① 全国の措置入院患者数に占める高齢者の割合 ―― ワンデイ調査 ――

図1は630調査（ワンデイ調査）の結果をもとに，厚生労働省社会・援護局障害保健福祉部精神・障害保健課が作成したデータを借用して作成したものである．630調査とは，厚生労働省が毎年6月30日付で都道府県・指定都市に報告を依頼している調査である．

このデータによるとわが国の措置入院患者数自体は減少の傾向にある．図1aに示されたように，措置入院患者数は年齢階級別にみるとすべての年齢階級で減少している．しかし各年齢階級によって多少の違いがある．平成16年と平成20年を比較して各年齢階級別の措置入院患者数の減少率をみてみると，20歳未満ではその減少率が27%，20歳以上40歳未満では21%，40歳以上65歳未満では30%，65歳以上では9%となる．必然的に措置入院患者全体に占める率は，高齢者で増加傾向となる（10.2→12.4%）．

図1bに各年度の診断割合を示した．措置入院患者全体での診断割合であり，高齢者に限定したものではない点に注意が必要であるが，各診断の割合の変化を，平成13年度と平成20年度で比較すると，統合失調症は81.5%から80.2%，認知症は0.3%から0.4%，気分障害は3.2%から5.7%の変化であるが，いずれも一定の増減傾向を確認することはできない．

② 東京都および東京都立松沢病院における措置入院の対象となる高齢者

措置入院の運用や措置入院患者数などについては，自治体によって差があることは数々の研究で報告されている[1-9]．東京都では全国に先駆けて精神科救急診療体制が整備されたこともあり，警察官通報から措置入院へのアクセスがしやすい環境が整っているといわれている[4]．

東京都の精神科救急医療体制は，「ハード救急」の先駆けであることと「転送システム」に特徴がある．システムについて簡単に説明すると，夜間休日の警察官通報に基づく措置診察は都立4病院で行われる．指定医1人による診察が行われ，緊急措置入院の要否を判断する．緊急措置入院が決まれば，そのまま当該の都立病院に入院し，その後72時間以内に2人の指定医による措置診察が行われる．措置入院が決定すると，原則として都内の精神科病院に転院となり，そこで治療を継続することとなる．このシステムは，毎日の空床確保のためのものであり，「転送システム」と呼ばれている．以上のシステム上の特徴を踏まえたうえで，東京都の精神科救急システムにおける措置入院の対象となる高齢者の動向についてみてみたい．

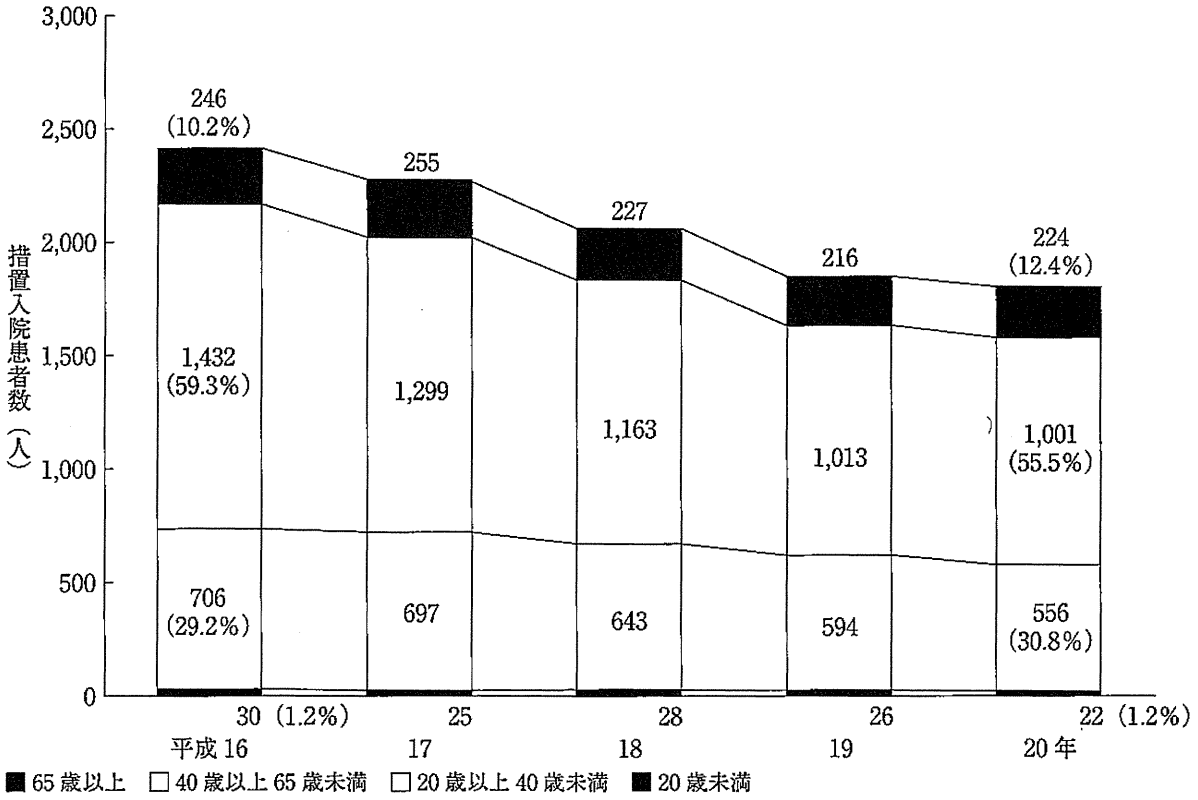
図2は，平成19年～平成23年までの5年間に東京都全体の精神科救急システムを利用して入院した措置入院患者の総数とそれに占める高齢者の割合を示している．平成20年度から21年度にかけての措置入院総数の増加は，警察官通報から診察命令の手順を厳密化したことによるものと思われるが，その後の3か年では措置入院総数自体は厚生労働省の報告と同様に減少傾向にある．しかし，そのうち高齢者の占める率は増加傾向にあることが見て取れる．

厚生労働省ならびに東京都のデータから，全国の措置入院の総数自体は減少傾向にあること，しかしそのうちに占める高齢者の率は増加傾向にあることが推測できる．

③ 東京都立松沢病院における精神科救急高齢者の臨床特性など

東京都立松沢病院は東京都の精神科救急医療を行っている都立4病院のうちのひとつである．筆者らの調査によると，当院の精神科救急に搬送される高齢者の数は10年間で約1.6倍に増加していた．図3に昭和61年から当院精神科救急を利用した患者総数のうち60歳以上の占める割合を示しているが，高齢で救急搬送される患者の率が

a. 措置入院患者数の推移



b. 疾患内訳

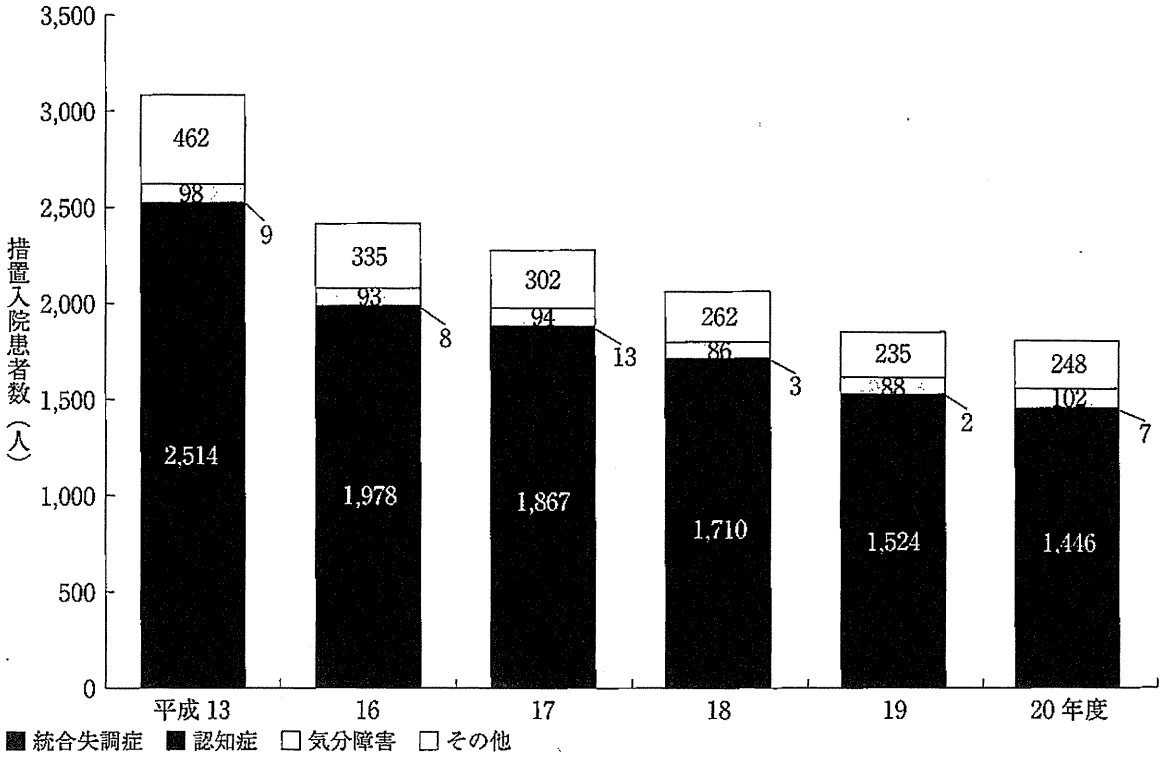


図 1　全国の措置入院患者数の推移と措置入院患者の疾患内訳（ワンデイ調査）

□特集

増加している．

このような患者の臨床上の特徴を調べるために，平成19年1月1日～平成21年12月31日までの3年間において，当院の精神科救急に搬送された全患者（1,475例）のうち，60歳以上の患者205例（男性138例〈67.9±6.6歳〉，女性67例〈68.0±6.6歳〉）について，診断，入院の直接の理由，家族背景，生活保護受給率，身体合併症の有無，入院後の転帰について調査を行った．この205例の入院形態については，医療保護入院が120例（59%），措置（緊急措置）入院が81例（39%），応急入院が4例（2%）であった．措置入院に限定した解析ではない点に留意いただきたい．

