4. 反応時間とエラー率

年少群は刺激モダリティにかかわらず年長群や成人よりも有意に反応時間が遅延していた．判断別では，一致判断に比べて不一致判断時の反応時間遅延が3刺激条件とも認められた（有意差はなし）．また，視聴覚同時刺激の際にもっとも反応時間が短縮していた．一方，10歳以上の年長群は成人群とほぼ同じ値を示した（視覚モダリティ不一致判断時反応時間は各々902.5 ± 261.3 ms，799 ± 168 ms）が，視覚単独刺激の場合に反応時間はもっとも短縮した．発達性読み書き障害では視覚単独刺激による反応時間短縮がみられず，逆にもっとも遅延する（1181.0 ± 569.5 ms）という特徴を示した．

エラー率は健常年少児では視覚刺激でもっとも高い傾向があり，聴覚，視聴覚同時刺激の順にエラー率が低くなった（有意差はなし）．年長群は成人群とほぼ同じエラー率を示した．読み書き障害児は視覚エラーが目立っており，成人群との間に有意差（ANOVA，$p < 0.05$）があった．

Ⅲ 考 察

1. 意味処理機構のモダリティ別発達について

事象関連電位N400は主に単語の意味判断（語彙判断）の際の脳活動に伴って出現する電位である．単語認知過程の中では特に，音韻など感覚入力分析（語彙処理前過程）や心内辞書における特定の単語同定（語彙処理過程）に引き続く，単語の持つ意味情報の選択，統合といった「語彙処理後過程」を反映するものとされている[1]．N400に関する研究は多いものの，同一の課題を同一人で刺激モダリティ別に比較したものやその発達的変化を検討した研究はこれまでほとんどみられていない．今回採用した「意味カテゴリー一致判断課題」は幼児の表現語彙集を基に作成されており，学童期における単語の意味理解の発達について検討できたと思われる．

今回もっとも特徴的であった点は，刺激モダリティによってN400波形が異なっていた点であった．特に聴覚刺激時，6～9歳児にみられた大きなN400成分は前頭部から頭頂部の広い範囲に分布しており，成人のN400波形や分布とは全く異なっていた．このことは小学校低学年では音韻処理と意味処理の際に広汎な脳部位の活動が必要なことを示唆し，そのエネルギーが大きいことを推測させた．文末の意味的逸脱語課題や単語の語彙判断課題を聴覚提示した際にも，小児（5～11歳）では成人と比べて広範囲にN400が認められており[9][10]，高振幅パターンは年少児での聴覚性N400の特徴のひとつと考えられる．一方10歳以上の聴覚性N400は成人群の二峰性パターン[7]と類似し，ピーク潜時の差がない点からも音声による意味処理は10歳過ぎに成熟するものと推測された．

視覚性N400は年齢とともに二峰性から単峰性へと波形が変化した．7歳小児[11]や9～10歳小児[12]の視覚性N400は二峰性ピークを持つと報告され，大きな矛盾はないと思われる．そして，二番目の陰性ピーク成分は単語がターゲットと合っているのか，もしくは誤っているのか，という脳内過程を反映したものと考えられている[12]．今回，年少群の二峰目のピーク潜時（平均491 ms）は聴覚提示の単峰性ピーク潜時（平均511 ms）とほぼ同じであった．このことは，年少例における単語の意味カテゴリーの認知，そして照合という語彙処理後過程はモダリティ間で時間的な差がほとんどなく進行することを示唆している．しかし，視聴覚モダリティ同時に単語を提示すると，N400ピーク潜時は有意に短縮がみられた（Fz部；450 ms，$p < 0.05$）．また，キー押し反応時間も同時提示がもっとも早いという結果であった．したがって，年少群では刺激情報が重複して与えられると，単語の意味処理過程が促進されることも推測される．

10歳以上の年長群と成人群の視覚モダリティN400はCz部ではほぼ同じ波形を示し，ピーク潜時もほぼ同じであった．すなわち，視覚モダリティにおいても聴覚モダリティと同様に10歳以降で意味処理が成熟化することが推測された．さらに，10歳以上の場合は視聴覚同時提示と視覚単独提示におけるN400波形パターンがほぼ同じとなっており，意味処理における視覚優位性がうかがえる結果でもあった．視覚単独の場合に反応時間がもっとも短縮していたことも読字における聴覚情報非依存性処理を示唆している．LPCについても視覚提示の際10歳以上群のピークは明瞭であり，意味処理の成熟化がうかがえた．Robinsonら，Napolitanoらの報告[13][14]によると，4歳までの乳幼児は一般に，画像と音を同時刺激すると聴覚モダリティへの注目が優勢であり，年齢とともに徐々に視覚モダリティ優位となり，成人では完全に視覚モダリティ優位となるとしている．つまり，言語の習得のため発達初期には一過性に聴覚優位の時期があると考えると理解しやすい．

2. 発達性読み書き障害のN400異常について

発達期に生じる読み書き障害機序として，①言語音想起の発達の遅れや偏倚，②文字の形の視覚的認知や文字列の位置情報についての視空間認知障害など複数の説が呈示されている[15][16]．平仮名は音と文字とが1対1に対応し，対応が複雑なアルファベットに比べて通常，その学習が容易であると考えられる．しかし，就学後に学習する漢字は読みが音読み，訓読みなど複数あり，文字と音の対応がアルファベットよりむしろ複雑になっているともいえる．すなわち，今回の8例のように平仮名の習得がかろうじてできてきた読み書き障害児が漢字の学習でつまずくことや，中学校以降に英語学習の際，困難度が増すことは充分考えられる．そして，読みの障害があれば意味の把握が不良となりやすく，N400異常が出現することも当然予想される．

これまで，dyslexiaのN400異常は適用課題や刺激モダリティによって異なるものの，波形消失あるいは逆に振幅増加といった相反する結果が示されている[5][6][17][18]．Bonteらはプライミングを含めた音韻処理の異常を指摘している[10]が，今回の発達性読み書き障害児における聴覚性N400は健常群と同

様に二峰性を示した．Fz部のみでピーク潜時が有意（P＜0.05）に遅延したものの，等電位分布図からも聴覚モダリティによるN400には明らかな異常がないものと考えられた．一方，視覚モダリティでは健常群と比較すると二峰目のN400潜時の有意な遅延が認められた．N400，LPCの等電位分布も健常児のパターンとは異なり，行動的な指標でも視覚モダリティでの異常が強かった．

しかしながら，視聴覚同時刺激によってN400は明瞭化し，ピーク潜時の短縮がみられ改善した．漢字の読みと書きは，文字形態に音を想起して意味が結びつく「音韻処理過程」と文字と意味とが直接結びつく「視覚的意味処理過程」が脳内で並列して進行すると考えられている[19]．つまり今回の読み書き障害群は，神経心理検査上，1例（症例2）を除いて視覚認知機能の著明な障害は確認できなかったものの，文字認知以降の視覚的意味処理過程になんらかの機能障害があり，聴覚情報処理が比較的優位となっているものと思われた．そして，二つのモダリティを使って刺激量を増加した場合には，健常年少群でみられるような意味処理の促進効果が生じていることも考えられた．

今回の対象例は少ないため，得られたN400結果が発達性読み書き障害のすべてにあてはまるとはいえず，漢字の書字機構の異常を直接的に反映するものではないとも考えられる．しかしながら，読み書き障害例に対して刺激モダリティを工夫した指導法の開発によって，読みの能力改善，さらには意味理解力の獲得，そして書字の能力改善につながることも報告されており[20]，モダリティ別N400検査が読み書き障害の背景病態の一部を反映する可能性も考えられる．今後は，神経心理検査所見と事象関連電位との詳細な対応，評価を個々の症例で進めていく必要があると思われる．

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文　献

1) 小山紗智子，柿木隆介．単語認知と事象関連電位．丹羽真一，鶴　紀子，編．事象関連電位－事象関連電位と神経情報科学の発展－．東京：新興医学出版社，1997；82-95.
2) Kutas M, Hillyard SA. Reading senseless sentences: brain potentials reflect semantic incongruity. *Science* 1980;**207**:203-5.
3) Koyama S, Nageishi Y, Shimokochi M, et al. The N400 component of event-related potentials in schizophrenic patients: a preliminary study. *Electroencephalogr Clin Neurophysiol* 1991;**78**:124-32.
4) Stelmack RM, Saxe BJ, Noldy-Cullum N, Campbell KB, Armitage R. Recognition memory for words and event-related potentials: a comparison of normal and disabled readers. *J Clin Exp Neuropsychol* 1988;**10**:185-200.
5) Stelmack RM, Miles J. The effect of picture priming on event-related potentials of normal and disabled readers during a word recognition memory task. *J Clin Exp Neuropsychol* 1990;**12**:887-903.
6) Brandeis D, Vitacco D, Steinhausen HC. Mapping brain electric micro-states in dyslexic children during reading. *Acta Paedopsychiatr* 1994;**56**:239-47.
7) 佐田佳美，稲垣真澄，矢野岳美，堀本れい子，加我牧子．意味カテゴリー一致判断課題における事象関連電位N400の特徴－等電位分布図（topography）による検討－臨床神経生理学 2001;**29**:342-51.
8) 佐々木匡子，稲垣真澄，加我牧子．言語性意味理解障害児にみられた事象関連電位N400の異常について．脳と発達 2003;**35**:167-70.
9) Juottonen K, Revonsuo A, Lang H. Dissimilar age influences on two ERP waveforms (LPC and N400) reflecting semantic context effect. *Brain Res Cogn Brain Res* 1996;**4**:99-107.
10) Bonte M, Blomert L. Developmental changes in ERP correlates of spoken word recognition during early school years: a phonological priming study. *Clin Neurophysiol* 2004;**115**:409-23.
11) Coch D, Holcomb PJ. The N400 in beginning readers. *Dev Psychobiol* 2003;**43**:146-66.
12) Silva-Pereyra J, Rivera-Gaxiola M, Fernandez T, et al. Are poor readers semantically challenged? An event-related brain potential assessment. *Int J Psychophysiol* 2003;**49**:187-99.
13) Robinson CW, Sloutsky VM. Auditory dominance and its change in the course of development. *Child Dev* 2004;**75**:1387-401.
14) Napolitano AC, Sloutsky VM. Is a picture worth a thousand words? The flexible nature of modality dominance in young children. *Child Dev* 2004;**75**:1850-70.
15) Valdois S, Bosse ML, Tainturier MJ. The cognitive deficits responsible for developmental dyslexia: review of evidence for a selective visual attentional disorder. *Dyslexia* 2004;**10**:339-63.
16) Shaywitz SE, Shaywitz BA. Dyslexia (specific reading disability). *Biol Psychiatry* 2005;**57**:1301-9.
17) Dykman RA, Ackerman PT, Loizou PC, Casey PH. An event-related potential study of older children with an early history of failure to thrive. *Dev Neuropsychol* 2000;**18**:187-212.
18) Robichon F, Besson M, Habib M. An electrophysiological study of dyslexic and control adults in a sentence reading task. *Biol Psychol* 2002;**59**:29-53.
19) 佐藤睦子．失読と失書．宇野　彰，編著．高次神経機能障害の臨床　実践入門．東京：新興医学出版社，2002：16-9.
20) 宇野　彰，春原則子，金子真人．発達性読み書き障害への訓練と訓練効果－バイパス法－．原　　仁，編．発達障害医学の進歩　17．東京：診断と治療社，2005：35-47.

