6 (11%)	28 (53%)	19 (36%)	30 (71%)	8 (19%)	4 (10%)	$p<0.001$
38	13 (25%)	17 (32%)	23 (43%)	35 (83%)	5 (12%)	2 (5%)	$p<0.001$
39	12 (23%)	22 (42%)	19 (36%)	29 (69%)	9 (21%)	4 (10%)	$p<0.001$
40	22 (42%)	12 (23%)	19 (36%)	31 (74%)	8 (19%)	3 (7%)	$p<0.001$
41	13 (25%)	17 (32%)	23 (43%)	36 (86%)	4 (10%)	2 (5%)	$p<0.001$
42	9 (17%)	23 (43%)	21 (40%)	29 (69%)	9 (21%)	4 (10%)	$p<0.001$
43	27 (51%)	12 (23%)	14 (26%)	40 (95%)	2 (5%)	0 (0%)	$p<0.001$
44	7 (13%)	22 (42%)	24 (45%)	30 (71%)	8 (19%)	4 (10%)	$p<0.001$
45	5 (9%)	22 (42%)	26 (49%)	26 (62%)	11 (26%)	5 (12%)	$p<0.001$
46	11 (21%)	15 (28%)	27 (51%)	33 (79%)	8 (19%)	1 (2%)	$p<0.001$
47	27 (51%)	11 (21%)	15 (28%)	37 (88%)	4 (10%)	1 (2%)	$p<0.001$
48	36 (68%)	7 (13%)	10 (19%)	31 (74%)	9 (21%)	2 (5%)	n.s.
49	38 (72%)	12 (23%)	3 (6%)	28 (67%)	13 (31%)	1 (2%)	n.s.
50	34 (64%)	14 (26%)	5 (9%)	42(100%)	0 (0%)	0 (0%)	$p<0.001$
51	31 (58%)	15 (28%)	7 (13%)	35 (83%)	6 (14%)	1 (2%)	$p<0.01$
52	24 (45%)	18 (34%)	11 (21%)	30 (71%)	6 (14%)	6 (14%)	$p<0.05$
53	34 (64%)	12 (23%)	7 (13%)	30 (71%)	11 (26%)	1 (2%)	n.s.
54	17 (32%)	16 (30%)	20 (38%)	23 (55%)	13 (31%)	6 (14%)	$p<0.01$
55	8 (15%)	18 (34%)	27 (51%)	23 (55%)	11 (26%)	8 (19%)	$p<0.001$
56	19 (36%)	16 (30%)	18 (34%)	21 (50%)	13 (31%)	8 (19%)	n.s.
57	19 (36%)	18 (34%)	16 (30%)	21 (50%)	10 (24%)	11 (26%)	n.s.

表4　幼児期項目と思春期成人期項目の総得点の群別比較

	幼児期項目総得点 (0~68)	思春期成人期項目総得点 (0~66)
非PDD群(n=42)		
M(SD)	3.79(5.34)[a]	11.90(10.48)[b]
PDD群(n=53)		
M(SD)	31.66(13.63)[a]	30.28(10.75)[b]
知的障害の有無		
なし 高機能群(n=26)	28.04(14.44)[c]	28.65(12.26)
あり 非高機能群(n=11)	40.45(11.67)[c]	31.27 (7.54)
下位診断名		
自閉症(n=14)	40.29(11.19)[d]	35.93 (9.32)
アスペルガー症候群(n=28)	26.36(12.92)[d]	29.00(11.43)
その他のPDD(n=11)	34.18(12.74)	26.36 (8.30)

[a] PDD群＞非PDD群，[b] PDD群＞非PDD群，[c] 非高機能PDD群＞高機能PDD群，
[d] 自閉症＞アスペルガー症候群

表5 PARS思春期成人期尺度のカットオフと関連指標

カットオフポイント	感度	特異度	陽性的中率	陰性的中率
幼児期回顧評価				
7	0.962	0.786	0.850	0.943
8	0.962	0.833	0.879	0.946
9	0.943	0.881	0.909	0.925
10	*0.943*	*0.929*	*0.943*	*0.929*
11	0.943	0.929	0.943	0.929
12	0.925	0.929	0.942	0.907
13	0.906	0.929	0.941	0.886
現在評価				
16	0.925	0.738	0.817	0.886
17	0.887	0.762	0.825	0.842
18	0.849	0.810	0.849	0.810
19	0.811	0.833	0.860	0.778
20	*0.811*	*0.857*	*0.878*	*0.783*
21	0.774	0.881	0.891	0.755
22	0.774	0.881	0.891	0.755
23	0.755	0.905	0.909	0.745
24	0.717	0.905	0.905	0.717

イタリックで示した幼児期回顧評価の10点と現在評価の20点はそれぞれカットオフとして最適と判断された。

期と思春期成人期のカットオフを超えた。

7. PDD群における発達的変化：幼児期・思春期成人期共通項目の比較

項目25から項目34までの10項目は，幼児期，児童期，思春期以降成人期のすべてにおいてPDDに特徴的な行動であり，各時期で評価される。幼児期は回顧的情報による評価，思春期成人期は現在の情報による評価であり，両者の厳密な比較はできないが，これら10項目の幼児期の回顧評価と現在評価を周辺等質性検定で比較した。得点が，回顧評価で現在評価より有意($p<0.05$)に低かったのは3項目(項目26，29，32)，有意($p<0.05$)に高かったのは2項目(項目25，28)であり，有意差がなかったのは5項目(項目27，30，31，33，34)で，うち4項目は感覚反応や衝動性に関連する行動であった。