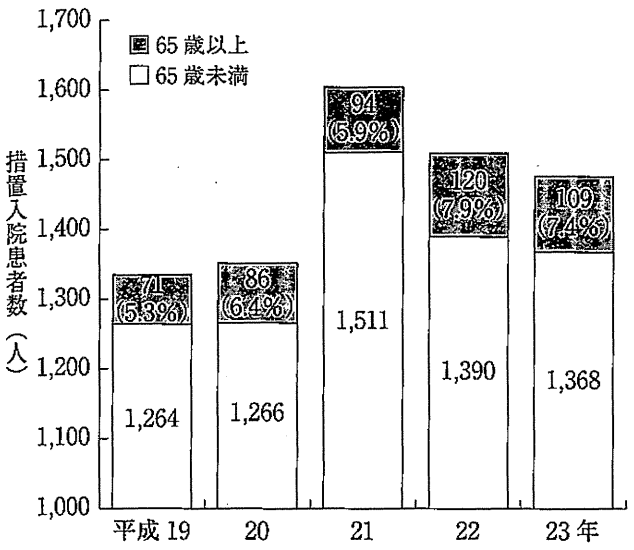


図2　東京都精神科救急入院患者のうち，措置入院患者の総数とそれに占める高齢者の割合（直近5年間の動向）

1．入院時診断

入院時診断を図4に示した．統合失調症が最多で，ほぼ1/3を占め，以下，気分障害，認知症と続いた．入院時診断であるため，「急性一過性精神病」などの暫定診断も含まれている．

気分障害34例のうち，双極性障害（躁状態）20例，双極性障害（うつ状態）4例，単極性障害（うつ状態）10例であった．認知症はアルツハイマー型認知症14例，血管性認知症4例，前頭側頭葉変性症1例，その他，特定不能の認知症8例であった．物質使用障害17例において，ほとんど（16例）がアルコール関連障害であった．

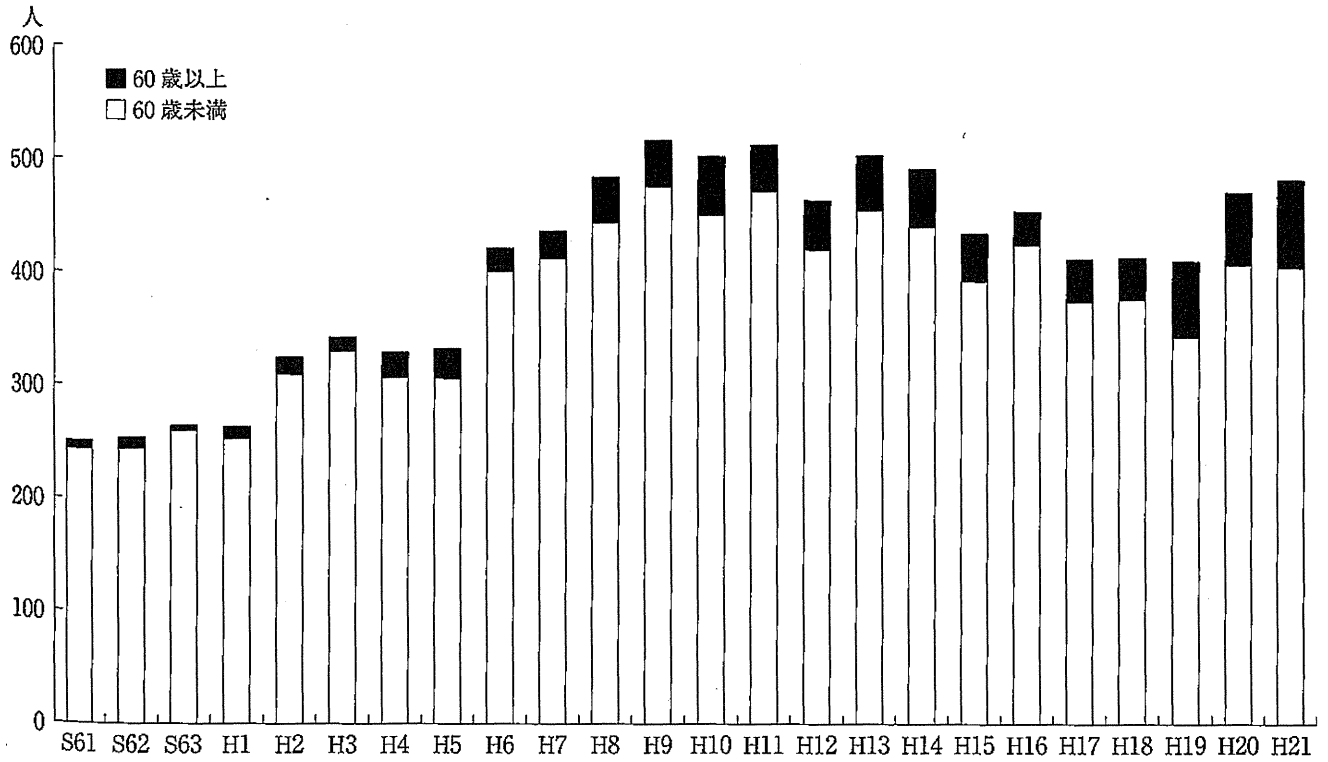
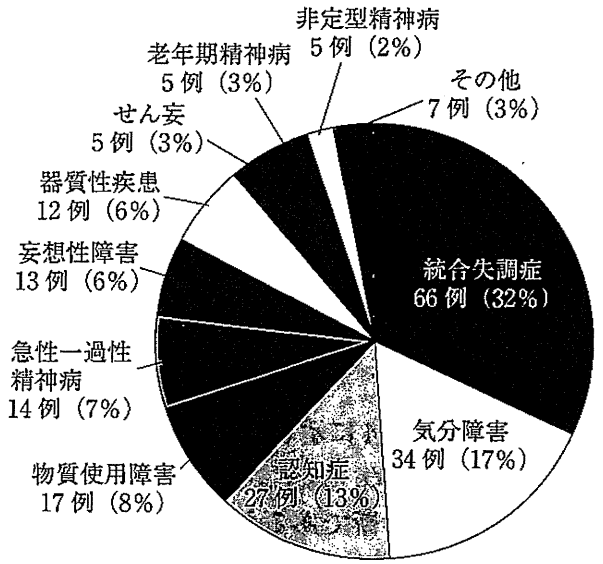


図3　都立松沢病院精神科救急を利用した患者総数に占める60歳以上の比率の年次変化



$N=205$

図4　精神科救急を経て都立松沢病院に入院した60歳以上患者の入院時診断

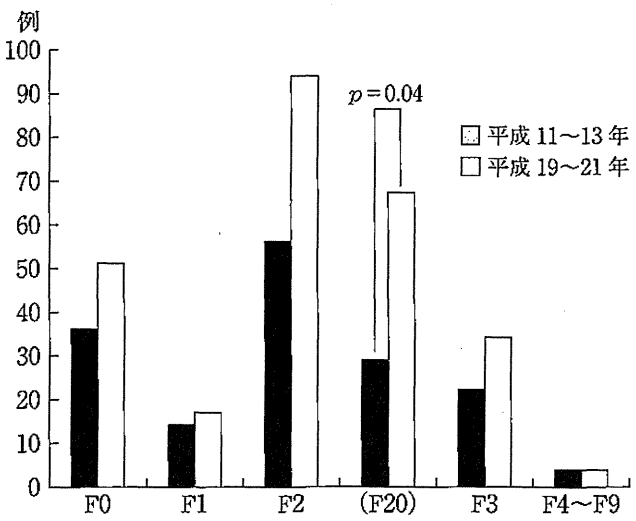
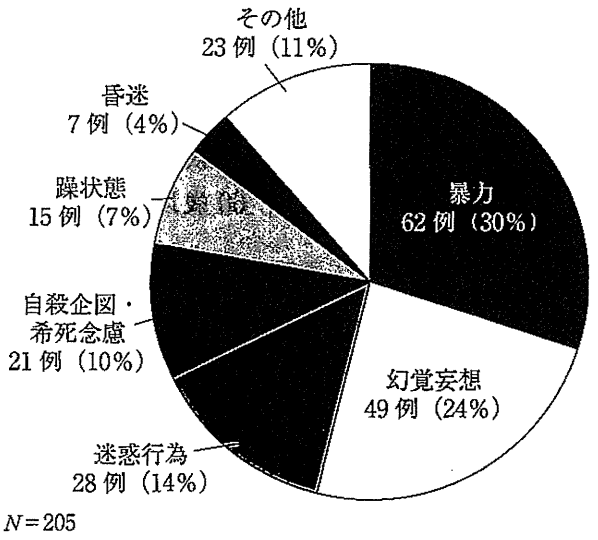
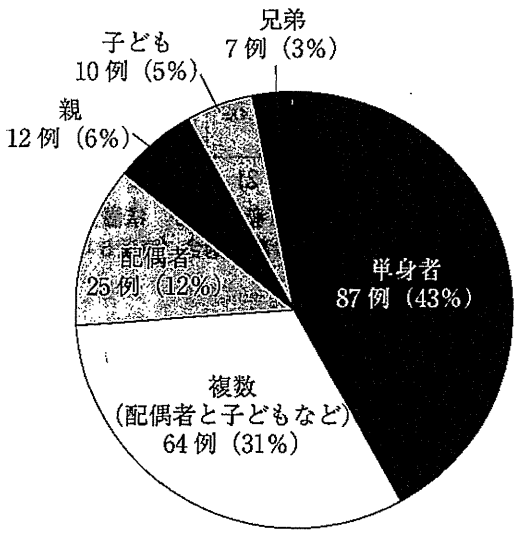