Developmental Changes of N400 Event Related Potential of a Semantic Category Decision Task and Modality Specific Findings in Patients with Developmental Dyslexia

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We investigated modality-specific changes in N400 event related potential using a semantic category decision task in 38 control subjects and 8 patients with developmental dyslexia. In control children under 10 years old, auditory N400 showed a negative deflection over the fronto-centro-parietal areas with substantial amplitude. Control children over 10 years old showed a similar pattern of N400 waves in a visual and an auditory-visual modality, suggesting that the visual modality becomes dominant in the late teens. Dyslexic children showed more errors on a visual than auditory modality task with poorer N400 waves for visual stimuli. However, peak latencies of N400 in an auditory-visual modality were almost the same for auditory stimuli in control children. Differences in the N400 pattern in children might reflect the fragility and reversibility of the semantic processes through stimulus modalities.

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神経学の散歩道(52)

Apgarの寸鉄詩

1949年以前は米国でも，新生児の状態を判断するのに，呼吸開発までの時間や，産ぶ声をあげるまでの時間が用いられてきた．

しかし，その後，Virginia Apgarによって開発されたApgar採点法が開発され，全世界で広く用いられるようになった．Apgarの採点法は，皮膚色，心拍数，反射亢奮性，筋トーヌス，呼吸努力の5項目の各々に，0，1，2のいずれかの点数を与え，合計点によって新生児の状態を判断する方法である．その1分値は新生児の生命予後と，5分値は後遺症の予後と密接に相関すると考えられている．

Apgarの採点法は，方法自体は簡単であるが，観察項目を暗記するのは面倒である．この点についてButterfield JとCovey MJは，記憶のためのEpigram（寸鉄詩）を提唱した．*JAMA* 1962;**181**:353. Colorの代りにappearance, hertrateの代りにpulse, reflex irritabilityの代りにgrimace, muscle toneに代えてactivity, respiratory effortの代りにrespirationを置き換えて見れば，頭文字をつなぐとAPGARとなり，たやすく記憶することがと主張している．

（馬 場 一 雄）

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Chapter 34

Multimodal evoked potentials in patients with pediatric leukodystrophy

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1. Introduction

Leukodystrophies comprise a group of inherited white matter degenerating disorders characterized by demyelination and/or dysmyelination in the central and/or peripheral nervous systems. In almost all early onset disease phenotypes, symptom progression is fairly rapid and death usually occurs within a few years. Recent studies have revealed their etiologies through genetics and metabology, and the pathophysiological findings through pathology, radiology, and neurophysiology. In short, X-linked adrenoleukodystrophy has two distinct neurological phenotypes: adrenomyeloneuropathy (AMN), a non-inflammatory axonopathy found mostly in adults, and an intensely inflammatory cerebral myelinopathy found mostly in children. A great number of mutations in the defective gene (ATP-binding cassette, subfamily D, member 1; ABCD1) has been identified (Kemp et al., 2001; Moser et al., 2004), but there is no obvious correlation between the phenotypes of adrenoleukodystrophy (ALD) patients and their genotypes (Takano et al., 1999). In the 1980s, some families with Pelizaeus–Merzbacher disease (PMD) were reported as having a point mutation of the proteolipid protein (PLP) gene, which results in PLP deficiency. Metachromatic leukodystrophy (MLD) is caused by arylsulfatase A (ASA) deficiency in early life, and the ASA gene was found to be localized to the chromosome 22q13 area. Krabbe disease (globoid cell leukodystrophy (GLD)) is a progressive disorder of the central and peripheral nervous system transmitted through autosomal-recessive inheritance and caused by deficient activity of β-galactocyl ceramidase, the gene localized to the chromosome 14q31 area. However, in most of these diseases, the mechanisms and serial physiological changes during development of the pathological lesion, especially in the same patients, have not yet been established.

During recent years, several non-invasive procedures for the evaluation of different afferent pathways from the peripheral nerves to the cerebral cortex, such as somatosensory evoked potentials (SEPs), auditory brainstem responses (ABRs), and visual evoked responses (VEPs), have been widely applied for the

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detection of clinical or subclinical lesions in diseases of the nervous system. De Meirleir et al. (1988) reported that multimodal evoked potentials (EPs) are useful for establishing the diagnosis of degeneration in the central nervous system in leukodystrophy. However, specific serial EP profiles of different leukodystrophies at each stage have not yet been established. Although clinical and neuroradiological examinations are obviously significant, the diagnosis and determination of the stage are important to both exclude other treatable diseases, and assess the prognosis of each patient. In addition, recent studies have shown effective intervention by means of bone marrow transplantation (BMT) or hemopoietic stem cell transplantation (HSCT) in ALD, MLD, and GLD, and gene therapy with several mutant mice (Krivit et al., 1999; Maria et al., 2003; Peters et al., 2003). Serial EP findings will be helpful to evaluate the effect of transplantation or future gene therapy. In this study, we present the characteristic electrophysiological findings and their serial progress in patients with 5 different leukodystrophies.

2. Methods

2.1. Patients

Twenty-four children, diagnosed with leukodystrophy, were selected for a serial study of multimodal EPs. They comprised 8 patients with ALD, 5 with PMD, 4 with Alexander's disease (ALX), 4 with MLD, and 3 with GLD. Their clinical profiles are listed in Table 1.

The average onset age was 8.6 years old (range, 6–11 years old). The chief complaints at onset were visual abnormality in 5 and gait disturbance in 2. One boy showed behavioral abnormalities such as attention-deficit disorder. The previous and developmental histories before onset were both normal. Three patients had a family history; a sister of patient no. 1 was a carrier, and the mother and grandmother of patient no. 4 had AMN. The elder brother of patient no. 7 also had ALD symptoms and their mother was determined to be an ALD carrier. The diagnosis of ALD was confirmed by a lack of response to ACTH, the presence of very long chain fatty acids (VLCFA) (C26) in urine and fibroblasts, and abnormal findings of white matter on cranial CT and/or MRI. Demyelination in the occipital subcortical area occurred in 7 patients, whereas patient no. 8 was a non-typical type ALD case whose central nervous system (CNS) lesion started from the frontal subcortical white matter. No treatment was effective (3 underwent glyceryltrioleate oil (GTO) dietary therapy, 3 underwent VLCFA elimination therapy, and 2 received γ-globulin). All showed progressive deterioration such as a bedridden state in 1, the need for mechanical ventilation in 2, and death in one for whom the cause was respiratory disturbance at 16 years of age.

Four patients with the connatal form had typical clinical features consisting of nystagmus and delayed development appearing in the first few months of life, while one patient with the classical form (no. 5) showed psychomotor retardation at the age of around one year. The results of a cranial MRI study on 2 patients (no. 3 and no. 4) suggested dysmyelination in the white matter of both the cerebrum and cerebellum at 4 and 7 months of age, respectively. The diagnosis of PMD was established from the clinical findings and the results of a typical neuroradiological study. One patient (no. 4) had a mutation of the PLP gene, identical to the *jimpy*^{msd} mouse mutation (Yamamoto et al., 1998). Two patients were bedridden during the observation periods and one patient (no. 4) died suddenly at 8 months of age, an autopsy study (Komaki et al., 1999) revealing diffuse scant myelination in the cerebral white matter but preserved peripheral nerve myelin.

In ALX patients, the head circumference increased and motor developmental delay was observed during early childhood. Cranial CT or MRI demonstrated a low density area or high signal intensity lesions on T2-weighted imaging in the cerebral white matter. Disease progression was slower in 3 patients (no. 1, no. 3, and no. 4), however, patient no. 2 died of convulsion and pneumonia at 10 years of age. No autopsy was performed.