考察

本研究において，PARS思春期成人期尺度の幼児期項目は高い内部一貫性を示し，ほとんどすべての幼児期項目と総得点はPDD群を非PDD群から有意に区別し，高い弁別妥当性を示した。思春期成人期項目については，高い評価者間信頼性と内部一貫性を有し，かつ多くの項目と総得点はPDD群を非PDD群から有意に区別し，十分な弁別妥当性が示された。また幼児期回顧評価と現在評価は相関しており，PDDのスクリーニングにはいずれを用いても有用なことが示された。

PARSの幼児期項目は，PDD診断に必須の対人相互性・コミュニケーション・反復常同的パターンの3徴候に含まれない，感覚，情緒，多動性に関連する項目がその約1/3を占める。これらのPDD非特異的な行動がきっかけとなり，受診や診断につながることは少なくない[8,11,17]。本研究において，このような非特異的行動に関連した幼児期項目も，特異的行動項目と同様に，PDD群と非PDD群を高い精度で識別することが示され，スクリーニングに含めた意義が支持された。唯一，異食行動では有意差がなかったが，これはこの行動がPDD群の15％のみに報告された低頻度行動のためと考えられる。

幼児期項目のカットオフを10点とすると，青年成人臨床群におけるPDDの判別は，高い精度で可能であった。カットオフに満たなかったPDD群の3名は，アスペルガー症候群で，カットオフを超えた非PDD群の3名は，重度の知的障害2名と，AD/HD1名であった。一般に，アスペルガー症候群は幼児期での診断は困難とされる[9,17]。また重度の知的障害を持つ幼児では，親面接による評価尺度[16]，子どもの行動観察による評価尺度[14,20]のいずれを用いても，PDDと非PDDの判別は難しい。PARSの幼児期回顧評価項目を用いてPDDをスクリーニングする際には，他の尺度と同様，アスペルガー症候群や重度の知的障害群についての判別力がやや弱い点に留意して，他の情報と組み合わせて用いるとより精度が高まるであろう。

青年や成人になると，早期幼児期の発達情報が不十分な場合がしばしばあり，現在の状態像のみに基づいて診断評価を行わざるを得ない場合もある。本研究では非PDDの精神障害を有する青年

成人を対照群としたため，思春期成人期項目の判別力は幼児期項目と比べるとやや低くなったが，PDDのスクリーニングとしては満足すべき結果であった。カットオフ20点に満たなかったPDD群10名は，アスペルガー症候群7名と知的障害を伴うPDD-NOSの2名(知的水準は不明)，そして高IQのPDD-NOSの1名であった。カットオフを超えた非PDD群6名は，統合失調症4名，行為障害とてんかんの合併1名，そしてAD/HD1名(幼児期項目でもカットオフを超えた青年と同一人物)であった。このように，アスペルガー症候群やPDD-NOSについては，思春期成人期項目の得点は低くなりやすく，一部の非PDD青年成人は高得点となったので，実際の青年成人の評価に際しては，より判別力の高い幼児期回顧評価項目とともに他の情報と組み合わせることが望ましい。対照群のAD/HD青年1名は，DSM-IVの除外診断ルールにより非PDDとされたが，実際にはPARSがとらえたようにPDDの特徴を持っていたことから，臨床的にはPARS思春期成人期尺度は適切であったと思われる。

PARSはスクリーニング機能に加えて，支援計画立案に必要な情報を提供する。PDDの判別力が低かった項目は，低頻度だが存在すると日常生活への影響が大きく，極端な場合，社会生活に破壊的影響を与えるという点で，支援ニーズの総合的評価に必要と考えられる。逆に判別力が低かった思春期成人期項目には，非PDD群にもPDD群と同程度に高頻度にみられた行動も含まれた((項目56「被害念慮」と項目57「気分変動」)など)。PDDは思春期以降，PDD固有の症状に加えて2次的，3次的な症状が複合化し，複雑な臨床像となることが少なくない。PDDの判別力が劣るこれらの項目も，青年成人の複雑な臨床像を総合的に把握するうえでは重要な情報を提供すると考えられる。

本研究には限界点が複数存在する。第一に，思春期成人期の各項目について，評価者間の一致度がばらつく要因を明らかにするために，評価者および対象の人数を増やして検討する必要がある。第二に，回顧評価の幼児期項目についても評価者間信頼性を検討する必要がある。第三に，PDD群を知能水準や下位診断によって下位群に分類すると，それぞれの人数が少なくなり詳細な分析ができなかった。第四に，対照群との比較において，性比が統制されていなかったので性比の影響が検討できなかった。今後，より大きなサンプルに基づいた青年成人臨床群との比較研究を行って，以上の問題の解決と，PARS思春期成人期尺度の利点と限界点をより明確にしていく課題が残された。

本研究は，PDD思春期成人期尺度が，スクリーニングツールとして，また総合的な支援計画立案の基礎資料として，医療，教育，福祉，司法など幅広い臨床場面で用いるのに有用な尺度である可能性を示した。