図5　入院時診断の比較



$N=205$

図6　入院理由



$N=205$

図7　家族背景

筆者らは10年前（平成11～13年）にも同様の調査を行っており[3,7]，診断に関して，10年前の結果との比較検討を行った．それぞれの診断を国際疾病分類（ICD）のF0～9にまとめ，前回と今回の比較を行ったものが図5である．結果としては，「統合失調症」（F20）の確定診断を受けた者が29例（22%）から66例（32%）と有意な増加を示していた（$p = 0.04$）．一方で，認知症を含めその他の疾患において，10年前の結果との比較検討においては有意な差は認めなかった．

2．入院の理由

入院理由を図6に示した．暴力行為が最多であり，高齢者においても，他害の危険性が高い患者が最も精神科救急に搬送されやすい傾向がうかがわれた．

3．家族背景

高齢精神科救急患者の家族背景を図7に示した．単身者が4割強を占め最多であった．親との同居

例も6%と高く，対象者のうち生活保護受給率は21%であった．

4．合併症の有無

入院時に身体合併症を有していた対象者は103例（50%）であった．疾患内訳としては糖尿病34例，高血圧13例の順に多かった．また，入院後の下肢静脈超音波検査にて下肢静脈血栓症を9例に認めた．

5．入院後転帰

前述した東京都の救急システムによる転送例53例を除いた152例の解析のうち，自宅退院可能であった例は97例（64%）であり自宅退院可能であった患者は2/3にとどまっている．残りの1/3の患者は自宅退院が不可能であり，転院後他院での療養を継続しているか，高齢者施設への転入所となっていた．

当院の高齢精神科救急患者の調査から，近年高齢者の救急搬送例が増加していることが示された．増加の要因は高齢の統合失調症者の増加であった．入院の理由としては，暴力行為が3割，自殺企図・希死念慮が1割であった．単身者の率が高いのが特徴であり，全体の43%を単身者が占めていた．厚生労働省の調査などでは，高齢者の単身世帯率は高齢者世帯全体に対して22～23%と報告されている[6]ので，入院者の単身率はきわめて高い値である．配偶者との二人暮らしは全体の12%であった．親との同居が6%であり，高齢に至った統合失調症患者をさらに高齢の親が面倒をみる状況のなかで，親の支援力の低下が救急介入を要する事態を増加させている可能性が考えられる．入院時合併症を認める率は50%であり，一度入院してしまうと1/3の患者で退院が困難となっており，病院への転院や施設への転入所を余儀なくされていた．

④ 考　察

法的強制力が最も強い措置入院は，全国的にはその数は漸減傾向にある．しかし高齢者の措置入院数はほぼ横ばいかわずかな減少にとどまっており，全体に占める割合は漸増傾向にあることが今回の調査から明らかとなった．この事実は，精神科救急の場で自傷他害の危険性の高い高齢者に遭遇する機会が増えることを意味している．当院での研究からも示されたように，高齢者といえども入院の理由として暴力や幻覚妄想が最多であり，いわゆるハード救急の臨床特徴を呈する患者が大多数である．この救急高齢患者の臨床的特徴は過去の報告[2]とも合致する．高齢者には認知症や身体合併症など特有な病態があり，精神―身体の両面を含めた診断と治療のスキルがわれわれに求められるということである．精神科救急の現場においても，高齢患者への治療技術に習熟する必要性が今後いっそう高まっていくことは自明であろう．

認知症で激しい暴力や徘徊などで目の離せない状態となり，緊急の危機介入を必要とすることはまれならずある．急性増悪期の治療とケアを充実させることで不測の事態を避けるシステムづくりが必要である．具体的には短期入所（ショートスティ）の利用，認知症疾患医療センターへの入院やそのトリアージ機能を充実させるということである．入院以外のサービスを用いるにあたっては，要介護認定を受けているということが前提であるが，現実的には第3者のかかわりを頑なに拒否して，介護保険の導入が図れないケースも多々存在する．そのような場合には，医療や行政の側から出向いていくほかはない．平成24年6月に公表された厚生労働省の「今後の認知症施策の方向性について」[5]のなかで挙げられた「認知症初期集中支援チーム」において，訪問による支援の対象とする患者のなかに，受診やかかわりを拒否する患者群を含めることで，急性増悪期の危機介入の閾値を数段下げることが可能である．

当院での研究からは，10年前と比較して有意な増加を示した患者群は統合失調症のみであった．救急搬送される高齢統合失調症患者の増加は，高齢人口増による患者数の自然増加に加え，患者を含む家族の高齢化の影響が考えられる．長期間，

統合失調症患者を支えてきた親世代の死亡等による単身患者，あるいはその予備軍ともいうべき，高齢患者の面倒をさらに高齢の親がみている世帯への支援が急務である．医療政策の変換により病院から地域へ出て生活をする統合失調症患者の数も近年増えつつあるが，他の報告[8]にもあるように，周囲の偏見などにより社会的サポートが質，量ともに不足している．高齢の統合失調症患者に対して，どのようなサポートが必要でなにが可能なのかについて考えていくことは，もう1つの重要な課題であると考える．

630調査の結果については，厚生労働省社会・援護局障害保健福祉部精神・障害保健課のデータをお借りした．東京都の措置入院の動向については，東京都福祉保健局障害者施策推進部のデータをお借りした．集計の労と転載のご快諾をいただきました関係各位の方々に心よりお礼を申し上げる．

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Frontal and right temporal activations correlate negatively with depression severity during verbal fluency task: A multi-channel near-infrared spectroscopy study

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ABSTRACT

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain activity. Previous NIRS studies indicated the oxy-hemoglobin (oxy-Hb) increase during a verbal fluency task (VFT) is attenuated in patients with major depressive disorder (MDD) as compared with healthy controls. However, the possible relationship between depression symptom severity and oxy-Hb change on NIRS has not yet been elucidated. To examine this relationship, we recruited 30 patients with MDD and 30 age-, gender- and intelligence quotient-matched controls. All underwent NIRS during VFT. As expected, the oxy-Hb increase during the task was significantly smaller in patients than in controls. After false discovery rate correction using 31 channels, the mean increase in oxy-Hb during the task showed a significant negative correlation with the total score of the Hamilton Rating Scale for Depression 21-item version (ch25: rho = −.56; FDR-corrected *p*: .001). When each item of the HAM-D21 was examined individually, insomnia early in 9 channels (rho = −.63 to −.46; FDR corrected *p*: .000–.014), work and activity in 2 channels (rho = −.61 to −.57; FDR corrected *p*: .001 to .003) and psychomotor retardation in 12 channels (rho = −.70 to −.44; FDR corrected *p*: .000–.018) showed significant negative correlations with the mean oxy-Hb increase in the right frontal temporal region. Although it is possible that our results were affected by medication, these data suggest reduced right frontal temporal activation on NIRS during VFT is related to the symptom severity of MDD.

1. Introduction

Major depressive disorder (MDD) is a severe and common psychiatric disorder with a lifetime prevalence of 6.7 per 100 (Waraich et al., 2004). Although depressive symptoms per se do not specifically appear in MDD but also in other psychiatric disorders including bipolar disorders, we do not have an objective diagnostic marker to obtain a clear-cut diagnosis for those patients. In Japan, a relatively new neuroimaging method, near-infrared spectroscopy (NIRS) has been approved by the Ministry of Health, Labor and Welfare as a highly advanced medical technology to help distinguish between schizophrenia, depression and bipolar disorders in 2009. Verbal fluency task (VFT) is recommended as an activation task because of a relatively rich store of data. VFT is an easy task to examine the executive function and frequently used in neuroimaging studies (Alvarez and Emory, 2006) and is known to activate prefrontal cortex (PFC) in healthy subjects (Frith et al., 1991; Schlösser et al., 1998). Numerous neuropsychological studies suggest that patients with MDD show executive dysfunction (Gohier et al., 2009; Rose and Ebmeier, 2006; Fossati et al., 2003; Porter et al., 2003; Degl'Innocenti et al., 1998).

Multi-channel near-infrared spectroscopy (NIRS) is a noninvasive, on-the-spot, restraint-free functional neuroimaging technique allowing detection of the spatiotemporal characteristics of brain

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function near the brain surface using near-infrared light (Strangman et al., 2002a; Boas et al., 2004). NIRS has enabled bedside measurement of the concentrations of oxy-hemoglobin (oxy-Hb) and deoxy-hemoglobin (deoxy-Hb) changes with a high time resolution (.1 s). The concentrations of oxy-Hb and deoxy-Hb are assumed to reflect the regional cerebral blood volume (rCBV) changes, which was supported by the simultaneous NIRS and PET study (Villringer et al., 1997; Ohmae et al., 2006).

In fact, numerous studies have demonstrated that the oxy-Hb increase in the fronto-temporal regions during a VFT is significantly smaller in patients with MDD than in those with bipolar disorder or healthy controls (Pu et al., 2008; Kameyama et al., 2006; Suto et al., 2004; Matsuo et al., 2002). Moreover, NIRS studies using VFT have also demonstrated frontal lobe dysfunction in schizophrenia (Suto et al., 2004; Takizawa et al., 2008), and panic disorder (Nishimura et al., 2007). However, the relationship between depression symptom severity at the time of examination and oxy-Hb change on NIRS has not yet been clarified.

In neuroimaging studies using other methodologies, focusing on cortex level that NIRS reflects, positron emission tomography (PET) studies found that abnormal reductions of cerebral blood flow (CBF) and metabolism in patients with MDD in PFC (Kimbrell et al., 2002; Bench et al., 1995; Mayberg et al., 1994; Baxter et al., 1989). As for the relationship between executive function and CBF or metabolism, Elliott et al. (1997) showed activation in PFC was significantly attenuated relative to controls during the Tower of London planning task in PET study. In a functional magnetic resonance imaging (fMRI) study, depressed patients showed significant decreased prefrontal activation during VFT (Okada et al., 2003).