The MLD patients consisted of 3 males and one female. The mean age at onset was one year in 2 with the infantile type, 4 years in one with the late infantile type, and 6 years in one with the juvenile type. Developmental milestones were almost normal before onset. The chief complaints at onset were

TABLE 1

INFORMATION ON THE PATIENTS WITH LEUKODYSTROPHY

Patient no.		Sex	Age	Chief complaint at onset	Observation periods	ABR occasions	f-VEP	(S)SEP	Outcome	Classification
ALD	1	M	6 y 2 m	Visual abnormality	6 y 10 m–8 y 11 m	6	4	0	Unknown	
	2	M	6 y 4 m	Strabismus	9 y 11 m–16 y 1 m	3	2	0	Death at 16 year onwards	
	3	M	6 y 6 m	Visual abnormality	7 y 1 m–15 y 5 m	6	1	0	Respiration from 11 year onwards	
	4	M	7 y 10	Visual abnormality after seizure	9 y 11 m–16 y 11 m	17	12	10	Respiration from 19 year onwards	
	5	M	8 y 1 m	Visual field defect	8 y 11 m–11 y 2 m	7	7	0	Unknown	
	6	M	11 y 3 m	Gait disturbance, visual abnormality	21 y 10 m	1	0	0	Unknown	
	7	M	11 y 7 m	Gait disturbance	12 y–14 y 6 m	8	5	2	Unknown	
	8	M	11 y	Behavioral abnormality	20 y	1	1	0	Bedridden	Frontal lesion
PMD	1	M	1 w	Nystagmus, seizure	4 m–6 m	2	0	0	Bedridden	Connatal form
	2	M	1 w	Nystagmus, seizure	11 m	1	0	0	Unknown	Connatal form
	3	M	3 m	Nystagmus, seizure	4 m–3 y 7 m	6	4	4	Bedridden	Connatal form
	4	M	4 m	Developmental delay, nystagmus	7 m	1	1	1	Death at 8 m	Connatal form
	5	M	1 y	Developmental delay	2 y 4 m–2 y 7 m	2	0	0	Unknown	Classical form
ALX	1	M	1 y	Motor developmental delay	1 y 2 m–2 y 10 m	2	1	0	Unknown	
	2	F	1 y	Motor developmental delay	3 y 9 m–7 y 6 m	1	3	0	Death at 10 year onwards	
	3	F	1 y 2 m	Developmental deterioration, macrocephaly, seizure	1 y 4 m	1	1	1		
	4	F	2 y 7 m	Seizure, gait disturbance, macrocephaly	9 y 6 m–17 y 4 m	5	4	0	Unknown	

(Continued)

TABLE 1

INFORMATION ON THE PATIENTS WITH LEUKODYSTROPHY—Cont'd

Patient no.	Sex	Age	Chief complaint at onset	Observation periods	ABR occasions	f-VEP	(S)SEP	Outcome	Classification
ML D 1	M	1 y 7 m	Developmental delay, seizure	2 y 4 m–4 y 3 m	3	2	0	Bedridden	Late infantile type (LI)
2	M	1 y 8 m	Developmental deterioration	1 y 11 m–9 y 5 m	4	2	1	Unknown	LI
3	M	4 y 4 m	Seizure, gait disturbance	4 y 7 m–8 y 2 m	2	1	0	Unknown	LI or juvenile type
4	F	6 y 6 m	Developmental deterioration	17 y 3 m–17 y 4 m	2	1	2	Bedridden	Juvenile type
GLD 1	F	3 m	Developmental deterioration	5 m–5 y	3	1	1	Respiratior from 6 year onwards	Infantile form
2	F	6 m	Developmental deterioration	11m–15 y 3 m	8	2	2	Respirator from 2 year onwards	Infantile form
3	F	11 m	Developmental deterioration after varicella	4 m–3 y 6 m	6	2	1	Bedridden	Late infantile form

developmental deterioration in 2 patients, seizure in 2, and gait disturbance in one. Patient no. 1 had a dead sister with MLD. The diagnosis of MLD was confirmed by the absence of ASA activity in lymphocytes or fibroblasts, and delayed motor nerve conduction velocity (NCV) of the peripheral nerves. CT showed a low density area in the white matter and diffuse atrophy in the cortex. Patient no. 4 underwent amniotic tissue transplantation and granulocyte transfusion, but they had little effect. All patients finally became bedridden.

The 3 GLD patients were noticed to have developmental deterioration from three months to 11 months of age. Their previous history was normal before onset. Patient no. 1 had a dead brother with GLD. All patients exhibited increased CSF protein, decreased NCV of the peripheral nerves, diffuse low density areas on cranial CT, and β -galactocerebrosidase deficiency in fibroblasts or lymphocytes. Two patients (no. 1 and no. 3) were treated with dietary dimethyl sulfoxide and the irritability in 1 patient was slightly decreased. The deterioration was rapid and two patients needed mechanical ventilation.

2.2. Procedures

EPs were recorded on silver–silver chloride disk electrodes and amplified. They were summated with MEB-7202, MEM-4104, and MEB-4208 (Nihon Kohden Co., Ltd., Japan), and obtained during sleep stage I or II, during natural sleep or sleep induced by the oral administration of trichlor ethylphosphate. Individual runs were repeated more than twice to establish the reproducibility of record potentials. The electrode impedance was maintained lower than 5 kΩ.

Auditory brainstem response (ABR): The method for obtaining ABR was reported previously (Kaga et al., 1982). The latency of waves I, III, and V, the I–V interval, and the V/I amplitude ratio were measured to evaluate the brainstem auditory pathways.

Flash visual evoked potential (f-VEP): The methods used to record the f-VEP were reported elsewhere (Yamanouchi et al., 1993). The latency of the major positive peak (wave IV; P100) and its amplitude were measured.

Somatosensory evoked potential (SEP)/short latency SEP (SSEP): Parameter settings have been described in a previous article (Ozawa et al., 1998). The latencies of the negative peak at Erb's point (N9), the negative peak of the response record over the cervical spine (N13), the negative peak of the scalp SEP (N20), and the N13–N20 interval were measured. SEPs were obtained in response to stimulation of the contralateral median nerve at the wrist. SEPs were recorded so that relative negativity at the recording electrodes resulted in an upgoing waveform. The latencies of the first negative peak (N20) were measured.

Multimodal EP findings were evaluated from 5 months to 10 years after onset in ALD patients, 1 month to 3 years in PMD patients, 2 months to 15 years in ALX patients, 3 months to 10 years in MLD patients, and 2 months to 14 years in GLD patients (Table 1). Different investigators evaluated them blindly. Informed consent was obtained from all parents or guardians before electrophysiological examinations.

3. Results

3.1. ALD

Serial changes of the ABR waveform in patient no. 5 are illustrated in Fig. 1A. At one year from onset, the latencies and amplitudes of waves I, III, and V were normal, however, the I–V interpeak latencies became increasingly prolonged and the amplitudes of all waves decreased gradually. At 2–3 years from onset, most ALD patients exhibited an abnormal ABR with prolonged I–V interpeak latencies (Fig. 2) and a decreased V/I amplitudes ratio (0.87 ± 0.76). At 2–4 years from onset, the later components of ABR became prolonged and disappeared in three patients (no. 2, no. 3, and no. 4); however, the latencies of waves I and II were within the normal limits for a relatively long time.

In the early stages, prolonged IV latencies of f-VEP were observed within one year from onset in 3 patients (no. 1, no. 5, and no. 7). There was fluctuation of the wave IV latency in patient no. 5 for several years (Fig. 3A). In the advanced stage (after 3 years from onset), wave IV of f-VEP disappeared in no. 2, no. 4, and no. 5. On the other hand, although SEP and SSEP