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Summary

Reliability and Validity of the Pervasive Developmental Disorder(PDD)—Autism Society Japan Rating Scale(PARS)：A behavior checklist for adolescents and adults with PDDs

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A behavior checklist, the Pervasive Developmental Disorder(PDD)—Autism Society Japan Rating Scale (PARS), was developed as a screening questionnaire to determine Pervasive Developmental Disorders(PDDs) and also as a rating scale to evaluate the severity of a wide range of PDD symptoms. When assessing adoles-

cents and adults using the PARS for these purposes, 34 toddlerhood items are evaluated retrospectively and 33 items are used for current evaluation. In this study, the reliability and validity of the PARS was tested on a clinical sample of 53 adolescents and adults with PDD and 42 with non-PDD diagnoses. Interrater and internal reliability was found to be adequate. Both the 34 toddlerhood evaluation items and the 33 current evaluation items accurately discriminated PDD from non-PDD. Results suggested that the PARS may be a useful screening scale for various clinical settings.

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Increased serum levels of glutamate in adult patients with autism

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Abstract

Background: Precise mechanisms underlying the pathophysiology of autism are currently unknown. Given the major role of glutamate in brain development, we have hypothesized that glutamatergic neurotransmission plays a role in the pathophysiology of autism. In this study, we studied whether amino acids (glutamate, glutamine, glycine, D-serine, and L-serine) related to glutamatergic neurotransmission are altered in serum of adult patients with autism.
Methods: We measured serum levels of amino acids in 18 male adult patients with autism and age-matched 19 male healthy subjects using high-performance liquid chromatography.
Results: Serum levels (mean=89.2 μM, S.D.=21.5) of glutamate in the patients with autism were significantly ($t=-4.48$, $df=35$, $p<0.001$) higher than those (mean=61.1 μM, S.D.=16.5) of normal controls. In contrast, serum levels of other amino acids (glutamine, glycine, D-serine, L-serine) in the patients with autism did not differ from those of normal controls. There was a positive correlation ($r=0.523$, $p=0.026$) between serum glutamate levels and Autism Diagnostic Interview–Revised (ADI-R) social scores in patients.
Conclusions: The present study suggests that an abnormality in glutamatergic neurotransmission may play a role in the pathophysiology of autism.

Keywords: Amino acids; Autism; D-Serine; Glutamate; HPLC; Human serum

1. Introduction

Autism is a neuropsychiatric disorder characterized by severe and sustained impairment in social interaction, deviance in communication, and patterns of behavior and interest that are restricted, stereotyped, or both (Volkmar and Pauls, 2003). Although genetic and environmental factors are implicated in the pathophysiology of autism, the precise mechanisms underlying the pathophysiology of this disorder remain to be determined (Volkmar and Pauls, 2003; Baron-Cohen and Belmonte, 2005; Polleux and Lauder, 2004; McDougle et al., 2005).

Glutamate, the major excitatory neurotransmitter in the brain, plays a major role in brain development, affecting neuronal migration, neuronal differentiation, axon genesis, and neuronal survival (Coyle et al., 2002). Accumulating evidence suggests that abnormalities in glutamatergic neurotransmission may play a role in the pathophysiology of autism (McDougle et al., 2005). First, cDNA microarray technology has demonstrated that the glutamate neurotransmitter system is abnormal in postmortem brain samples of autism (Purcell et al., 2001). The mRNA levels of genes, including excitatory amino acid transporter 1 (EAAT 1) and AMPA-type glutamate receptor, are significantly increased in the brain of autism, suggesting abnormalities of glutamatergic neurotransmission in the pathogenesis of this disorder (Purcell et al., 2001). Genetic studies have demonstrated the involvement

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of single nucleotide polymorphisms (SNPs) in the genes encoding both metabotropic and ionotropic glutamate receptors in autism (Jamain et al., 2002; Serajee et al., 2003). Furthermore, a strong association of autism with SNPs within SLC25A12, a gene encoding the mitochondrial aspartate/glutamate carrier (AGC1), has been demonstrated, suggesting the potential etiological role of AGC1 in autism (Ramoz et al., 2004; Segurado et al., 2005). However, recent two studies using large samples did not confirm the association of SLC25A12 gene and autism, suggesting that the SLC25A12 gene is not a major contributor to genetic susceptibility of autism (Blasi et al., 2006; Rabionet et al., 2006).

Second, it has been reported that blood levels of glutamate are altered in patients with autism (Rolf et al., 1993; Moreno-Fuenmayor et al., 1996; Aldred et al., 2003). Rolf et al. (1993) have reported that plasma levels of glutamate in children (8–14-year-olds) with autism are significantly decreased compared to age-matched healthy controls. In contrast, Aldred et al. (2003) have reported that plasma levels of glutamate in patients (4–29 year-olds) with autism or Asperger's syndrome are significantly increased compared with controls. One of the reasons for such contradictory findings could be a difference in sample composition; the study by Aldred et al. (2003) incorporated a wider age range. Nonetheless, previous studies indicate alterations in the glutamatergic system expressed at the periphery level. The studies reporting on blood levels of glutamate in autistic patients present inconsistent results. Therefore, it is of great interest to examine whether levels of amino acids such as glutamate are altered in autistic patients.