As for the relationship between depression symptom severity and frontal lobe function, Brody et al. (1999) found a positive correlation between change in Hamilton Rating Scale for Depression (HAM-D) scores and change in normalized inferior frontal gyrus (IFG) and ventrolateral PFC (VLPFC) metabolism, which indicates that IFG metabolism increased and VLPFC metabolism decreased as depression symptoms became better. Other initial studies also suggest that abnormal functions in dorsolateral PFC (DLPFC) are mood state dependent, attenuated during the depressed mood and reversing during symptom remission (Bench et al., 1995; Mayberg et al., 1994). In contrast, Drevets et al. (2002) showed the persistence of abnormal metabolic deficits using PET measures in the dorsomedial/dorsal anterolateral PFC in MDD during treatment. According to a review by Drevets (2000), a complex relationship exists between depression symptom severity and metabolic activity in the orbital cortex and VLPFC.

Findings obtained by more recent studies investigating cross-sectional relationship between depression symptom severity and brain function assessed by basal regional CBF and metabolism are also inconsistent. For example, Périco et al. (2005) reported that depression symptom severity was negatively correlated with regional CBF (rCBF) in the left amygdala, lentiform nucleus, and parahippocampal gyrus, and positively correlated with rCBF in the right postero-lateral parietal cortex, whereas Milak et al. (2005) showed only positive correlations in bilateral mesiotemporal cortex, parts of the ventral subgenual basal forebrain, and most of the thalamus, hypothalamus, ventral striatum, and midbrain. Accordingly more studies are warranted to clarify the relationship between depression severity and brain activity including frontal lobe function.

In the present study, considering the consistent finding of attenuated oxy-Hb changes during VFT in the fronto-temporal regions in depression, we hypothesized that oxy-Hb changes during VFT in NIRS could be objective indicators of depressive symptom severity. Thus, we used multi-channel NIRS to investigate the relationship between oxy-Hb changes and symptom severity in patients with MDD. Because NIRS can be measured easily and noninvasively in a restraint-free environment over a short amount of time we expect that NIRS can be widely used to assess objectively depressive symptom severity as a clinical examination.

2. Materials and methods

2.1. Subjects

The subjects were 30 patients with MDD, and 30 healthy volunteers matched for age, gender and premorbid intelligence quotient (IQ). Premorbid IQ was estimated using the Japanese version of the National Adult Reading Test (Matsuoka et al., 2006). All subjects were right-handed according to the Edinburgh Inventory (Oldfield, 1971) and were native speakers of Japanese. All MDD subjects were outpatients of the National Center of Neurology and Psychiatry Hospital in Tokyo, Japan. They were diagnosed according to the Structured Clinical Interview for the Diagnostic Statistical Manual of Mental Disorders, 4th edition (DSM-IV) Axis I Disorders (SCID-I; First et al., 1995) by experienced psychiatrists. All patients were medicated with antidepressants. Twenty-seven out of 30 patients were prescribed with one or two antidepressants, 16 with SSRIs, 12 with tricyclics, 7 with milnacipran, 5 with tetracyclics, 2 with trazodone and 1 with mirtazapine. In addition, 20 patients were prescribed with anxiolytics, 16 with hypnotics, 7 with mood stabilizers and 9 with antipsychotics (Supplementary Table 1). Daily doses of all antidepressants were converted to an equivalent dose of imipramine (Inagaki and Inada, 2006) and anxiolytics/hypnotics to that of diazepam (Inagaki and Inada, 2006) for each patient. The controls were healthy volunteers recruited from the same geographical area through advertisements in free local magazines and our website announcement. They were interviewed using the SCID-I for MDD or SCID-NP for healthy volunteers and an unstructured interview for family history, and those individuals who had a current or past history of Axis I psychiatric disorder or a positive family history of Axis I psychiatric disorder within their first degree relatives were excluded. The exclusion criteria for both groups were previous head trauma, neurological illness, a history of electroconvulsive therapy, alcohol/substance abuse or addiction.

After the study procedures had been fully explained, written informed consent was obtained from every participant. This study was approved by the ethics committee of the National Center of Neurology and Psychiatry.

2.2. Clinical assessment

Depressive symptoms and the level of social functioning were evaluated by a single experienced psychiatrist using the GRID Hamilton Rating Scale for Depression 21-item version (GRID HAM-D21; Kalali et al., 2002) and Global Assessment of Functioning scores (GAF; American Psychiatric Association, 1994), respectively, without knowledge of the NIRS data on the same day that the NIRS measurements were conducted. Sleepiness was evaluated as the score on the Stanford Sleepiness Scale (SSS; Hoddes et al., 1973).

2.3. Activation task

The activation task was a letter version of VFT similar to that described by Takizawa et al. (2008). During the VFT, changes in oxy-Hb and deoxy-Hb were measured. The VFT consisted of a 30-sec pre-task baseline, a 60-sec VFT, and a 70-sec post-task baseline. The subjects were instructed to repeat the syllables /a/, /i/, /u/, /e/ and /o/ during the pre-task and post-task baseline periods. For the VFT, the subjects were instructed to generate as many words as possible.

One of the three initial syllables (A; 0–20 s /a/, /to/, or /na/, B; 20–40 s /i/, /ki/, or /se/, C; 40–60 s /o/, /ta/, or /ha/) was randomly

presented on the computer display placed in front of the subjects, every 20 s during the 60-sec task. The number of possible combinations of syllables is 27 (A;3 × B;3 × C;3 = 27). We adopted 15 among the possible combinations. The number of correct words generated during the task was determined as a measure of task performance.

3. NIRS measurements

3.1. NIRS device

We used a 52-channels NIRS (ETG-4000 Optical Topography System; Hitachi Medical Co., Tokyo, Japan) which measures relative changes in oxy-Hb and deoxy-Hb using two wavelengths (695 nm and 830 nm) of infrared light based on the modified Beer–Lambert law (Yamashita et al., 1996). With this system, these Hb values include a differential pathlength factor (DPF). In the NIRS system, "hemoglobin concentration change*DPF" is calculated as a solution to the simultaneous equations based on the Beer–Lambert law, which cannot escape the effect of DPF. Although DPF varies among various brain regions Zhao et al., using a Monte Carlo simulation, reported the estimated DPF variation in the forehead region of adult humans was roughly homogeneous (Zhao et al., 2002).

The distance between a pair of source-detector probes was set at 3.0 cm and each area measured between a pair of source-detector probes was defined as a 'channel'. The NIRS device is considered to measure 'channels' at a 2–3 cm depth from the scalp, that is, at the surface of the cerebral cortex (Hock et al., 1997; Okada and Delpy, 2003, Toronov et al., 2001).

3.2. Probe positioning and measurement points

The NIRS probes were fixed with 3 × 11 thermoplastic shells, with the lowest probes positioned along the Fp1–Fp2 line according to the international 10–20 system used in electroencephalography. The probes can measure Hb values from bilateral prefrontal and temporal surface regions. The measuring points were labeled ch1 to ch52 from right-posterior to left-anterior (Fig. 1). The correspondence between these NIRS channels and the measurement points on the cerebral cortex was confirmed by a multi-subject study of anatomical cranio-cerebral correlations (Okamoto et al., 2004) and presented on the basis of results obtained by the virtual registration method (Tsuzuki et al., 2007).

3.3. Measurement parameters

The rate of data sampling was .1 second (s). The obtained data were analyzed using integral mode; the pre-task baseline was determined as the mean over a 10 s period just prior to the task period, and the post-task baseline was determined as the mean over the last 5 s of the post-task period. Linear fitting was then applied to the data between these two baselines. The moving average method using a window width of 5 s was applied to remove any short-term motion artifacts. Because we could not remove all artifacts in this way, we applied automatic rejection of data with artifacts separately for each channel (Takizawa et al., 2008).

According to the aforementioned measurement parameters for integral mode, the waveforms of oxy-Hb, deoxy-Hb and total-Hb

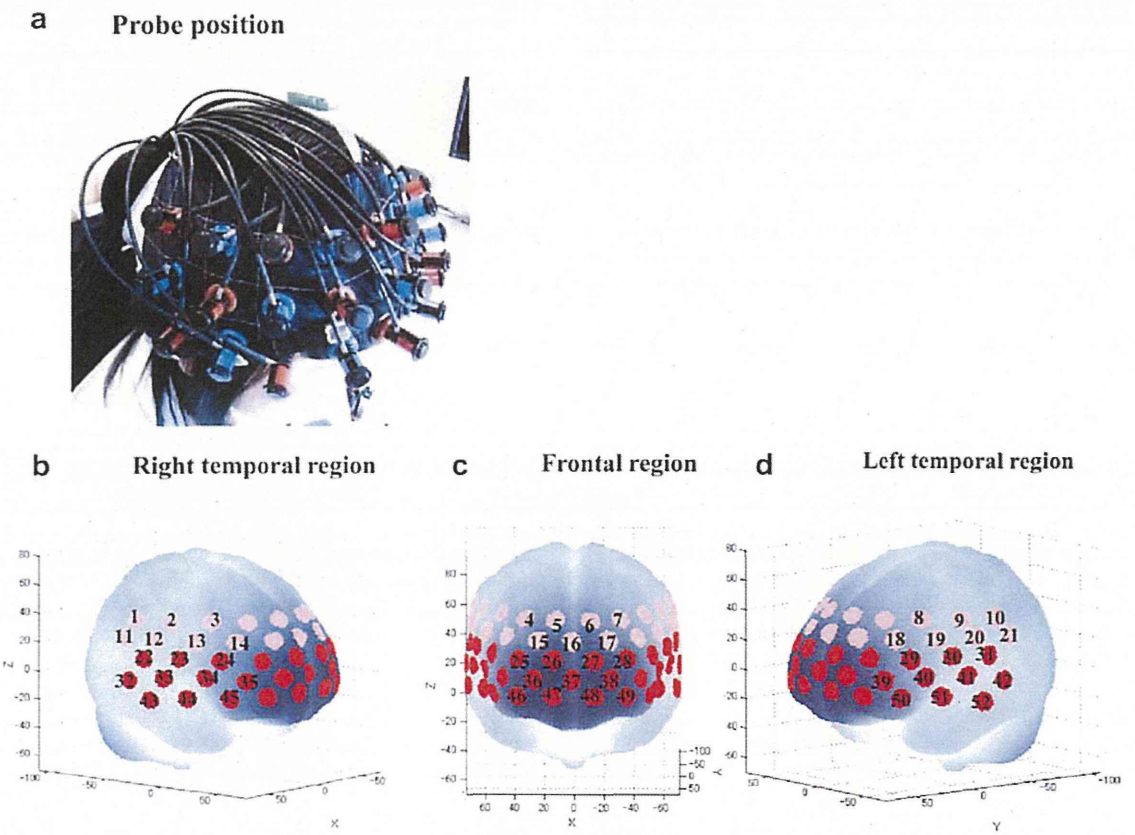

Fig. 1. Measurement points of 52 channels for near-infrared spectroscopy (NIRS) (a) Probes with 3 × 11 thermoplastic shells were placed over a subject's bilateral frontal regions. (b–d) The 52 measuring positions of the NIRS device are superimposed on the 3D-reconstructed cerebral surface, based on magnetic resonance imaging. The 52 measuring positions are labeled ch1 to ch52, from the right posterior to the left posterior. The dimensional figures b, c and d indicate the right temporal, frontal and left temporal brain regions, respectively. Because acquired NIRS data from the 21 channels in the upper two rows (pink channels) clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ratio seemed to be low, they were excluded from statistical analyses.

changes were acquired from each subject in all 52 channels during VFT.