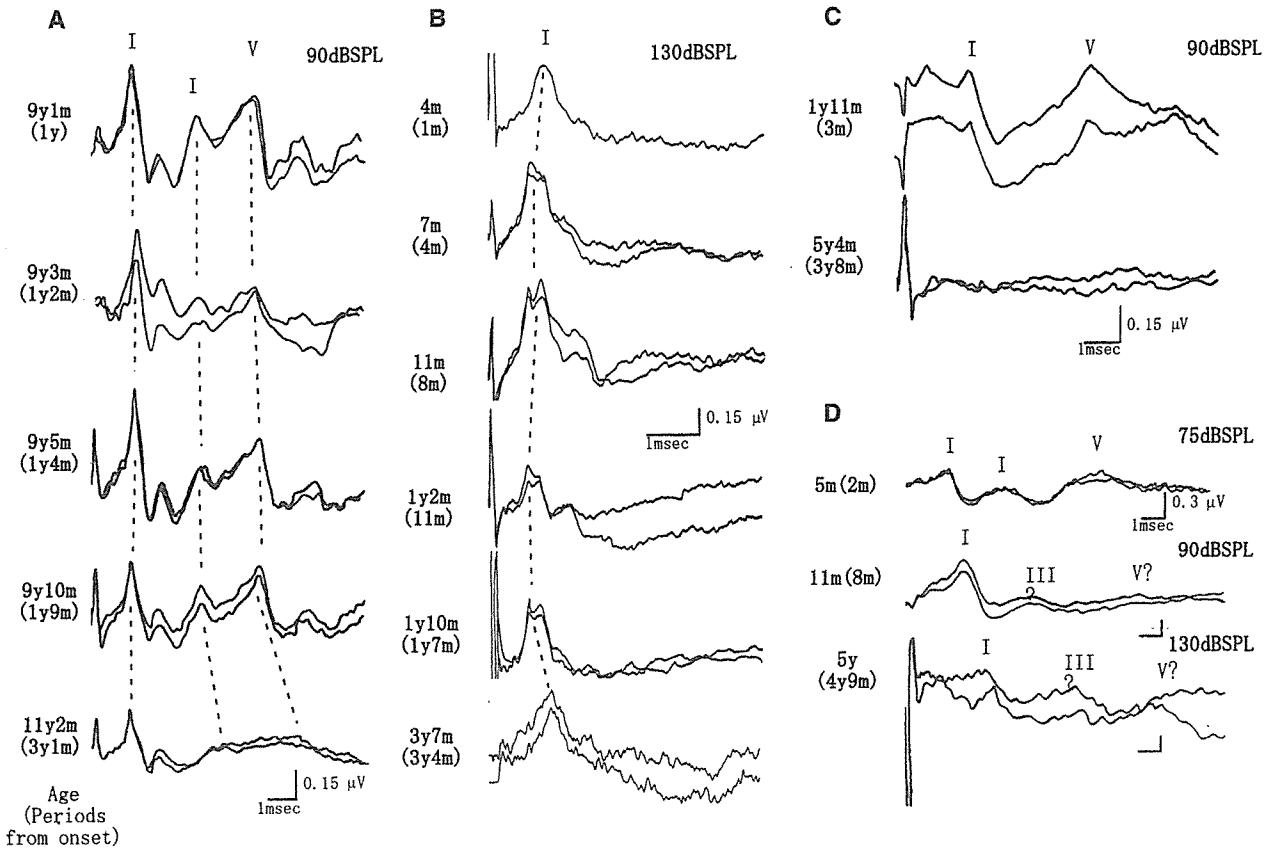

Fig. 1. Serial ABR waveforms in leukodystrophy. In ALD patient no. 5, the latencies and amplitudes of all waves were normal at 1 year from onset, however, the I–V interpeak latencies gradually became prolonged and the amplitudes of all waves were small, and finally, at 3 years and 1 month from onset, wave V was absent (A). It was most characteristic in ABR that only wave I was recorded, a few weeks after onset in PMD patient no. 3 (B). The wave I latency in that patient was prolonged in the advanced stage (at 3 years and 4 months from onset). Prolonged I–V interpeak latency and an absent wave III were already observed in MLD patient no. 2 at 3 months from onset (C), and all waves became absent at 3–4 years from onset. Wave V disappeared at 8 months from onset and a distorted waveform pattern with a severely delayed wave I (peak latency of 2.4–2.6 ms) was observed at the age of 5 years in GLD patient no. 1 (D).

were only evaluated in 2 patients, all the peripheral responses were found to be normal (N9 = 9.81 ± 0.56 ms, N13 = 11.81 ± 0.79 ms). However, one patient (no. 4) showed an almost total absence of cortical responses at 5 years and 8 months from onset (Fig. 4A), and another (no. 7) showed delayed latency of N20 (27.4 ms) at 7 months from onset. Table 2 is a summary of the serial EP findings in ALD with each modality.

3.2. PMD

The ABR findings in PMD were most characteristic a few weeks after onset. Only the wave I pattern, two peaks of waves I and II, or the broad wave I pattern were observed in all 5 patients. In patient no. 3, the latency of wave I was decreased in the early stage and wave II was evident in the late infantile period. Wave I latency was prolonged in the advanced stage (at 3.3 years from onset) (Fig. 1B). A delayed wave IV of f-VEP was observed a month after onset, and these latencies gradually prolonged and the amplitudes decreased (Fig. 3B). In the advanced stage, patient no. 3 showed absent waves in f-VEP. The peripheral components of SSEP were within normal limits, however, cortical components such as wave N20 had already disappeared one month after onset (Fig. 4B). The late components of ABR and cortical components of SEP/SSEP were absent at onset and were observed earlier than f-VEP abnormalities (Table 2).

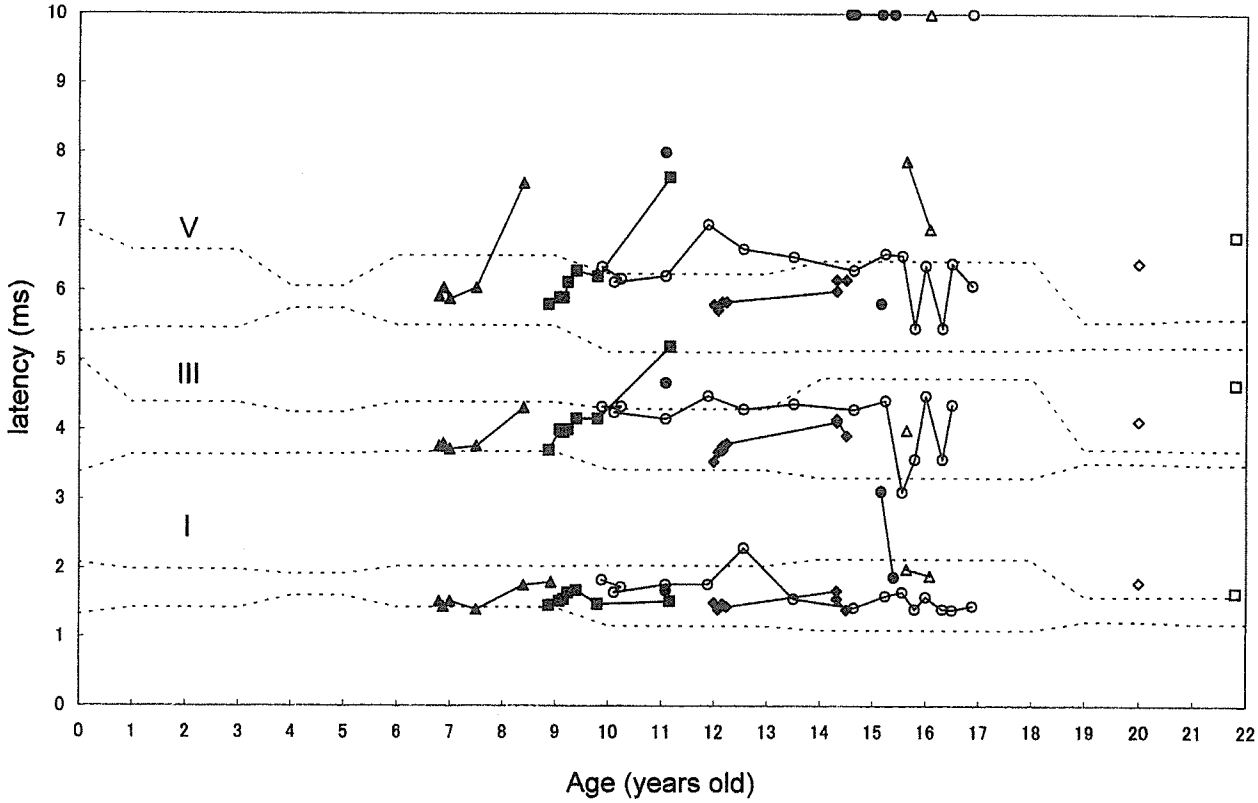

Fig. 2. Serial changes of ABR wave latencies in all ALD patients. Most patients had prolonged wave III and V latencies or an absent wave V in the advanced stage; however, in the early stage, all waves were almost within normal limits. Dotted lines indicate the range of ± 1 SD of the average value. ▲ – Pt.1, △ – Pt.2, ● – Pt.3, ○ – Pt.4, ■ – Pt.5, □ – Pt.6, ◆ – Pt.7, ◇ – Pt.8.

3.3. ALX

Patients no. 1 and no. 4 with ALX showed normal ABR even in the advanced stage. There was slight prolongation of I–V latency in patient no. 3 at 2 months from onset (I–V interpeak latency = 5.05 ms (i.e. + 2.9 SD)). In patient no. 2, later components of ABR were not observed following hypoxic episodes. Almost normal f-VEP findings were observed during the observation periods in 3 out of 4 patients. The peripheral components of SSEP were within normal limits, however, the cortical N20 latency was already prolonged at 2 months from onset (N20 = 20.95 ms; i.e. + 8.8 SD) (see Fig. 4C and Table 2).

3.4. MLD

All patients had abnormal ABR findings. In 2 patients with the late infantile type, prolonged I–V interpeak latency and the absence of wave III were already observed at 3 months from onset, and wave V disappeared at 1–2 years from onset (Fig. 1C). In the advanced stage, all ABR waves were absent (Table 2). One patient with the late infantile type or juvenile type (no. 3), whose onset was delayed until 4 years of age, showed abnormal ABR with increased I–V latencies and decreased V/I amplitude ratio at 3 years from onset. On the other hand, a patient with the definite juvenile type had all ABR waves bilaterally at 17 years old. Three patients (no. 1, no. 2, no. 3) had abnormal f-VEP with prolonged latency of wave IV at 1.5 years from onset, the amplitude of which decreased gradually thereafter (Fig. 3C). Two patients (no. 2 and no. 4) examined had delayed N9 and N13 latencies (ms) of SSEP (N9 = 15.6 ± 3.3, N13 = 22.53 ± 1.9) with prolonged N20 latencies (N20 = 29.33 ± 5.3). However, even in the advanced stage, these waves were present (Fig. 4D). Peripheral and central somatosensory components were also abnormally delayed in both the late infantile and juvenile types of MLD.