Several lines of evidence suggest that D-serine, an endogenous co-agonist at the NMDA receptors, plays a role in the pathophysiology of schizophrenia, which is a neurodevelopmental disorder (Snyder and Ferris, 2000; Coyle and Tsai, 2004; Hashimoto et al., 2005a). We have previously reported that serum levels of D-serine are significantly decreased in patients with schizophrenia (Hashimoto et al., 2003; Yamada et al., 2005). However, to our knowledge, serum D-serine levels have never been investigated in relation to autism.

The purpose of the present study was, therefore, to examine whether individuals with autism have aberrant serum levels of D-serine as well as other amino acids (glutamate, glutamine, glycine, and L-serine) associated with glutamatergic neurotransmission. Furthermore, we also examined any relationship between amino acid levels and clinical symptoms in autistic patients.

2. Methods

2.1. Participants

Eighteen male autistic subjects (mean age = 21.2 years, S.D. = 2.1, range = 18–26) and age-matched 19 male healthy control subjects (mean = 22.2 years, S.D. = 2.2, range = 18–26) were included in this study (Table 1). All participants for both groups were Japanese. The autistic subjects were recruited through advocacy groups in Nagoya and Hamamatsu cities, which are located in the middle of the mainland of Japan. For the diagnosis of autism, the recruited individuals were initially assessed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)(American Psychiatric Association, 1994), followed by assessment using the Autism Diagnostic Interview–Revised (ADI-R)(Lord et al., 1994) by trained child psychiatrists clinicians (KJT and AS). Participants were excluded from the study, if they had a diagnosis of fragile X syndrome, epileptic seizures, obsessive–compulsive disorder, affective disorders, or any additional psychiatric or neurological diagnoses. All the autistic subjects were drug-naive or had been free of psychoactive medications for at least 6 months. Healthy controls were recruited from Hamamatsu City by advertisement. All control-group participants underwent a comprehensive assessment of medical history to eliminate individuals with any neurological or other medical disorders. The Structured Clinical Interview for the DSM-IV (SCID) was also conducted to scrutinize any personal or familial history of past or present mental illness. None of the comparison subjects initially recruited was found to fulfill these exclusion procedures. After the participants were given a complete description of the study, written informed consent was obtained from all subjects before they entered the study. This study received approval from the ethics committee of the Hamamatsu University School of Medicine and Chiba University Graduate School of Medicine.

Table 1
Clinical characteristics of 18 adult patients with autism

Characteristics	Mean ± S.D. (range)
Age at onset (years)	3.72 ± 1.07 (1–5)
Duration of illness (years)	17.5 ± 2.23 (14–22)
ADI-R	
A. Social	22.11 ± 4.96 (14–29)
B. Communication	15.44 ± 4.84 (6–21)
C. Stereotype	5.22 ± 1.77 (3–10)
Y-BOCS	11.28 ± 5.39 (2–26)
Obsession	6.44 ± 3.13 (1–14)
Compulsion	4.94 ± 3.62 (0–14)
AQ-Aggression	50.56 ± 12.3 (34–69)
Theory of Mind—Faux Pas Test	23.44 ± 8.16 (6–34)
IQ	
Full-scale IQ	96.83 ± 20.33 (62–140)
Verbal IQ	95.11 ± 19.87 (53–131)
Performance IQ	100.4 ± 18.4 (75–137)

ADI-R: Autism Diagnostic Interview–Revised, Y-BOCS: Yale–Brown Obsessive–Compulsive Scale, AQ: Aggression Questionnaire, IQ: Intellectual Quotient.

2.2. Psychological measures

ADI-R is a semi-specially formulated structured psychiatric interview with a parent, especially a mother, which is administered to the parent. It is used to confirm diagnosis and also to evaluate the core symptoms of autism. ADI-R is based on three separate scores. Score A quantifies impairment in social interaction (the range of score: 0–32), score B quantifies impairment in communication (the range of score: 0–26), and score C quantifies restricted, repetitive, and stereotyped patterns of behavior and interests (the range of score: 0–16). Higher scores on each indicate worse performance.

Obsessional/repetitive behavior was rated using the Yale-Brown Obsessive–Compulsive Scale (Y-BOCS)(Goodman

et al., 1989a,b); additional aggression symptoms were also assessed using the Aggression Questionnaire (AQ)(Buss and Perry, 1992). We used a Faux Pas Test to evaluate the function of "Theory of Mind" (*mentalizing*) (Baron-Cohen et al., 1999; Stone et al., 2003). The performance of individuals with autism on the Faux Pas Test is an experimental demonstration of their theory-of-mind deficit at a higher level. There were 40 points possible for Faux Pas-related questions about 10 stories (range: 0–40, 1 point for each question).