3.4. Measurement environment

The subjects sat on a comfortable chair in a silent and day-lit room. They were instructed to minimize motions such as head movements, strong biting and blinking during the NIRS measurement, to avoid artifacts.

Data clearly containing motion artifacts, based on both our observations and the NIRS recording, were excluded from further analyses.

4. Statistical analysis

Because acquired NIRS data from the 21 channels in the upper two rows clearly contained artifacts presumably due to hair, as indicated by visual inspection of the waveforms, and signal to noise ration seemed to be low, they were excluded from statistical analyses.

The χ^2 test or Student's *t*-test was used to compare proportions and means, respectively, between the MDD and control groups.

As for the analysis of the NIRS data, we focused on oxy-Hb data, since oxy-Hb change (task period − pre- and post-task baseline period) is assumed to more directly reflect cognitive activation than deoxy-Hb change as shown by a stronger correlation with blood-oxygenation level-dependent signal measured by fMRI (Strangman et al., 2002b). The mean oxy-Hb changes were compared between the two groups (MDD and control) for each channel using Student's *t*-test. To examine the relationships between oxy-Hb changes and HAM-D21 total scores, HAM-D21 subscale scores, GAF, or other clinical variables, Spearman's rhos were calculated for MDD patients.

All statistical analyses were performed using SPSS for Windows, version 18.0.0 software (SPSS Japan, Tokyo, Japan). A value of $p < .05$ (two-tailed) was considered to be statistically significant. We set the value of q specifying the maximum false discovery rate (FDR) at .05, such that the false positive rate was no more than 5% on average in treating the oxy-Hb data obtained from multiple channels (Singh and Dan, 2006).

5. Results

5.1. Demographic and clinical data of patients and controls

Table 1 summarizes demographic characteristics of the patients and controls. The two groups did not differ significantly in age, gender, handedness, estimated premorbid IQ or SSS.

5.2. Task performance

The number of words generated did not differ significantly among the 15 combinations employed (15 combinations: $F[1, 45] = 1.1$, $p = .39$; three initial syllables: $F[2, 90] = 1.2$, $p = .31$) in either group. The number of generated words during VFT did not differ significantly (patients: 12.3 ± 3.9; controls 13.9 ± 4.3, $t = 1.5$, df = 58, $p = .13$) between the MDD and control groups.

5.3. Group comparison

As shown in Fig. 2, the MDD group had significantly smaller oxy-Hb increases than the control group in 22 channels (ch22–29, ch32–33, ch35–39 and ch44-50; FDR-corrected *p*: .000–.024) during VFT.

5.4. Relationship with symptom severity at the time of examination

As shown in Fig. 2, there were significant negative correlations between mean oxy-Hb changes during the task and HAM-D21 total scores in one channel (ch25: rho = −.56; FDR-corrected *p*: .001). Mean oxy-Hb changes during the task period showed significant negative correlations with three individual items of the HAM-D21 subscale scores (Fig. 3); insomnia early in 9 channels (ch23, ch25–27, ch36–37 and ch46–48: rho = −.63 to −.46; FDR corrected *p*: .000–.014), work and activity in 2 channels (ch44 and ch45: rho = −.61 to −.57; FDR corrected *p*: .001 to .003), and psychomotor retardation in 12 channels (ch22–24, ch32, ch35–36, ch41, ch43–ch45, ch47 and ch51: rho = −.70 to −.44; FDR corrected *p*: .000–.018). Mean oxy-Hb changes showed no significant correlations with the remaining HAM-D21 subscale scores (i.e., depressed mood, guilt, insomnia middle, insomnia late, psychomotor agitation, anxiety psychic, anxiety somatic, loss of appetite, somatic symptoms general, sexual interest, hypochondriasis, loss of weight, insight, diurnal variation, and obsessional symptoms;) (Fig. 4).

Furthermore, mean oxy-Hb changes showed no significant correlation with task performance during VFT or other clinical variables, such as age, duration of illness, and sleepiness (data not shown).

5.5. Relationships with medication

There were no significant correlations between the HAM-D21 total score and doses of antidepressants (rho = −.23, $p = .22$) or anxiolytics (rho = .25, $p = .18$). There were significant negative correlations between mean oxy-Hb changes during the task and doses of antidepressants in 6 channels (ch31, ch40–41, ch45, ch50–51: rho = −.57

Table 1
Demographic and clinical data of patients with major depressive disorder and controls.

Demographics	Patients with depression ($n = 30$)	Healthy controls ($n = 30$)	Group difference *p*-value
Age (years)	36.7 ± 11.6	35.1 ± 9.4	.871
Gender (female/male)	16/14	16/14	1.000
Edinburgh handedness inventory (%)	92.9 ± 9.7	92.0 ± 11.5	.753
Age at onset (years)	30.9 ± 10.8	–	–
Duration of illness (years)	5.8 ± 4.1	–	–
Duration of medication (years)	5.0 ± 3.6	–	–
GRID HAM-D21 total score	16.7 ± 4.8	–	–
Estimated premorbid IQ	105.7 ± 9.5	105.9 ± 8.3	.953
Sleepiness	3.3 ± 1.1	2.9 ± .9	.104
GAF	57.6 ± 9.3		
Medication			
Imipramine equivalent dose (mg/day)	141.9 ± 127.6	–	–
Diazepam equivalent dose (mg/day)	8.5 ± 11.6	–	–

The χ^2 test or *t*-test was used to compare these variables between patients and controls. GAF, Global Assessment of Functioning; GRID HAM-D21, GRID Hamilton Rating Scale for Depression 21 item; IQ, Intelligence Quotient.

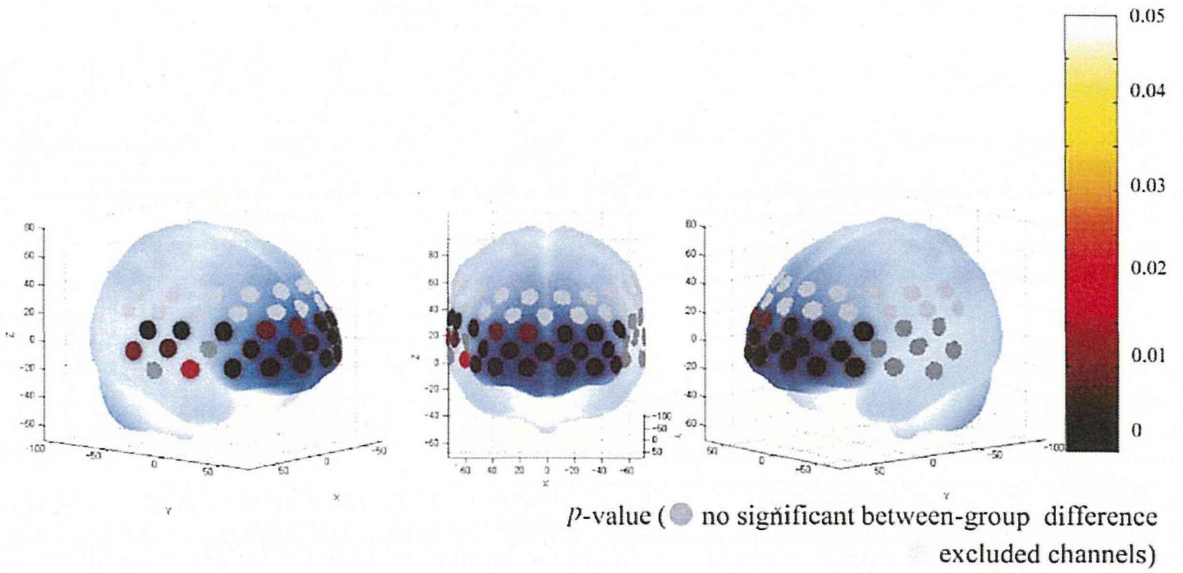

Fig. 2. *p*-value significance map of *t*-tests for oxy-Hb increases in patients with MDD compared with healthy controls during VFT using FDR correction. The warm colored circles represent significantly smaller oxy-Hb increases than in the control group at the channels indicated. There were 22 channels (ch22–29, ch32–33, ch35–39 and ch44–50; FDR-corrected *p*: 000–.024).

to –.48; FDR-corrected *p*: .002 to .007). Mean oxy-Hb changes showed no significant correlations with doses of anxiolytics.