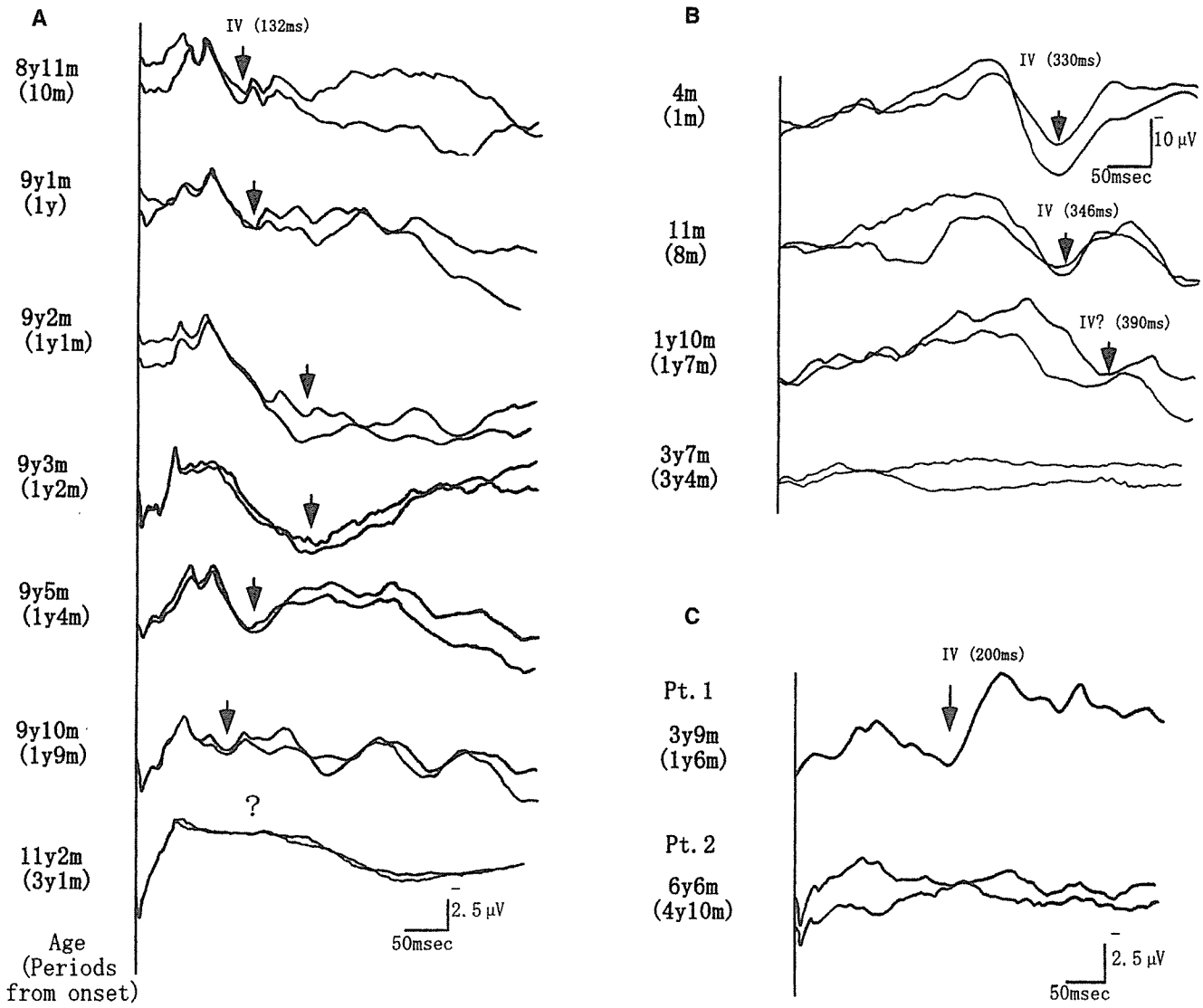

Fig. 3. Serial f-VEP findings in leukodystrophy. The wave IV (P100) latency of f-VEP was already prolonged at 10 months from onset in one ALD patient (no. 5), and wave IV could not be recorded at three years from onset (A). Prolonged f-VEP was recorded 1 month after onset, and wave IV decreased and finally disappeared at 3 years from onset in a PMD patient (B). In MLD patients, a prolonged wave IV was observed in the early stage. These findings became worse and there was no response at 4 and 10–12 years from onset in patient no. 2 (C).

3.5. GLD

In patient no. 1, prolonged I–V latency of ABR was observed at 2 months from onset, and the wave V amplitude was decreased at 8 months from onset (Fig. 1D). In all patients with GLD, the later components of ABR, such as waves III and V, disappeared after 1–3 years from onset. However, wave I of ABR was preserved in all patients for a relatively long time (4–13 years of age). These waveforms were disorganized and broad with severely prolonged peak latencies (2–2.8 ms). After 1 year and 7 months from onset, a prolonged IV wave of f-VEP was observed, which disappeared after 5 years (Table 2). Peripheral components (N9 and N13) of SSEP could not be elicited at 1.3 years in patient no. 3, at 4.8 years in patient no. 2, or 12.5 years from onset in patient no. 1. There was a defective cortical N20 component in all patients. In GLD patients, almost all ABR, f-VEP, and SEP/SSEP findings were abnormal in the initial stage,

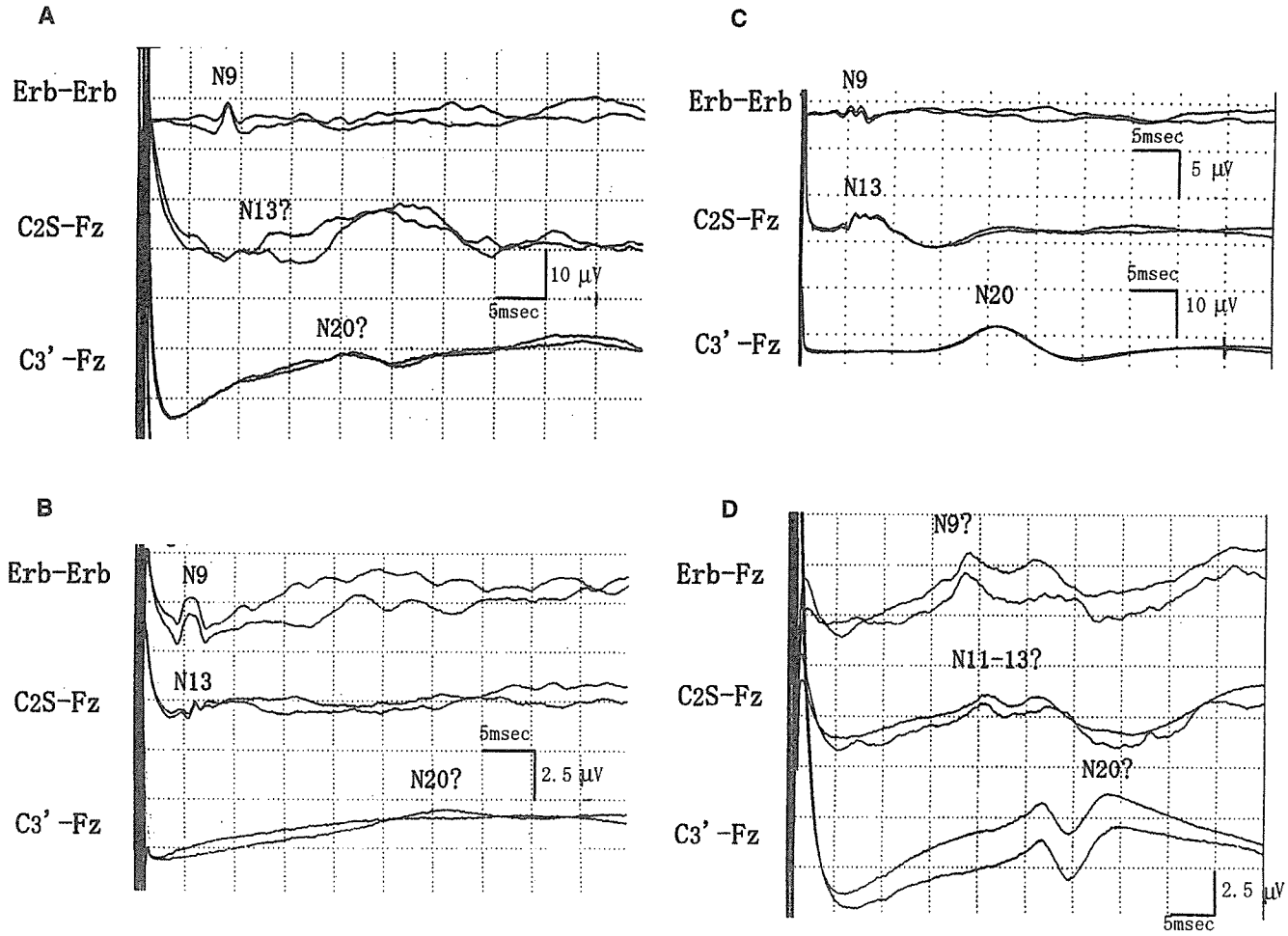

Fig. 4. Somatosensory evoked potentials (SEPs) in leukodystrophy. One patient (ALD no. 4) had normal peripheral nerve findings (N9 and N13), but the cortical wave (N20) was absent at 5 years and 8 months from onset (A). In PMD (no. 3), peripheral components (N9 and N13) were also positive; however, the cortical component (N20) was almost completely absent at one month after onset (B). On the other hand, the cortical component (N20) was evident but prolonged in ALX patient no. 3 at 2 months from onset (C). Both peripheral and cortical components (negativity of 33 ms peak latency) of SSEP were prolonged at 10 years and 10 months from onset in MLD patient no. 4 (D).

these changes being observed earlier than in MLD patients.

4. Discussion

In this study, multimodal EPs were serially evaluated in each patient in five different leukodystrophy groups. Most ALD patients initially exhibited visual and somatosensory evoked potential abnormalities, followed by prolonged I–V interpeak latencies of ABR. It has been suggested that degeneration of the brainstem in ALD occurs in the rostral to caudal direction based on the results of a comparative study on brainstem EPs and histology (Kaga et al., 1980). Other investigators also claimed that ABR in ALD is normal or subnormal in the early stage and I–V interpeak latencies increased in the advanced disease (Ochs et al., 1979; Markand et al., 1982; Tobimatsu et al., 1985). Our finding of ABR deterioration in each ALD case, i.e. delayed and decreased waves III and V in the advanced stage, coincides with serial observations in a typical patient as well as other studies (Kaga et al., 1980; De Meirleir et al., 1988),

TABLE 2

SUMMARY OF EVOKED POTENTIAL FINDINGS IN THE PRESENT LEUKODYSTROPHIES

Type of leukodystrophy	Stage	ABR	f-VEP	Peripheral SEP	Central SEP
ALD	Early	I, III, V: normal I–V, I–III latencies: normal	Prolonged IV latency, often fluctuated	N9, N13: normal	Prolonged N20 latency and low amplitude
	↓	Prolonged I–V latencies, low V/I amplitude			
	Advanced	Absent III, V	Absent IV	N9, N13: normal	Absent N20
PMD	Early	Typical I, II wave, absent III,V	Prolonged IV latency and normal amplitude	N9, N13: normal	Absent N20
	↓		Gradually prolonged IV latency with decreased amplitude		
	Advanced	Prolonged I latency, absent III, V	All waves absent	N9, N13: normal	Absent N20
ALX	Early ↓	I–V latencies: normal or slightly prolonged	Almost normal	N9, N13: normal	Prolonged N20 latency
	Advanced	I–V, I–III latencies: normal or slightly prolonged	Almost normal		
MLD	Early	Absent III, prolonged I–V latencies, low V/I amplitude	Prolonged IV latency and normal amptitude	Prolonged N9, N13 latencies	Prolonged N20 latency
	↓	Absent III, V	Prolonged IV latency and low amplitude		
	Advanced	Absent all waves	All waves absent	Prolonged N9, N13 latencies	Prolonged N20 latency
GLD	Early	Prolonged I–V latencies	Prolonged IV latency	Prolonged N9, N13 latencies	Prolonged N20 latency
	↓	Absent III, V		Absent N9, N13	
	Advanced	Absent III, V	All waves absent	Absent N9, N13	Absent N20

although conduction of the auditory nerve seemed to be preserved even in the final stage in our patients.