2.3. Amino acid measures

Serum samples of autistic patients and normal comparison subjects were collected from 11:00–12:00 a.m., and stored at −80 °C until assay. Measurement of amino acids levels was carried out according to the methods described in previous publications (Hashimoto et al., 2003, 2005b; Yamada et al., 2005). The serum levels of glutamate, glutamine, and glycine were measured according to the method using a high-performance liquid chromatography (HPLC) system, as reported previously (Hashimoto et al., 2005b). D- and L-serine measurements were made by the established method (Fukushima et al., 2004) using a column-switching HPLC system. Briefly, 20 μl of human serum was homogenized in 180 μl of methanol (HPLC grade). The homogenates were centrifuged at 4500×*g* for 10 min, and 20 μl of supernatant was evaporated to dryness at 40 °C. To the residue, 20 μl of H_2O (HPLC grade), 20 μL of 0.1 M borate buffer (pH 8.0), and 60 μL of 50 mM 4-fluoro-7-nitro-2,1,3-benzoxadiazole (NBD-F; Tokyo Kasei Kogyo Co., Ltd., Tokyo, Japan) in CH_3CN (HPLC grade) were added. The reaction mixture was then heated at 60 °C for 1 min and immediately supplemented with 100 μL of H_2O/CH_3CN (90/10) containing 0.1% trifluoroacetic acid (TFA) to stop the reaction. Ten microliters of the resultant solution was injected into the HPLC system, as

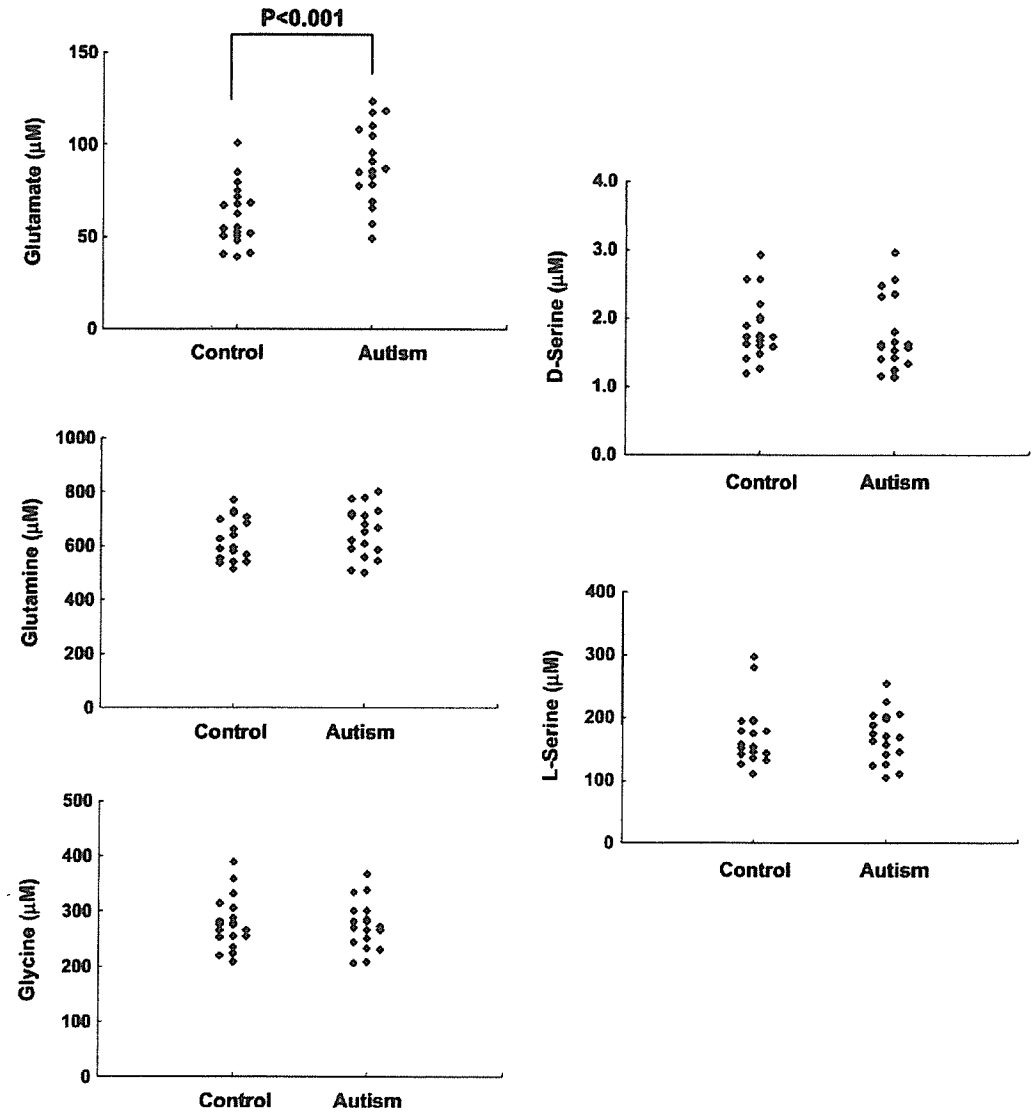

Fig. 1. Serum levels of amino acids in normal controls and autistic patients. Serum levels of glutamate in autistic patients were significantly higher than those of normal controls. In contrast, the levels of other amino acids (glutamine, glycine, d-serine, and L-serine) were not altered between two groups.

reported previously (Hashimoto et al., 2003, 2005b; Yamada et al., 2005).

2.4. Statistical analysis

The data were presented as the mean ± standard deviation (S.D.). Since all clinical and amino acids measures had an approximate standard normal distribution, we used an unpaired Student's *t*-test to compare the measures between patients and comparison subjects. The relationships between amino acid levels and clinical variables among patients with autism were evaluated by computing Pearson's correlation coefficients. We used a conservative α level of 0.01 for statistical significance in view of the number of variables examined. Additionally, we calculated the effect size (Cohen's *d*) for variables with a significant group mean difference. A *p* value of less than 0.01 was considered to be statistically significant.