6. Discussion

6.1. Task performance

The number of words generated during the VFT did not differ significantly between patients and controls, which is consistent with the majority of previous studies (Matsuo et al., 2002; Fossati et al., 2003; Suto et al., 2004; Kameyama et al., 2006). Previous studies reported impairment on semantic fluency tasks in depression (Calev et al., 1989; Tarbuck and Paykel, 1995). However, on phonemic fluency task conflicting results patients showing normal or impairment performance in depression (Albus et al., 1996; Degl'Innocenti et al., 1998). Type of psychiatric disorder and task time setting may reflect the discrepancies (Fossati et al., 2003). In the present study, the time setting of VFT was three phonemes within 60 s, that is, 20 s for each phoneme, which differs from the standard VFT usually using 60 s for one phoneme. The time setting condition was designed as it is, so that the subjects were able to keep generating words regularly within the task period to avoid the effect of "not speaking". It is possible that the time setting condition in the present study caused the lack of significant between group-difference in task performance.

6.2. Between-group comparison of oxy-Hb activation

The present study showed oxy-Hb activation during VFT to be significantly smaller in the MDD group than in age-, gender- and IQ-matched healthy controls. This result is essentially consistent with those obtained using NIRS (Matsuo et al., 2002; Herrmann et al., 2004; Suto et al., 2004; Kameyama et al., 2006; Pu et al., 2008), single photon emission computed tomography (SPECT) (Mayberg et al., 1994) or functional magnetic resonance imaging (fMRI) (Okada et al., 2003).

6.3. Relationships with symptom severity at the time of examination

Mean oxy-Hb changes during the task period showed a significantly negative correlation with HAM-D21 total score at ch25. Ch25 is located approximately in the right DLPFC. The finding is in line with some initial studies (Bench et al., 1995; Mayberg et al., 1994) which suggest that abnormal functions in DLPFC are mood dependent. However, other more recent studies investigating cross-sectional relationship between depression psychopathology and brain function do not coincide with our result (Périco et al., 2005; Milak et al., 2005). One of the reasons for the discrepancy may arise from the different methodologies; in the present study we adopted VFT for activation whereas the previous studies observed the basal activity with no activation task. Although speculative as it is, the activation of PFC by VFT may have led to the significant relationship between oxy-Hb changes and depression symptom severity in the right DLPFC.

More interestingly, mean oxy-Hb changes during the task period showed significant negative correlations with three individual HAM-D21 items in a wider area than they showed with HAM-D21 total scores; insomnia early in nine, work and activity in two and psychomotor retardation in twelve channels. The nine channels correlating with "insomnia early" were located approximately in the right pre-motor area, DLPFC and frontopolar and orbitofrontal areas. The two channels correlating with "work and activity" were located approximately in the right DLPFC and temporopolar area. The twelve channels correlating with "psychomotor retardation" were located broadly in the fronto-temporal areas with right hemispheric dominance. Although these findings should be treated with care given the exploratory nature of multiple analyses, it is noteworthy that at least some subscale scores of HAM-D21 appeared to show stronger relationship with oxy-Hb changes than HAM-D21 total scores. It has been pointed out that HAM-D17 and/or HAM-D21 are not necessarily unidimensional, and thus not adequate to assess depression severity (Bagby et al., 2004). Licht et al. (2005) showed that a set of the HAM-D containing six subscales constitute a unidimensional scale measuring severity of

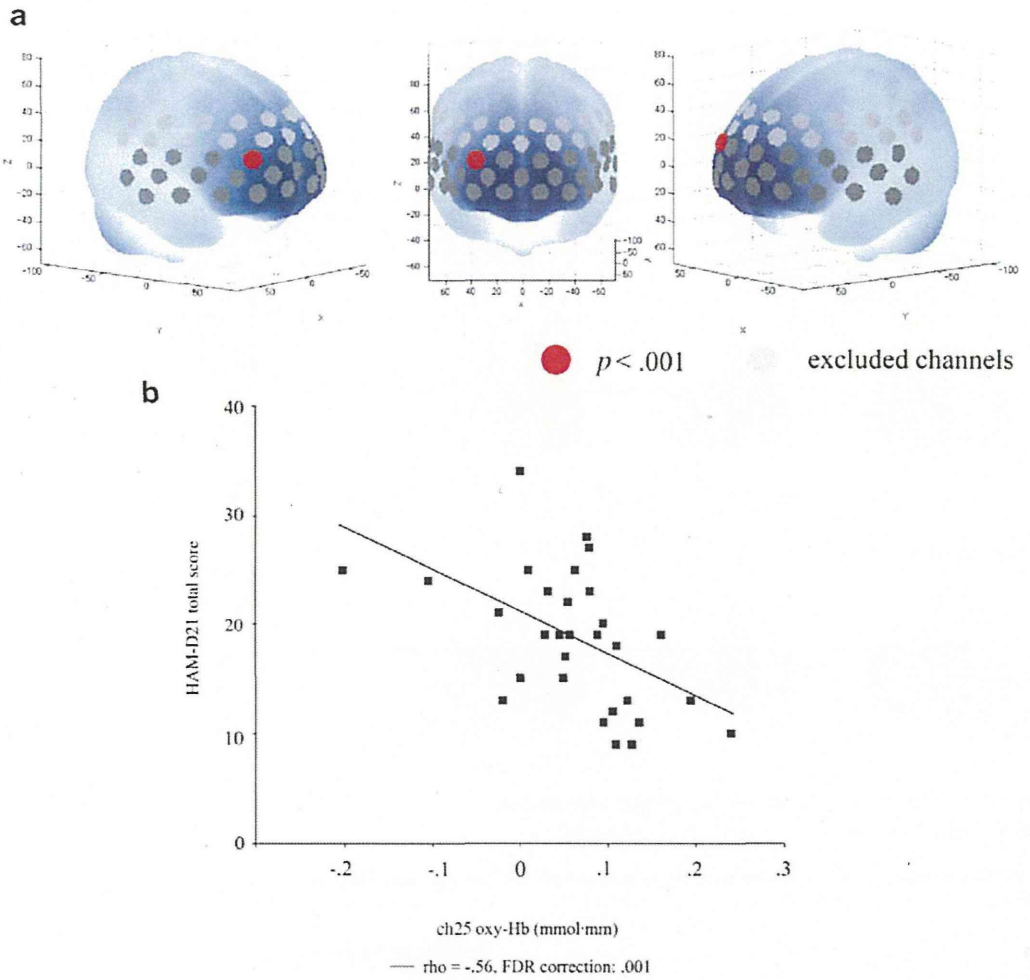

Fig. 3. (a) The channels with a significant correlation between oxy-Hb changes and HAM-D21 total score after FDR correction. (b) Scatter graph showing the relationship between HAM-D21 total scores and oxy-Hb activation in ch25.

depression, whereas the remaining items covering neurovegetative symptoms showed a problematic response somewhat insensitive to depression severity. In fact, the multidimensionality was highlighted in the unstable factor structure, which was demonstrated by a failure to replicate a single unifying structure across studies (Bagby et al., 2004). The relatively strong relationship indicated between HAM-D21 subscale scores and oxy-Hb changes in divergent areas, compared to HAM-D21 total scores may be due to the multidimensional properties of HAM-D21. Graff-Guerrero et al. (2004) also demonstrated that each HAM-D subscale score showed a significant correlation with the basal CBF in variant areas, in some cases showing positive correlation and others negative.

6.4. Relationships with medications

As all patients were taking antidepressants at the time of evaluation, the medication effect could not be ignored. Yet, there was no significant relationship between daily dose levels of antidepressants and the HAM-D21 total score. Although daily dose levels of antidepressants showed significant negative correlations with oxy-Hb changes in six channels, ch25, where a significant correlation between oxy-Hb changes and HAM-D21 total scores was observed, was not included in the six channels. Therefore, we suspect that the effect was small, if at all.

PET has been used to demonstrate that antidepressant medication normalizes both over-activity and under-activity in the frontal cortex (Kennedy et al., 2001, 2007; Mayberg et al., 2000; Goldapple et al., 2004). Unfortunately, our results could not clarify the relationship between medication and brain activation because our analysis was based on cross-sectional data. Although our data may reflect the more restraint-free, natural setting than those using fMRI or PET, further studies in drug-naïve patients are required to draw any conclusions as to the possible effects of medication on brain activation as measured by NIRS. Longitudinal studies investigating the relationship between the change in oxy-Hb data and symptom severity scores with a larger sample size are warranted to reach a conclusion on this matter.

The results of this study must be interpreted with caution due to certain limitations. First, because the analysis was based on cross-sectional data, causality cannot be determined. Longitudinal studies are needed to assess cause-and-effect relationships. Second, our sample size was not large, and is thus subject to type II error. Further studies with larger numbers of MDD patients are required. Finally, owing to the multidimensional properties of HAM-D21, assessment of depression symptom severity using HAM-D21 total scores may not be adequate, and thus, other scales such as Montgomery Asberg Depression Rating Scale (MADRS) or Beck Depression Inventory (BDI) should be tested in the future study.