All 5 PMD patients exhibited a loss of later ABR waves, consistent with the previous studies (Ochs et al., 1979; Markand et al., 1982; Nezu, 1995). In addition, there were slight waveform and latency changes of ABR wave I in patient no. 3 for 3 years from onset. The outer hair cell function in the cochlea of PMD patients was found to be normal in an otoacoustic emission study (Kon et al., 2000). The preservation of peripheral nerve myelin was confirmed histologically in another patient (no. 4) of 8 months of age (Komaki et al., 1999). The fluctuation of ABR wave I in the infantile period might therefore reflect the coexistence of myelinating and demyelinating processes at the type 1 cochlear nerve level in this disorder. With flash VEP, a severely prolonged wave IV or P100 was recorded in the early stage and gradually disappeared thereafter in one patient, confirming previous reports suggesting VEP deterioration in PMD (Markand et al., 1982; De Meirleir et al., 1988; Hayashi et al., 1990). Moreover, the absence of cortical SEP and delayed VEP in the same patient suggests that central conduction in connatal type PMD varies with each modality despite diffuse dysmyelination, whereas EPs in PMD have been reported as relatively stable over the pediatric age range (Taylor, 1993).

Although there have been few reports on EPs findings in ALX, 3 patients aged 6, 12, and 13 years, respectively, had normal f-VEP with absent cortical responses of SSEP (De Meirleir et al., 1988; Ichiyama et al., 1993). In an infantile case of Arend et al. (1991), VEP was of normal latency but reduced amplitude. The present 3 patients also showed almost normal VEP findings. ALX patients could therefore have normal ABR and VEP findings even in the advanced stage. On the other hand, the N20 component of SSEP was observed in the youngest patient (no. 3), although the latency was delayed. Therefore, neuron myelination from the thalamus to the sensory cortex might be preserved in the early stage and damaged thereafter in this type of leukodystrophy.

Several investigators have described marked abnormalities of EPs in MLD and GLD patients (Brown et al., 1981; Markand et al., 1982; Darras et al., 1986; De Meirleir et al., 1988; Yamanouchi et al., 1993). However, there have been few reports on repeat recordings of multimodal EPs in the same patients. Takakura et al. (1985) described the deterioration of EPs over 2 months in a 2 years 3 months-old girl with the late infantile form of MLD, which consisted of decreased f-VEP, a severely prolonged I–V interval of ABR, and delayed peak latencies of SSEP. Zafeiriou et al. (1999) also noticed that ABR wave V disappeared more than 1.5 years after onset and VEP could not be recorded at 2 years from onset in one patient with the same type of MLD. In our patients with the late infantile form of MLD, the auditory and then visual evoked response seemed to disappear 2–4 years from the onset. Autopsy studies on the late infantile form of MLD (Takashima et al., 1981) revealed that myelin sheath loss was apparent in the entire central nervous system including the brainstem and cranial nerves. D'Hooge et al. (1999) described a parallel relationship between the decline of the ABR waveform and the decrease of spiral ganglion cells in ASA-deficient mice. ABR change in the late infantile form of MLD, in which all waves finally vanish, might therefore be produced through both cochlear and brainstem pathology. On the other hand, ABR wave I in our GLD patients was present even in the advanced stage. Other investigators also noted that ABR wave I could be recorded during the infantile period in Krabbe disease (Darras et al., 1986; De Meirleir et al., 1988; Zafeiriou et al., 1997). Kurokawa et al. (1987) reported ABR changes in a girl with the late infantile form of Krabbe disease from the normal configuration to prolonged interpeak latencies in one month. It is suggested that the rapid deterioration of EPs, especially of ABR, in GLD is caused by disease progression in a rostro-caudal direction in the central nervous system; however, the VIII cranial nerve and cochlear function would be preserved. In conclusion, the order of combined EP changes in pediatric leukodystrophy might differ with the disease type and reflect underlying pathological alterations. These electrophysiological findings might be useful in determining the effectiveness of the intervention such as BMT or gene therapy for individual patients at each disease stage.

5. Acknowledgements

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References

Arend, A.O., Leary, P.M. and Rutherfoord, G.S. (1991) Alexander's disease: a case report with brain biopsy, ultrasound, CT scan and MRI findings. *Clin. Neuropathol.*, 10: 122–126.

Brown 3rd, F.R., Shimizu, H., McDonald, J.M., Moser, A.B., Marquis, P., Chen, W.W. and Moser, H.W. (1981) Auditory evoked brainstem response and high-performance liquid chromatography sulfatide assay as early indices of metachromatic leukodystrophy. *Neurology*, 31: 980–985.

Darras, B.T., Kwan, E.S., Gilmore, H.E., Ehrenberg, B.L. and Rabe, E.F. (1986) Globoid cell leukodystrophy: cranial computed tomography and evoked potentials. *J. Child Neurol.*, 1: 126–130.

D'Hooge, R., Coenen, R., Gieselmann, V., Lüllmann-Rauch, R. and De Deyn, P.P. (1999) Decline in brainstem auditory-evoked potentials coincides with loss of spiral ganglion cells in arylsulfatase A-deficient mice. *Brain Res.*, 847: 352–356.

De Meirleir, L.J., Taylor, M.J. and Logan, W.J. (1988) Multimodal evoked potential studies in leukodystrophies of children. *Can. J. Neurol. Sci.*, 15: 26–31.

Hayashi, T., Ichiyama, T., Koga, M., Okino, F., Katayama, K. and Kobayashi, K. (1990) A possible Japanese male case of Pelizaeus-Merzbacher disease. *Brain Dev.*, 12: 439–443.

Ichiyama, T., Hayashi, T. and Ukita, T. (1993) Two possible cases of Alexander disease. Multimodal evoked potentials and MRI. *Brain Dev.*, 15: 153–156.

Kaga, K., Tokoro, Y., Tanaka, Y. and Ushijima, H. (1980) The progress of adrenoleukodystrophy as revealed by auditory brainstem evoked responses and brainstem histology. *Arch. Otorhinolaryngol.*, 228: 17–27.

Kaga, M., Azuma, C., Imamura, T., Murakami, T. and Kaga, K. (1982) Auditory brainstem response (ABR) in infantile Gaucher's disease. *Neuropediatrics*, 13: 207–210.

Kemp, S., Pujol, A., Waterham, H.R., Van Geel, B.M., Boehm, C.D., Raymond, G.V., Cutting, G.R., Wanders, R.J. and Moser, H.W. (2001) ABCD1 mutations and the X-linked adrenoleukodystrophy mutation database: role in diagnosis and clinical correlations. *Hum. Mutat.*, 18: 499–515.

Komaki, H., Sasaki, M., Yamamoto, T., Iai, M. and Takashima, S. (1999) Connatal Pelizaeus-Merzbacher disease associated with the jimpy^{msd} mice mutation. *Pediatr. Neurol.*, 20: 309–311.

Kon, K., Inagaki, M., Kaga, M., Sasaki, M. and Hanaoka, S. (2000) Otoacoustic emission in patients with neurological disorders who have auditory brainstem response abnormality. *Brain Dev.*, 22: 327–335.

Krivit, W., Aubourg, P., Shapiro, E. and Peters, C. (1999) Bone marrow transplantation for globoid cell leukodystrophy, adrenoleukodystrophy, metachromatic leukodystrophy, and Hurler syndrome. *Curr. Opin. Hematol.*, 6: 377–382.

Kurokawa, T., Chen, Y.J., Nagata, M., Hasuo, K., Kobayashi, T. and Kitaguchi, T. (1987) Late infantile Krabbe leukodystrophy: MRI and evoked potentials in a Japanese girl. *Neuropediatrics*, 18: 182–183.

Maria, B.L., Deidrick, K.M., Moser, H. and Naidu, S. (2003) Leukodystrophies: pathogenesis, diagnosis, strategies, therapies, and future research directions. *J. Child Neurol.*, 18: 578–590.

Markand, O.N., Garg, B.P., DeMyer, W.E., Warren, C. and Worth, R.M. (1982) Brain stem auditory, visual and somatosensory evoked potentials in leukodystrophies. *Electroencephalogr. Clin. Neurophysiol.*, 54: 39–48.

Moser, H., Dubey, P. and Fatemi, A. (2004) Progress in X-linked adrenoleukodystrophy. *Curr. Opin. Neurol.*, 17: 263–269.

Nezu, A. (1995) Neurophysiological study in Pelizaeus-Merzbacher disease. *Brain Dev.*, 17: 175–181.

Ochs, R., Markand, O.N. and DeMyer, W.E. (1979) Brainstem auditory evoked responses in leukodystrophies. *Neurology*, 29: 1089–1093.