3. Results

The serum levels (mean = 89.2 μM, S.D. = 21.5) of glutamate in the patients with autism were significantly ($t = -4.48$, $df = 35$, $p < 0.001$) higher than those (mean = 61.1 μM, S.D. = 16.5) of normal controls (Fig. 1); the Cohen's *d* for the mean difference was 1.52. When the analysis was repeated for never-medicated patients only ($n = 13$) compared with controls, the difference remained highly significant ($t = -4.14$, $df = 30$, $p < 0.001$: Cohen's $d = 1.54$). In contrast, the serum levels of other amino acids such as glutamine, glycine, D-serine, or L-serine in patients did not differ significantly from those of normal controls (Fig. 1). Furthermore, we found a positive correlation between L-serine and glutamate in controls ($r = 0.633$, $p = 0.04$), but not patients ($r = 0.294$, $p = 0.237$). Moreover, we found a positive correlation between D-serine (or L-serine) and glycine in patients (D-serine: $r = 0.641$, $p = 0.004$, L-serine: $r = 0.683$, $p = 0.002$), but not controls (D-serine: $r = 0.141$, $p = 0.564$, L-serine: $r = 0.284$, $p = 0.239$).

We then examined the correlations between serum glutamate levels and clinical variables among patients with autism. There was a relatively high positive correlation ($r = 0.523$, $p = 0.026$) between the glutamate levels and social subscores as assessed by ADI-R, although this fell outside our stringent level of significance (Fig. 2). There were no marked or significant correlations between serum glutamate levels and other clinical symptoms studied, including the Faux Pas Test of "Theory of Mind" or Y-BOCS scores. Additionally, we examined any correlations between the serum levels of other four amino acids and clinical variables, but no correlations were evident.

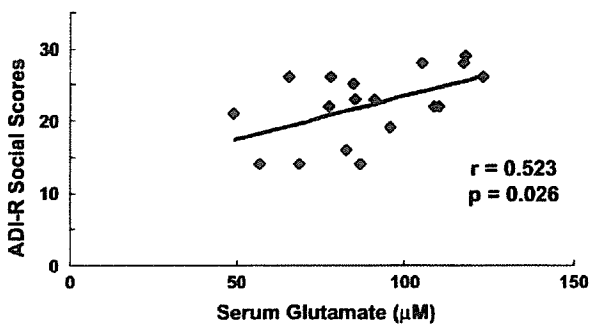

Fig. 2. Correlation between serum glutamate levels and ADI-R social scores in autistic patients. There was a positive correlation ($r = 0.523$, $p = 0.026$) between serum glutamate levels and ADI-R social scores in autistic patients.

4. Discussion

The major findings of the present study are that serum levels of glutamate in adult patients with autism are significantly higher than those of normal healthy controls, and that there is a positive correlation ($r = 0.523$, $p = 0.026$) between serum glutamate levels and ADI-R social scores in patients, although this result fell outside our stringent level of significance. To our knowledge, this is the first report demonstrating the increased serum levels of glutamate in adult male patients with autism. Our data showing higher glutamate levels in autistic patients is consistent with a previous report (Aldred et al., 2003). However, our findings are inconsistent with a previous report (Rolf et al., 1993). It seems that methodological differences (e.g., time of sample collection, serum vs plasma, age of subjects) may be involved in this discrepancy although the reasons underlying this discrepancy are currently unknown. It has been reported that levels of glutamate in human blood are positively correlated with CSF levels of glutamate in humans (McGale et al., 1977; Alfredsson et al., 1988). Therefore, it is likely that increased levels of glutamate may occur in the brains of autistic patients. In this study, we also found a positive correlation between L-serine and glutamate in controls ($r = 0.633$, $p = 0.04$), but not patients ($r = 0.294$, $p = 0.237$). These findings suggest that synthetic/metabolic pathways of L-serine and glutamate may be impaired in the autism although a further study using a large sample will be necessary.

Several reports have demonstrated that patients with autism are at greater risk for developing seizure disorders, particularly in adolescence (Volkmar and Pauls, 2003; Volkmar and Nelson, 1990; Tuchman and Rapin, 2002). It is well known that glutamate plays a role in the initiation and spread of seizure activity, and that it also plays a critical role in epileptogenesis (Meldrum, 1994). A number of antagonists for NMDA or non-NMDA receptors show potent protective effects in a variety of animal models of epilepsy. Furthermore, there have been several clinical reports demonstrating that the mood stabilizer valproic acid is effective in autistic patients with or without clinical seizures but with epileptiform abnormalities on electroencephalography (Tuchman and Rapin, 2002; Plioplys, 1994; Hollander et al., 2001). Valproic acid exerts neuroprotective effects against glutamate-induced excitotoxicity (Manji and Lenox, 2000; Chuang, 2004). In addition, postmortem brain studies have shown a variety of abnormalities, including a decreased number of neurons and reduced dendritic arborization in areas of the limbic system such as the amygdala, hippocampus, septum, and anterior cingulate cortex (Kemper and Bauman, 1998; Palmen et al., 2004). Taken together, these results suggest that increased glutamate levels may be implicated in the high rates of seizure disorder in autism, although further studies of the role of

glutamate in the high rates of seizure in autism are required for investigation of its pathological role in autism.