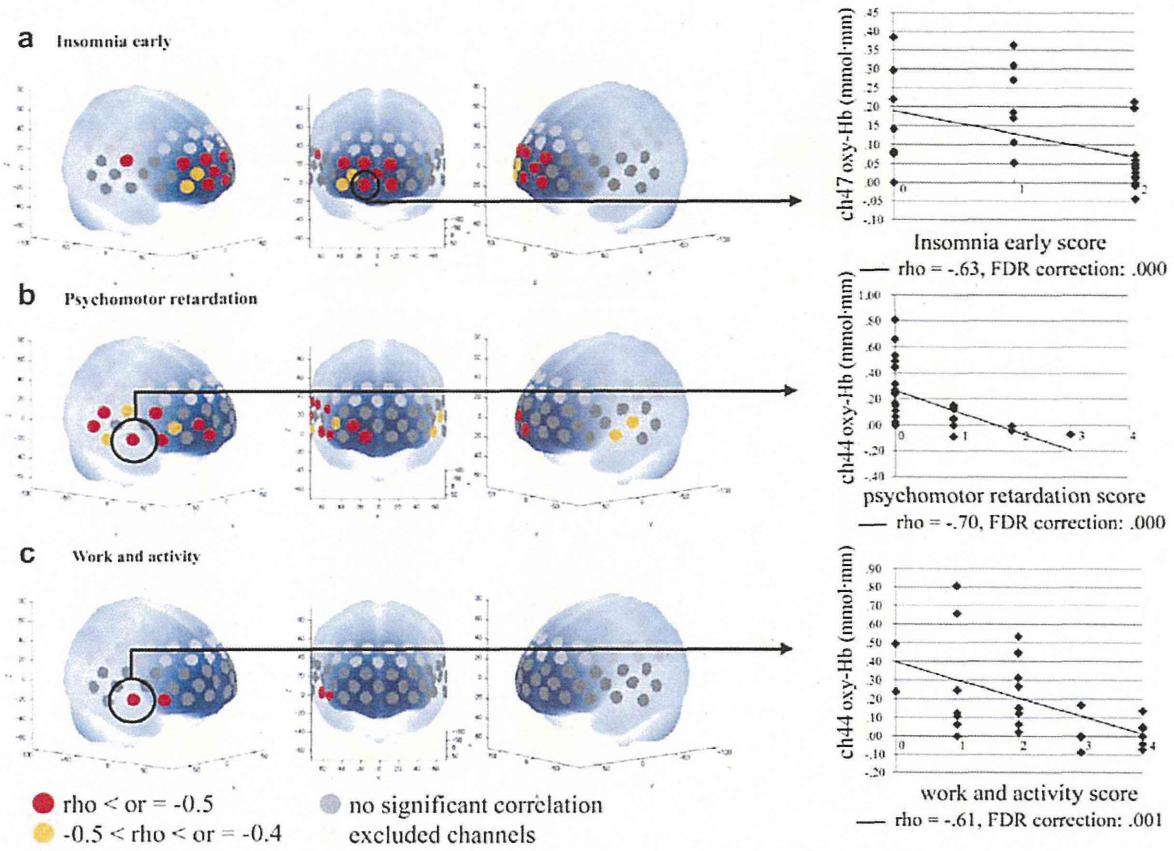

Fig. 4. rho-value map for the correlation between oxy-Hb activation in MDD patients and three individual HAM-D21 subscale scores after FDR correction. (a) insomnia early, (b) psychomotor retardation, and (c) work and activity.

7. Conclusion

In this study, we confirmed that the increase in oxy-Hb during a VFT task is significantly smaller in MDD than in age- and gender-matched healthy subjects. This difference could not be explained by a difference in task performance or premorbid IQ. The blunted increase in right DLPFC was associated with the symptom severity of MDD and therefore oxy-Hb changes during VFT in this region may be a state-dependent marker of depression.

Role of the funding source

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Contributors

T. Noda designed the study, wrote the protocol, assessment of depression severity, literature searches, statistically analyzed the data, and wrote the first draft of the manuscript. T. Matsuda was involved in patient recruitment and assessment of depression severity. H. Kunugi and S. Yoshida wrote the final version of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

All the authors declare that they have no conflicts of interest with respect to this study or its publication.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jpsychires.2012.04.001.

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シンポジウム

精神医学研究の到達点と展望*

脳科学研究から見えてきた統合失調症の病態および治療と予防の展開**

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Key words

Carbonyl stress, Schizophrenia, Preventive medicine

はじめに

統合失調症は，遺伝率(heritability)が0.8，λs(同胞間の相対危険率)が8.2(I型糖尿病15，アルツハイマー病4～5)と，遺伝要因が大きい疾患である(表1)。そこで，原因解明には遺伝学的アプローチが有望であると考えられてきた。90年代は，連鎖解析で位置的(positional)に染色体上の座位を決めて原因遺伝子をクローニングする研究が流行した。こうした研究は，主としてメンデル型遺伝形式をとる単一遺伝子疾患で成果を挙げたが，統合失調症でも同様の挑戦がなされdysbindinやneuregulin1など有望な遺伝子が同定された。しかし，その後の研究で，関連するSNP(single nucleotide polymorphism)が報告者間で異なる，あるいはSNPが一致してもリスクアレルが報告者によって逆向きであるといった不透明な結果が続いている。一方，近年は生活習慣病のような多因子疾患で，common disease-common variant仮説に基づいて，全ゲノム関連解析(genome-wide association study；GWAS)が行われている。統合失調症を対象としたGWASでも，

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表1　統合失調症の相対危険率とGWASで同定された遺伝子のオッズ比

Risk ratio[a]	Obserbed	GWAS		
		Odds ratio	gene	
λ_O	10.0			
λ_S	8.6			Rich 1990
λ_M	52.1			
λ_D	14.2			
		1.10	*ZNF804A*	Williams et al. 2010
		1.16	CACNA1C	Nyegaard et al. 2010
		1.87	*JARID2*	Liu et al. 2009
		1.22	*GENTG2*	Jianxin et al. 2009
		1.25	*NTRK3*	
		1.68	*DDX31*	
		2.02	*RNLS*	
		1.64	*GTF3C4*	
		1.30	*TRPA1*	
		1.15	*HIST1H2B*	
		1.20	*PRSS16*	
		1.24	*PGBD1*	Stefansson et al. 2009
		1.15	*NRGN*	
		1.23	*TCF4*	
		1.41	*RELIN*	Shifman et al. 2008

[a] Definitions of subscripts：O=offspring；S=siblings；M=MZ twins；D=DZ twins

いくつかの感受性遺伝子が報告されているが，いずれのオッズ比も1.5前後と小さい(表1)。遺伝率やλsは十分大きいのに，同定される感受性遺伝子は効果の小さいものばかりである。このようなmissing heritabilityを克服しようとして，最近の研究では数千の検体数と数十万のSNPを解析するに至っており，欧米では研究規模が競い合われるようにして拡大されている。

筆者らは，主として欧米で取り組まれている国家プロジェクト級のビッグサイエンスとは違ったアプローチを考え，以下の2点を工夫した。①遺伝子解析だけでなく生化学的解析を組み合わせ，②まれだが大きな遺伝子効果をもたらす変異を同定し，それをプロトタイプとして一般症例に敷衍する。上記2つを実施した結果，興味深い成果を得たので本稿にて紹介する。本研究は東京都精神医学総合研究所および関連施設の倫理委員会の承認を得て，被験者にインフォームドコンセントののち書面にて同意を得て行われた。

まれな遺伝子変異の同定

まれで比較的大きな遺伝子効果をもたらす変異は，単一遺伝子疾患に近い遺伝形式をとることを想定し，まず多発家系に注目した。機能変化の大きい変異はまれで新規であると考え，候補遺伝子の全塩基配列を解読するresequenceを実施した。候補遺伝子には，連鎖解析研究により複数のグループから統合失調症との連鎖が報告されている6番染色体短腕6p21[4,6,12]に注目し，ここにコードされている*glyoxalase I*(*GLO1*)を選択した。GLO1は，酸化ストレスなどで生じる有害なカルボニル化合物を分解解毒する酵素であり，発現量の違いが情動に影響することも報告されていた[5]。多発家系の発端者ばかり約50例でresequenceを行った結果，1例から*GLO1*遺伝子のexon1にadenineが1塩基挿入する新規のフレームシフト変異を同定した。症例の家系には，3親等内に同胞全員を含め5名の統合失調症罹患者がいた。症例の*GLO1*遺伝子ではフレームシフ

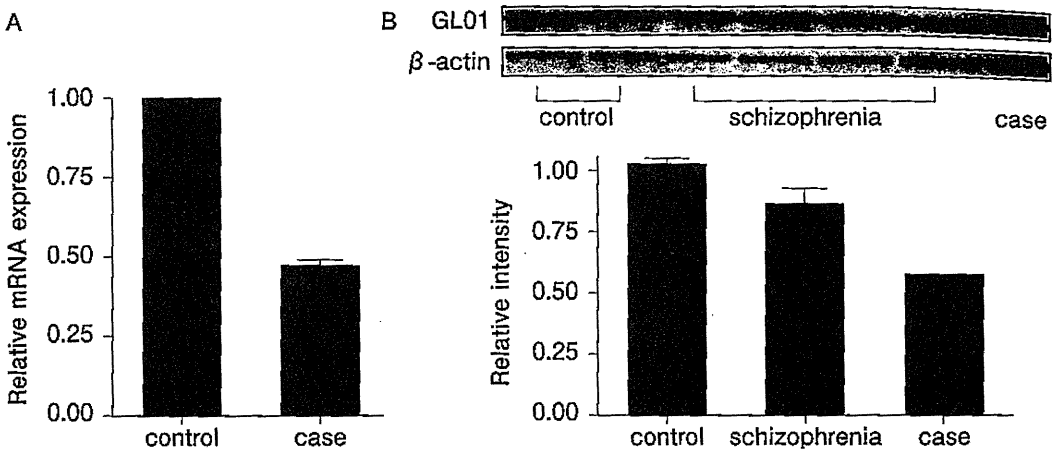

図1　症例におけるGLO1のmRNAおよび蛋白発現
A：GLO1のmRNA発現。対照を1.0としたときの相対発現量を示す。TaqMan法により定量。
B：GLO1の蛋白発現。対照を1.0としたときの相対発現量を示す。Western blot法によりβ-actinを内部標準として定量。
Case；*GLO1*にフレームシフトを持った発端症例，schizophrenia；*GLO1*にフレームシフトを持たない統合失調症，control；変異を*GLO1*に持たない健常対照

トにより早期終始コドンが発生し，全長184アミノ酸のGLO1が，症例では42アミノ酸しか合成されていない可能性が示唆された。そこで，症例のリンパ球を用いてGLO1の発現を測定したところ，mRNA，蛋白量ともに健常者の50%まで低下していた(図1)。カルボニル化合物はメイラード反応を介して蛋白質などを修飾し，終末糖化産物(advanced glycation end products；AGEs)を生成する。AGEsが蓄積する状態は「カルボニルストレス」と提唱され[7]，糖尿病性網膜症や動脈硬化の発症，進展，増悪に関与し，心不全や冠動脈疾患による死亡率とも相関する。カルボニルストレス消去系には，GLO1以外にビタミンB6があり，カルボニル化合物と結合してAGEsの腎排泄を促進し，メイラード反応も抑制する。症例ではGLO1活性が50%まで低下していることから，血中AGEs(ペントシジン)濃度の上昇，およびカルボニル消去に動員されることによるビタミンB6の低下が予測された。そこで，症例の末梢血を解析したところ，AGEs濃度は対照の3.7倍に増加し，ビタミンB6は対照の20%レベルまで低下していた。