Ozawa, H., Inagaki, M., Aikoh, H., Hanaoka, S., Sugai, K., Hashimoto, T., and Kaga, M. (1998) Somatosensory evoked potentials with a unilateral migration disorder of the cerebrum. *J. Child Neurol.*, 13: 211–215.

Peters, C. and Steward, C.G. (2003) National Marrow Donor Program; International bone marrow transplant registry; Working party on inborn errors, European bone marrow transplant group Hematopoietic cell transplantation for inherited metabolic diseases: an overview of outcomes and practice guidelines. *Bone Marrow Transplant.*, 31: 229–239.

Takakura, H., Nakano, C., Kasagi, S., Takashima, S. and Takeshita, K. (1985) Multimodality evoked potentials in progression of metachromatic leukodystrophy. *Brain Dev.*, 7: 424–430.

Takano, H., Koike, R., Onodera, O., Sasaki, R. and Tsuji, S. (1999) Mutational analysis and genotype-phenotype correlation of 29 unrelated Japanese patients with X-linked adrenoleukodystrophy. *Arch. Neurol.*, 56: 295–300.

Takashima, S., Matsui, A., Fujii, Y. and Nakamura, H. (1981) Clinicopathological differences between juvenile and late infantile metachromatic leukodystrophy. *Brain Dev.*, 3: 365–374.

Taylor, M.F. (1993) Evoked potentials in paediatrics. In: A.M. Halliday (Ed.), *Evoked Potentials in Clinical Testing*, 2nd ed. Churchill Livingstone, Edinburgh, pp. 489–521.

Tobimatsu, S., Fukui, R., Kato, M., Kobayashi, T. and Kuroiwa, Y. (1985) Multimodality evoked potentials in patients and carriers with adrenoleukodystrophy and adrenomyeloneuropathy. *Electroencephalogr. Clin. Neurophysiol.*, 62: 18–24.

Yamamoto, T., Nanba, E., Zhang, H., Sasaki, M., Komaki, H. and Takeshita, K. (1998) Jimpy^{msd} mouse mutation and connatal Pelizaeus-Merzbacher disease. *Am. J. Med. Genet.*, 75: 439–440.

Yamanouchi, H., Kaga, M., Iwasaki, Y., Sakuragawa, N. and Arima, M. (1993) Auditory evoked responses in Krabbe disease. *Pediatr. Neurol.*, 9: 387–390.

Zafeiriou, D.I., Anastasiou, A.L., Michelakaki, E.M., Augoustidou-Savvopoulou, P.A., Katzos, G.S. and Kontopoulos, E.E. (1997) Early infantile Krabbe disease: deceptively normal magnetic resonance imaging and serial neurophysiological studies. *Brain Dev.*, 19: 488–491.

Zafeiriou, D.I., Kontopoulos, E.E., Michelakakis, H.M., Anastasiou, A.L. and Gombakis, N.P. (1999) Neurophysiology and MRI in late-infantile metachromatic leukodystrophy. *Pediatr. Neurol.*, 21: 843–846.

今月のテーマ 認知の発達

発達障害のモダリティ別事象関連電位：自閉症スペクトラムにおける特徴

Modality specific findings of event related potentials in patients with autism spectrum disorder

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1）自閉症スペクトラムにおける視聴覚性事象関連電位 P300を健常児と比較検討した．
2）聴覚性事象関連電位では，トーンバーストに対する P300潜時の遅延がみられ，分布の異常もうかがえた．
3）一方，視覚性 P300潜時は健常児とほぼ同様であり，視覚優位性が示された．
4）両モダリティ刺激とも P300振幅が低めであり，自閉症スペクトラムでは脳内の情報処理機構が健常例とは質的に異なっていることが示唆された．

KEY WORDS 発達障害，自閉症，刺激モダリティ，事象関連電位，P300

はじめに

言語性意味理解障害児や自閉症では聴覚性言語理解力と視覚的な意味理解の能力に乖離がみられ，刺激ルートによって認知機能にアンバランスを示す症例が経験される[1)2)]．これは，感覚入力レベルの異常というよりも中枢神経系における情報処理機構の異常に基づくとされ，それらの病態解明のためにはモダリティ別認知機能の詳細な評価が必要と思われる．

われわれはこれまでに，小児における視・聴覚認知機能を評価するため，視覚刺激や聴覚刺激を用いた事象関連電位（ミスマッチネガティビティ，P300）を記録し，健常児の発達的変化と発達障害児の特徴を明らかにしてきた[3)]．たとえば，視・聴覚 P300ピーク潜時は年齢とともに短縮し特定の年齢で最短値をとることや，精神遅滞では漢字，図形といった視覚刺激に対する P300ピーク潜時の遅延がみられ，視覚情報処理機構の異常が示唆された[4)~6)]．

一方，注意欠陥 / 多動性障害（AD/HD）では，標的視覚刺激に対する弁別遂行能力には異常はなく，反応時間のばらつきや標的刺激性 P300の振幅変動が著しいことが観察されている[7)]．そこで今回われわれは，自閉症スペクトラム（Autism spectrum disorder, ASD）の弁別機能について視・聴覚性 P300検査を行って，モダリティ別の特徴的な変化がみられるか否か検討した．本稿ではその一部を報告する[8)9)]．

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方　　法

聴覚性P300の対象は平均年齢8歳半のASD児14名で，知的には軽度精神遅滞（FIQ 66±9，VIQ 67±15，PIQ 76±6，WISC-Ⅲ）を呈した．視覚性P300はASD児10名（平均年齢9.0±1.3歳，すべて男児）を対象とし，知能検査上FIQ70未満が4名みられた（10名のFIQ 73.8±20.0，VIQ 72.4±24.1，PIQ 80.7±15.3）．発達障害の診断はDSM-Ⅳに基づいた．なお，聴覚課題では神経学的異常を認めない健常小児13例（10.0±2.4歳）を対照に，視覚課題では健常小児10名（9.1±1.3歳，うち女児4名）を対照とした．全員右利きで，検査内容を説明したうえで，本人（小児では本人および親権者）から同意を得て以下の検査を施行した．

1．聴覚性オドボール課題

①トーンバースト音（TB）課題は標的刺激音周波数を1 kHz，非標的刺激音周波数を700Hzとし，②一音節言語音（VS）課題は標的刺激音を[æ]，非標的刺激音を[a]とした．TB音はヘッドホンより，VSはスピーカーからそれぞれ耳元での音圧が70dB SPLになるように呈示した．以前と同じ方法[10]で標的刺激を20%，非標的刺激を80%の確率でランダムに呈示し，標的刺激に対するキー押し反応を右拇指で行わせた．

国際10-20法に基づくFz，Cz，Pz，Ozの4ヵ所に皿電極を置き，両耳朶連結を基準電極とした脳波を記録した．そして刺激開始前100msceより後1,000msecまでを10回加算した．なお，左眼裂の左側および下側中央に電極を置いて眼球運動をモニターし，±100 μV以上のアーチファクトが認められた試行を脳波加算から除外した．バンドパスフィルターは0.05Hzから50Hzに設定した．刺激呈示100msec前から刺激呈示時までを基線区間とし，刺激呈示後250msecから600msecまでに出現する陽性頂点を視察的にP300として同定し，頂点潜時と振幅を刺激課題別に計測した．さらに，P300より早期の陰性頂点，すなわち成人群で刺激呈示後100msec前後に出現するN1と200msec前後にみられるN2に関しても同様に計測した．

2．視覚性オドボール課題

未知の漢字ペア（鵜/鵜）提示による視覚性オドボール課題を用いた．佐田らの報告[5][6]と同様に前者を標的刺激（提示確率20%）として，キー押し反応を求めた．漢字は被験者の1メートル前に置いた17インチCRT上に白の背景に黒字で表示した．刺激提示時間は1,000msecで，刺激間隔は3,000±500msecに設定した．脳波記録は聴覚オドボール課題と同じ正中線上4部位として，加算条件・アンプの条件も同様とした．なお，刺激提示から300msec以降700msecまでに出現する最大陽性頂点を視覚性P300と同定した．

統計学的な解析は両モダリティ刺激とも，平均反応時間，P300波形の平均頂点潜時，P300平均振幅値の差の有無を検討し，$p < 0.05$を有意とした．なお，聴覚オドボール課題ではN1，N2頂点潜時についても比較検討した．

結　　果

1．聴覚性オドボール課題

1）N1およびN2頂点潜時

健常群のFz部N1平均頂点潜時（±標準偏差）はTB, VS刺激それぞれ114（±20）msec，113（±14）msecであり，刺激音の間に有意差は認められなかった．N2頂点潜時はTB, VSそれぞれ225（±15）msec，250（±22）msecであり，健常群では言語音刺激でのN2潜時が有意に延長していた．一方，ASD群のN1平均頂点潜時は両刺激音とも健常例と有意差はみられず，N2頂点潜時には言語音での延長パターンがみられなかった（図1）．

2）P300潜時および振幅

健常小児群Pz部P300頂点潜時（msec）は，言語音呈示において有意に延長していた（TB：356±82，VS：454±74，$p < 0.0001$）が，振幅（μV）に刺激間の差はなかった（TB：32.2±13.8，VS：