In the present study, we found no change in D-serine levels in autistic patients, inconsistent with the results of schizophrenia (Hashimoto et al., 2003; Yamada et al., 2005), suggesting that D-serine may not play a role in the pathophysiology of adult patients with autism. However, it has been suggested that D-serine plays an important role in neuronal migration (Kim et al., 2005), suggesting that D-serine serves as a co-agonist for the NMDA receptor-dependent cell migration at the development stage. Therefore, it may be of interest to examine serum D-serine levels in children with autism.

One may raise the question as to whether the higher levels of serum glutamate observed in this study of adult patients with autism reflect a persistent abnormal function that is invariably present at an earlier stage, i.e., in childhood. It could be that factors related to the illness course rather than the process of the development of the disorder itself may be pertinent to our observation. However, there was no correlation between the duration of the disorder and the serum glutamate levels in our sample ($r=-0.018$, $p=0.94$), implicating that glutamate dysfunction may occur in the early stage and be maintained through adulthood. Furthermore, it is of interest to measure serum glutamate levels in children with and without autism in order to determine the role of glutamate as a serological marker in children who will go on to develop an autistic disorder.

Accumulating evidence suggest that abnormality of inflammatory events may be implicated in the pathophysiology of autism (Licinio et al., 2002; Cohly and Panja, 2005). It has been reported that excessive production of pro-inflammatory cytokine tumor necrosis factor-α (TNF-α) with stimulation of endotoxin lipopolysaccharide is shown in children with autism spectrum disorders (Jyonouchi et al., 2002, 2005a,b). Interestingly, it has been demonstrated that patients with Rett syndrome had high cerebrospinal fluid glutamate levels (Riikonen, 2003), and that levels of TNF-α are increased with glutamate (McNearney et al., 2004). Taken together, it is likely that increased glutamate levels may contribute to raised levels of TNF-α although we did not measure serum TNF-α levels in these patients. Further investigation measuring levels of glutamate and cytokines including TNF-α will be necessary to unravel the role of glutamate/cytokines imbalance in autism.

Our findings have led us to the hypothesis that hyperglutamatergic neurotransmission in the brain may contribute to the pathophysiology of autism. We will attempt to confirm our hypothesis in further studies, particularly through the use of high-resolution magnetic resonance spectroscopy, which can directly measure the levels of glutamate in the brain of autism.

5. Conclusion

In conclusion, the present study suggests that abnormalities in glutamatergic neurotransmission may play a role in the pathophysiology of autism. In the future, we hope to gain a more complete understanding of glutamatergic neurotransmission in the pathophysiology of autism in order to provide new perspectives on treating autism.

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Short communication

Reduced serum levels of brain-derived neurotrophic factor in adult male patients with autism

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Abstract

Background: The precise mechanisms underlying the pathophysiology of autism are currently unknown. Given the key role of brain-derived neurotrophic factor (BDNF) in brain development, we hypothesized that BDNF may play a role in the pathophysiology of autism. In this study, we studied whether serum levels of BDNF are altered in patients with autism.
Methods: We measured serum levels of BDNF in 18 adult male patients with autism and 18 age-matched healthy male control subjects.
Results: The serum levels of BDNF in patients with autism (25.6±2.15 ng/ml (mean±S.D.)) were significantly ($z=-4.42, p<0.001$) lower than those of normal controls (61.6±10.9 ng/ml (mean±S.D.)). Nevertheless, we found no correlations between BDNF levels and clinical variables in autistic patients.
Conclusions: This study suggests that reduced BDNF levels may play a role in the pathophysiology of autism.

Keywords: Autism; Brain-derived neurotrophic factor; Neurodevelopmental disorder; Serum

1. Introduction

Autism is a developmental disorder characterized by severe and sustained impairment in social interaction, deviance in communication, and patterns of behavior and interest that are restricted or stereotyped, or both. The precise mechanisms underlying the pathophysiology of this disorder remain to be determined (Volkmar and Pauls, 2003; Baron-Cohen and Belmonte, 2005; McDougle et al., 2005).

Multiple lines of evidence suggest that brain-derived neurotrophic factor (BDNF) plays a critical role in brain development, and that it might play a role in the pathophysiology of psychiatric diseases, including mood disorders and schizophrenia (Hashimoto et al., 2004; Angelucci et al., 2005; Berton and Nestler, 2006). Nelson et al. (2001) initially reported higher BDNF levels in archived samples (dried blood spot) of neonatal blood obtained from children with autism compared with normal controls based on data obtained by recycling immunoaffinity chromatography (RIC; a single-antibody system). However, further analysis using Luminex technology (a double-antibody system) did not confirm this reduction in BDNF in autism (Nelson et al., 2006). Furthermore, Miyazaki et al. (2004) reported that serum BDNF levels in patients with autism were higher than those in normal controls; however, the age range (3- to 27-year-olds) of their patients was too large compared with that of normal controls (22- to 24-year-olds). Interestingly, it has been reported that serum BDNF levels in rats (Karege et al., 2002) and healthy human subjects (Nelson et al., 2006) are markedly altered by age. Given these data,

Abbreviations: ADI-R, Autism Diagnostic Interview–Revised; BDNF, brain-derived neurotrophic factor; IQ, intellectual quotient; Y-BOCS, Yale–Brown Obsessive–Compulsive Scale.