まれな症例から一般症例への敷衍

症例ではまれな新規のフレームシフト変異をヘテロ接合に持つことにより，GLO1活性が50%低下するという大きな機能変化がもたらされていた。一般症例では，より軽度な活性低下を伴った頻度の高い多型が存在するのではないかと考え，*GLO1*遺伝子の関連研究を行った。統合失調症202例と年齢・性別の一致した対照187例を用いて，データベースに登録されている9か所のSNPの頻度を比較した。その結果，3つのハプロタイプで有意な関連を認めた。ハプロタイプが重なりあう部分のGlu111Alaは，有意ではないがAlaのアレルが統合失調症で高い頻度で認められた(患者8%，対照5%)。特にAla111ホモ接合体は4例同定されたが，すべて統合失調症だった。そこで，Glu111型とAla111型の*GLO1*のcDNAにGFPを融合したコンストラクトをCOS-7細胞へ導入し，強制発現させたGLO1蛋白をGFPで免疫沈降して回収し活性を測定した。その結果，Glu111型よりAla111型のGLO1で活性が低かった。次に，Alaホモ接合体3例の赤血球を用いて酵素活性を測定したところ，Glu/Glu，Glu/Ala型のヒトより有意にGLO1活性が低下していた(16%低下，$P=0.0003$)。

50%活性低下を伴うフレームシフト変異のヘテロ接合体だけでなく，一般症例にも16%活性低下を伴うAla111ホモ接合体が存在すること

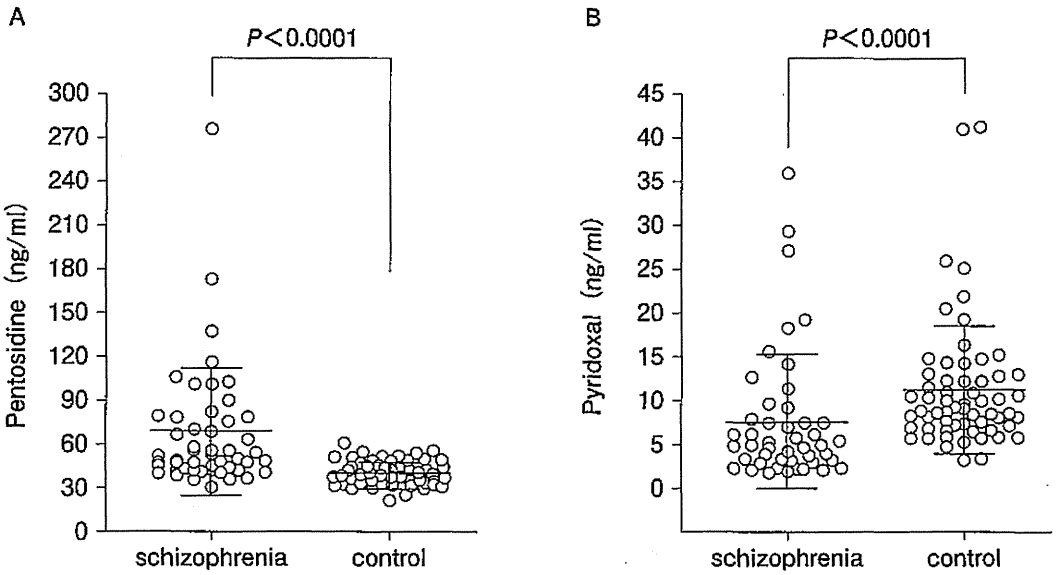

図2 統合失調症と対照の末梢血におけるAGEsとビタミンB6濃度
DSM-IVで統合失調症と診断された患者45例と健常対照61例の末梢血を用いAGEs(ペントシジン)とビタミンB6(ピリドキサール)を定量した。A：血清ペントシジン濃度。B：血清ビタミンB6濃度。文献[2]から一部改変して引用。

から，統合失調症には軽度にAGEsが蓄積している症例が広く存在する可能性があると考えた。そこで，AGEsの蓄積要因である糖尿病，腎障害，炎症性疾患を除外規定にして，45例の統合失調症と61例の健常対照の末梢血を用いてAGEsとビタミンB6を測定した。その結果，統合失調症では対照より有意にAGEs濃度が上昇し($P<0.001$)，ビタミンB6濃度が有意に低下していた($P<0.001$)(図2)[2]。AGEs蓄積の有無と患者・対照をχ^2検定したところ，統合失調症はAGEs蓄積と有意に関連した($\chi^2=28.69$，df=1，$P<0.0001$，Odds比=25.81，95%信頼区間=3.515～57.64)。ビタミンB6低下の有無と患者・対照をχ^2検定した結果，統合失調症はビタミンB6低下と有意に関連した($\chi^2=25.90$，df=1，$P<0.0001$，Odds比=10.58，95%信頼区間=3.942～28.27)。

治療と予防

ビタミンB6はピリドキサール，ピリドキシン，ピリドキサミンからなり，互いに平衡関係にある。生体内ではピリドキサールがほとんどを占め，今回計測したビタミンB6もピリドキサールである。カルボニル消去作用を持つのはピリドキサミンだけであり，市販のビタミンB6(ピリドキサール)を服用しても，体内でピリドキサミンに移行する量は微量である。我々は，カルボニルストレスの改善効果を狙いピリドキサミンの第一相臨床試験を実施した。有害事象を認めず，Zucker fatty ratでAGEs生成阻害に有効な1日暴露量(AUC_{0-24})46 μg·hr/ml[1]に達するピリドキサミン投与量も決定した。第二相試験を医師主導型治験として2011年10月24日に開始した。

また，遺伝子変異を持った症例については，カルボニルストレスが発症前から存在した可能性が考えられる。実際に，未服薬のARMS(at risk mental state)症例で，113.2 ng/mlのAGEsを認めた(対照の平均+2SD；55.2 ng/ml)[3]。こうした症例に顕在発症前からピリドキサミンの投与を行うことで，発症予防の可能性が期待できる。

考察

多発家系の発端者から，*GLO1*遺伝子に新規のフレームシフト変異を同定し，この変異のヘテロ接合体では50%の活性低下を認めた。症例では，カルボニル消去系に機能不全を招来しAGEs

が対照の3.7倍に増加し，カルボニルスカベンジャーであるビタミンB6の枯渇を認めた。まれだが大きな活性低下をもたらす変異を持った症例において，顕著なAGEs蓄積を同定し，これをプロトタイプとして一般症例に敷衍し46.7%の患者でAGEs蓄積を認めることができた(AGEs蓄積あり＞55.2 ng/ml；対照の平均＋2SDをカットオフ値)。強い効果の単一遺伝子が病態に関与することを予測し多発家系に注目したからこそ，顕著なカルボニルストレスを同定することができた。また，この症例をプロトタイプとしてとらえた結果，一般症例からもカルボニストレスを見出せたと考える。発端第1症例が示したような130 ng/mlを超える顕著なAGEs蓄積と3 ngを下回る顕著なビタミンB6低下を併せ持つ症例は全体の6%にすぎない。やみくもに検体を検討しても，カルボニルストレスを見逃した可能性が高かった。

対象からAGEsの増加要因である糖尿病，腎障害，炎症性疾患は除外してあるため，AGEs蓄積を示した統合失調症は特発性のカルボニスルトレスと考える。カルボニルストレスを認めた症例の一部はGLO1の遺伝的活性低下がAGEs蓄積に寄与したと考える($\chi^2=7.727$；df＝1；$P=0.0054$；Odds比＝5.632)。しかし，フレームシフトやAla111ホモ接合体を認めた症例は一部であり，多くのカルボニルストレスの発生機序解明は不明である。*GLO1*遺伝子に変異を持たない症例から，その後の解析で複数のカルボニル消去経路に異常を同定しており，統合失調症のカルボニルストレスにも異種性がある可能性が示唆された(未発表)。

統合失調症の死後脳解析や三次元MRIでの形態計測の結果，前頭葉—側頭葉ならびに視床の細胞構築や形態異常が知られている。カルボニルストレスとこれら脳病変との関連は，いまだに報告がない。Villarrealらは，培養神経細胞を用いた検討で，AGEsが受容体(receptor for AGE；RAGE)を介してNF-kBシグナルを発生し，神経細胞死を惹起することを報告した[11]。このことから，カルボニルストレスがNF-kBなど炎症シグナルを介して神経毒性を生じている可能性が示唆される。RAGEは中枢神経系に広く発現しているため[9]，AGEsによる炎症シグナルは脳のどの部位でも発生し得ると考えられる。データベース[9]によると，統合失調症で形態異常が報告された視床でRAGEの発現は高いが，特に視床とカルボニルストレスによる神経毒性の関連はまだ報告されていない。ただ，GLO1のノックアウトマウスの脳を海馬，皮質，脳幹などに分けた予備的検討で，AGEsの蓄積に脳部位特異性が示唆された(Arai M, Dan T, et al. 未発表)。このことから，カルボニルストレスが発生しやすい脳局在が考えられるが，皮質をさらに分割した検討が今後の課題であると考える。

また，糖尿病がアルツハイマー型認知症の進行を早めることから[10]，毒性AGE仮説(toxic advanced glycation end products "TAGE" theory)としてカルボニルストレスと神経細胞死の関連が詳細に検討されている[8]。しかし，これらは成人脳におけるAGEsの影響を検討したものである。GLO1にフレームシフト変異を持つ症例やAla111のホモ接合体では，発症前かなり早期からカルボニルストレスを生じていた可能性が示唆される。こうした幼児期からAGEsシャワーを脳に浴び続けることによる神経発達への影響はまだ報告がなく，今後動物モデルを用いた検討が重要な課題となる。

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