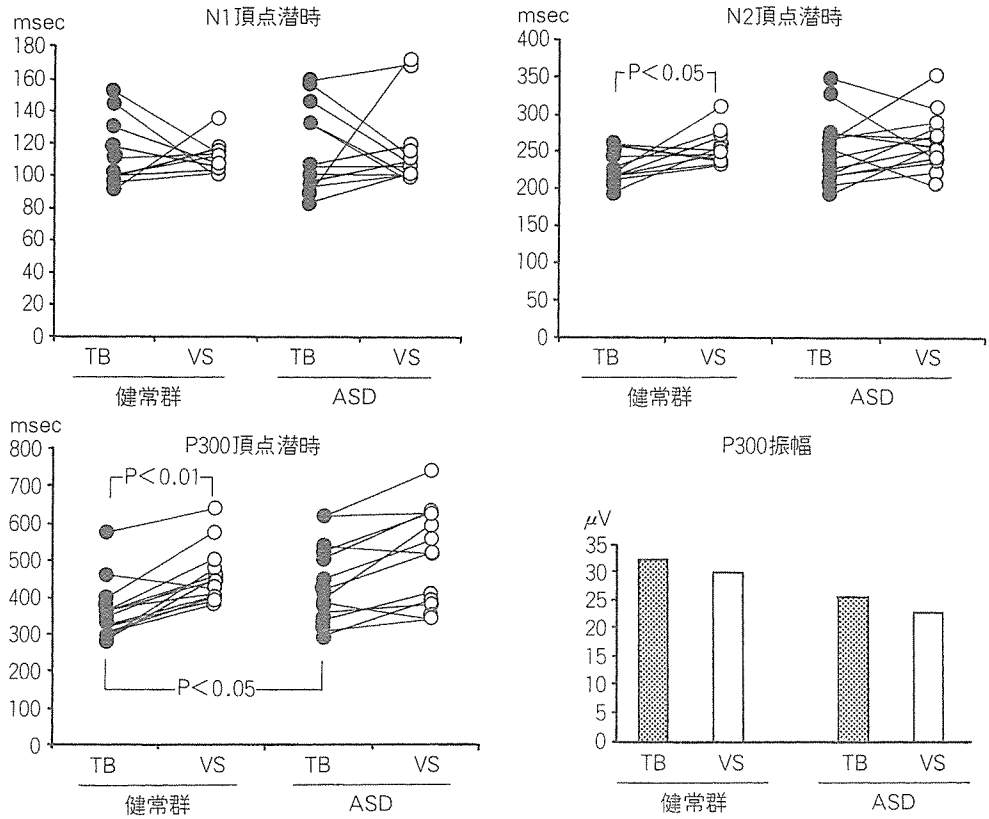

図1　各成分の頂点潜時および振幅

自閉症スペクトラム（ASD）は健常児と比べてN1成分，N2成分の頂点潜時の有意な遅延はみられなかった．一方，P300潜時は健常例と比べてトーンバースト音（TB）刺激で有意に遅延していた．健常例では言語音（VS）刺激のP300潜時が遅延したが，ASDでは刺激音間の潜時差がみられなかった．

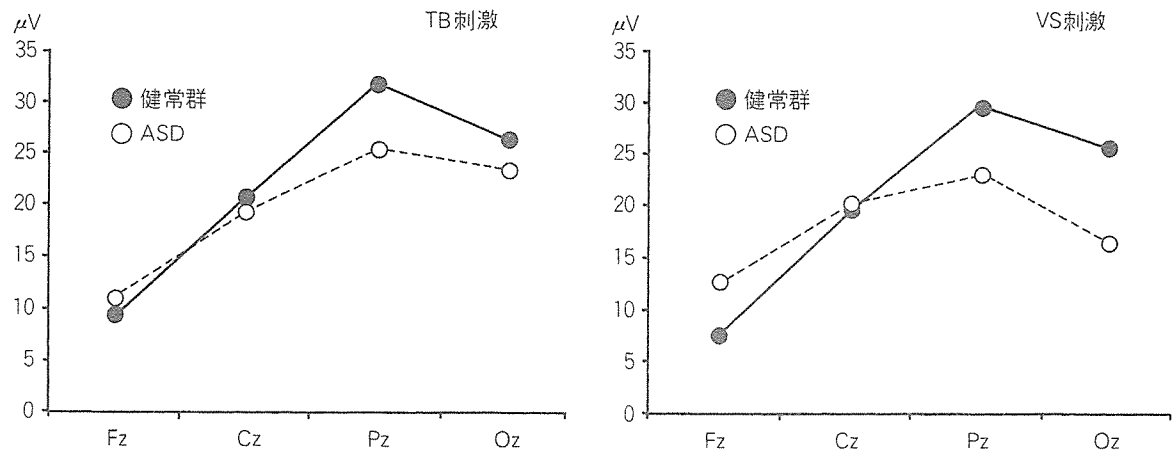

図2　聴覚性P300分布

健常例ではP300の分布はTB，VS刺激ともPz優位な陽性変化が明らかであったが，ASDでは言語音刺激でも非言語音刺激でも，頭頂部の陽性度が最も高いもののその分布は不明瞭なパターンを示した．

30.0±12.8)．ASD群は，TB刺激に対するP300頂点潜時（平均444msec）が健常児に比べて有意に延長していたが，言語音刺激に対するP300（平均519msec）は健常群と差はみられなかった．P300は健常群，ASD群ともにPz部でもっとも優位であり，前者は4部位中Pzで有意（$p<0.01$）な振幅増加がみられた（図2）．ASD群も記録4部位の中ではPzでもっとも陽性度が高かったが，健常児と比べて低振幅であり，部位間の電位の差は健常群ほど明らかではなかった．Pz部振幅につ

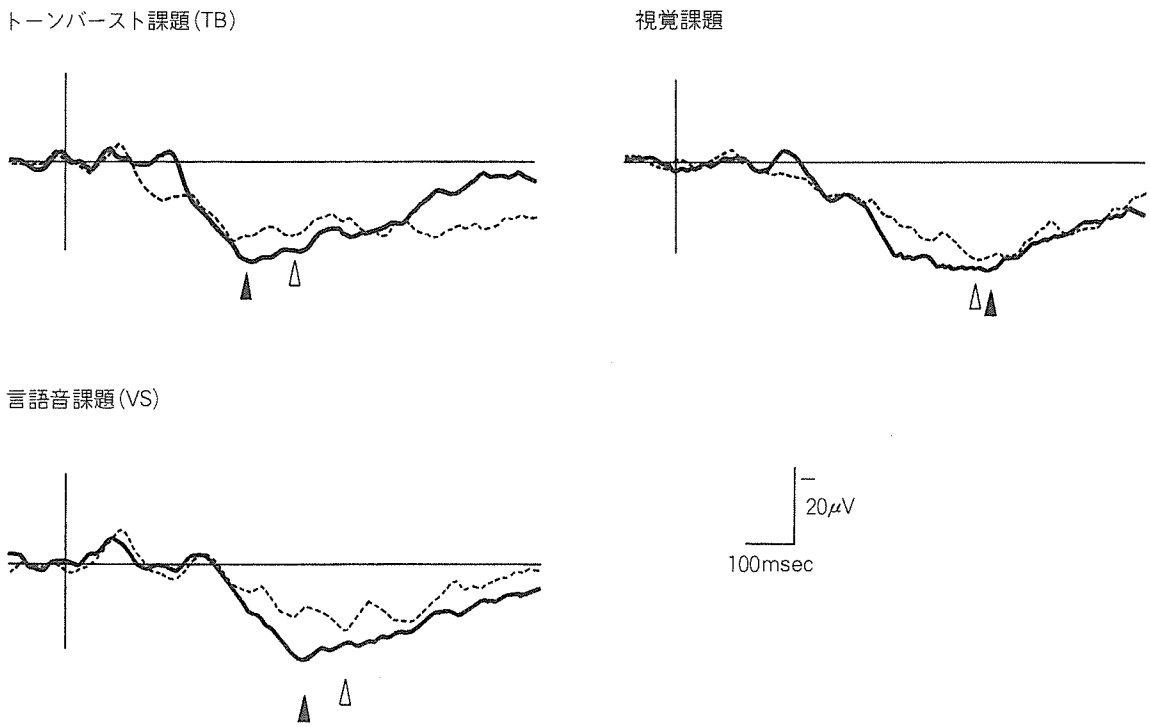

図3　視聴覚性P300総加算波形（Pz部）
実線が健常児群，波線がASD群を示す．黒三角，白三角が各々健常群，ASD群のP300ピークを示す．

いては，健常児とASD児に有意な差は得られなかった．健常小児の総加算波形では，TB，言語音ともに非標的刺激音に対しては，N1とN2のみが記録され，標的刺激に対してはN1，N2，に加えて，P300成分が明瞭に得られた（図3）．このP300の分布は頭頂部優位であり，これまで報告されている聴覚性P300と類似していた．

3）反応時間

健常群よりASD群で延長しており，言語音課題で有意に遅延していた（$p < 0.01$）．

2．視覚性オドボール課題

1）P300潜時および振幅

健常児群では標的刺激性P300がPz部優位に得られ（図3），全例その波形は明瞭であった．そのピークは刺激提示後550～600msec付近にみられた．ASD群もPz部が優位であったが，4電極間に振幅の有意差はなかった．図4にみられるように，P300頂点潜時および振幅には健常群とASD群に差はみられなかった（健常児：ASD児，Pz部潜時は586.6±84.2msec：557.3±124.6msec，振幅は35.4±11.0 μV：27.6±13.4 μV）．

2）平均反応時間

健常児群に比べてASD群で長い傾向があったが，有意差はなかった（表1）．

考　　察

今回対象とした自閉症スペクトラム（ASD）児童は，視聴覚オドボール課題は可能で，標的刺激と標準刺激を十分弁別できたが，モダリティ間で異なった結果を示した．すなわち，聴覚刺激のうちトーンバースト音（TB）に対する事象関連電位はN2潜時から健常児と比べて遅延傾向がみられ，TB刺激性P300潜時は有意に遅延がみられた．しかし，健常例では言語音性P300がTB性P300よりも遅延するという刺激音間の相違がASD群では得られず，300Hzの周波数の違いといった比較的単純な聴覚刺激と，複数の周波数の差をもつ言語音の弁別に要する時間がほぼ同じであるという奇異な結果が得られた．一方，視覚性P300は潜時，振幅ともに健常児と比べて異常はなかった．