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it is of interest to determine whether serum BDNF levels differ between patient and control groups within a small age range. The purpose of the present study, therefore, was to examine whether serum levels of BDNF are altered in adult autistic patients.

2. Materials and methods

2.1. Subjects

Eighteen male autistic subjects (21.2±2.1 years (mean±S.D.); 18–26 years (range)) and 18 age-matched healthy male control subjects (22.2±2.2 years (mean±S.D.); 18–26 years (range)) were enrolled in the present study (Table 1). All participants in both groups were Japanese. The autistic subjects were recruited through advocacy groups in the cities of Nagoya and Hamamatsu, which are located in the middle of mainland Japan. For the diagnosis of autism, the recruited individuals were initially assessed according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994), followed by further assessment using the Autism Diagnostic Interview–Revised (ADI-R) (Lord et al., 1994). Potential participants were excluded from the study if they had a diagnosis of fragile X syndrome, epileptic seizures, obsessive–compulsive disorder, affective disorders or any additional psychiatric or neurological conditions. All autistic subjects were drug-naive or had been free of psychoactive medications for at least 6 months. This study was approved by the Ethics Committees of the Hamamatsu University School of Medicine and Chiba University Graduate School of Medicine. The control participants were given a complete description of the study, and their written informed consent was obtained before they entered the study.

Healthy controls were recruited from Hamamatsu City by advertisement. All control group participants underwent a comprehensive assessment of medical history to eliminate individuals with any neurological or other medical disorders. The Structured Clinical Interview for the DSM-IV (SCID) was also conducted in order to determine the existence of any personal or familial history of past or present mental illness. None of the control subjects initially recruited was found to fulfill these exclusion criteria.

Table 1
Clinical characteristics of 18 adult patients with autism

Characteristics	Mean±S.D. (range)
Age at onset, year	3.72±(1–5)
Duration of illness, year	17.5±2.23 (14–22)
ADI-R	
Social	22.11±4.96 (14–29)
Communication	15.44±4.84 (6–21)
Stereotype	5.22±1.77 (3–10)
Y-BOCS	11.28±5.39 (2–26)
Obsession	6.44±3.13 (1–14)
Compulsion	4.94±3.62 (0–14)
AQ–Aggression	50.56±12.3 (34–69)
Theory of Mind–Faux Pas Test	23.44±8.16 (6–34)
IQ	
Full scale IQ	96.83±20.33 (62–140)
Verbal IQ	95.11±19.87 (53–131)
Performance IQ	100.4±18.4 (75–137)

ADI-R: Autism Diagnostic Interview–Revised, Y-BOCS: Yale–Brown Obsessive–Compulsive Scale, AQ: Aggression Questionnaire, IQ: intellectual quotient.

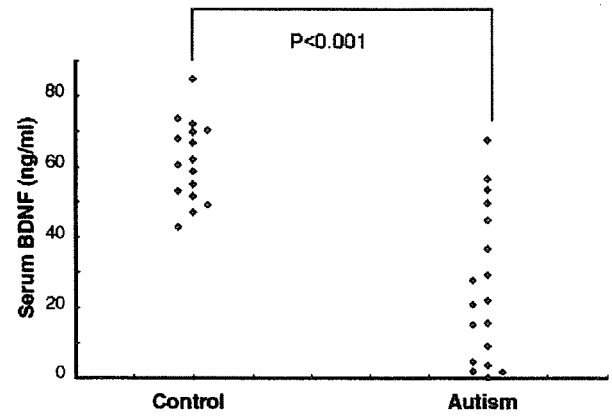

Fig. 1. The serum levels of BDNF in normal controls and autistic patients. The serum levels of BDNF in autistic patients ($n=18$) were significantly ($z=-4.42$, $p<0.001$, Mann–Whitney U-test) lower than those of normal controls ($n=18$).

2.2. Measurement of serum BDNF levels

Serum samples of autistic patients and normal comparison subjects were collected between 11:00 a.m. and noon, and were stored at −80 °C until assay. Serum BDNF levels were measured using a BDNF Emax Immuno Assay System (Promega Corporation, Madison, WI, USA). To minimize the assay variance, serum BDNF levels were measured in all subjects on the same day.

2.3. Data analysis

The data were presented as mean±S.D. The data were analyzed by Mann–Whitney U-test. The relationships between BDNF levels and clinical variables among patients with autism were evaluated by Spearman correlations. A p value of less than 0.05 was considered to be statistically significant.

3. Results

Serum levels of BDNF in patients with autism (25.6±2.15 ng/ml (mean±S.D.)) were significantly ($z=-4.42$, $p<0.001$) lower than those of age-matched healthy controls (61.6±10.9 ng/ml (mean±S.D.)) (Fig. 1). We also examined correlations between serum BDNF levels and clinical variables among patients with autism, finding no marked or significant correlations; the tested clinical variables were age of onset, duration of illness, ADI-R scores, Yale–Brown Obsessive–Compulsive Scale (Y-BOCS) scores, aggression, Theory of Mind assessment and Intellectual Quotient (IQ) (Table 1).

4. Discussion

In the present study, we found that serum BDNF levels in adult patients with autism were significantly lower than those of age-matched normal controls. To the best of our knowledge, this is the