Paroxysmal discharges on EEG in young autistic patients are frequent in frontal regions

Toshiaki Hashimoto*, Masayuki Sasaki**, Kenji Sugai**, Shigeru Hanaoka**, Michio Fukumizu**, and Takeji Kato†.

*Department of Education for Handicapped Children, Naruto University of Education, Tokushima, Japan ; **Department of Child Neurology and †Department of Center Laboratory, National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry (NCNP), Kodaira, Tokyo, Japan.

Abstract: EEGs were recorded in 86 autistic patients during sleep. Epileptic discharges were observed in 37 cases (43%). Twenty-seven (73%) of these 37 cases had localized spikes, 8 had multiple spike foci, one had generalized spikes, and one had both multiple spike foci and generalized spikes. Fourty-seven epileptic discharge foci were registered in 36 cases, the exception being one with generalized spikes. Thirty-six (76.6%) of the registered 47 epileptic discharge foci were in the frontal region, one (2.1%) in the temporal region, 7 (14.1%) in the centro-parietal region, and 3 (6.4%) in the occipital region. Twenty (55.6%) of the 36 frontal spikes were at midline (11 at Fz and 9 at Cz), 8 on the left side, and 8 on the right side. The dipole of midline spikes was in the deep midline frontal region. These results suggest that frontal dysfunctions are important in the mechanism of symptoms in autism.
J. Med. Invest. 48 : 175-180, 2001

Keywords : *EEG, autism, epileptic discharge, dipole, mapping*

INTRODUCTION

Autism is a behavioral syndrome including problems in relatedness, communication disorders, and repetitive and stereotyped patterns of behavior. Evidence of neurobiological abnormalities has been obtained in some cases of autism (1), but in many instances the etiology has been unknown since Kanner' study (2). Underlying functional and organic brain abnormalities due to prenatal insults have been revealed by means of brain imaging studies, electroencephalography (EEG), neuropsychological studies and so on (3-10). As symptoms of brain damage, about half or one-third of autistic patients may have electroencephalographic abnormalities and epileptic seizures, respectively. In EEG studies on patients with autism, epileptic discharges, slowing and/or prematurity have been observed in many studies (11-13). However, foci of EEG paroxysms in autism have been reported in various regions and the results of previous studies have been contradictory.

The aim of the present study was to determine whether there are peculiar localizations and abnormalities of epileptic discharges on EEG in autistic patients.

SUBJECTS AND METHODS

The subjects were 86 autistic patients, ranging from 2 years and 3 months to 19 years and 5 months of age (mean +/- SD= 6 years and 3 months +/- 3 years and 6 months), who were referred to the Department of Child Neurology, National Center Hospital for Mental, Nervous and Muscular Disorders, National Center of Neurology and Psychiatry (NCNP) between

Received for publication May 29, 2001 ; accepted July 27, 2001.

Address correspondence and reprint requests to Toshiaki Hashimoto, Department of Education for Handicapped Children, Naruto University of Education, 748 Nakashima, Takashima, Naruto-cho, Naruto-city, Tokushima 772-8502, Japan and Fax : +81-88-687-6019.

January, 1995 to June, 1998, and had sleep EEGs recorded. The gender ratio, male to female, was 69 : 17. Their development quotients, DQ (or intelligence quotient, IQ), ranged from 13 to 114 (mean +/- SD= 50.6 +/- 21.7). DQ or IQ was measured by means of the Enjyoji developmental test, or Binet or WISC Å [R, respectively. EEGs were recorded during sleep, induced by medication such as triclofos syrup, hydrochrolide or pentobarbital, using a digital EEG machine (Ceegraph C-32, Biologic System Co.), the electrodes were placed according to the 10/20 international system. EEGs were stored on photo-discs, and analyzed using the Brain Atlas IIIs and Dipole Source Localization (Biologic System Co.). The electrode sites were divided into 4 regions : frontal region including Fp1, Fp2, F3, F4, F7, F8 and Cz, temporal region including T3, T4, T5 and T6, centro-parietal region including C3, C4, P3, P4 and Pz, and occipital region including O1 and O2. The EEG assessment was performed blindly by two physicians (psychiatrist in the EEG laboratory and T. Hashimoto). When the two physicians agreed, the EEG findings were judged to be abnormal.

The diagnosis of autism was made using the DSM-IV criteria. Five patients showed regressive autism spectrum disorders. Eighteen patients had a history of seizures. The backgrounds of the subjects were compared as groups with and without spikes.

The Student t test and chi square test were used for statistical analysis.

RESULTS

There were no differences in the mean age, sex ratio and percentage of regression between the groups with and without spikes. However, the DQ (IQ) and percentage of cases with seizures were lower and higher, respectively, in cases with spikes than in those without spikes (Table 1).

Spike discharges were observed in 37 cases (43%), and abnormal sleep spindles, such as the scarce appearance and/or alternate appearance of sleep spindles, were observed in 11 (12.8%) of the 86 autistic patients. Twenty-seven (73%) of these 37 cases had localized spikes, 8 had multiple spike foci, one had generalized spikes, and one had both multiple spike foci and generalized spikes (Fig. 2a, b). Thirty-six cases, the exception being one with generalized spikes, exhibited a total of 47 spike foci. Thirty-six (76.6%) of the 47 registered spike foci were in the frontal region, one (2.1%) in the temporal region, 7 (14.1%) in the centro-parietal region, and 3 (6.4%) in the occipital region. Twenty (55.6%) of the 36 frontal spikes were at midline (11 at Fz and 9 at Cz), 8 on the left side, and 8 on the right side. In the centro-parietal region, 2 were on the left side, 4 on the right side, and one at midline. In the occipital region, two were on the left side and one on the right side. In the temporal region, one was on the left side. The numbers of spikes did not differ between the left and right hemispheres (13 spikes on the left side and 13 spikes on the right side) (Figs. 1 and 3). The spikes at the frontal midline were analyzed for mapping and a single dipole source by means of the Brain Atlas

Table 1. The backgrounds of the subjects.

	Cases with spikes (n=37)	Cases without spikes (n=49)
age (months)	78.6 +/- 49.2	70.3 +/- 36.6
sex ratio (M : F)	30 : 7	39 : 10
DQ (IQ)	43.1 +/- 17.0	56.2 +/- 23.2**
seizures (+)	13/37 (35.1%)	5/49 (10.2%)*
regression	2/37 (5.4%)	3/49 (6.1%)

** : p<0.005 (Student t test), * : p<0.05 (chi-square test)

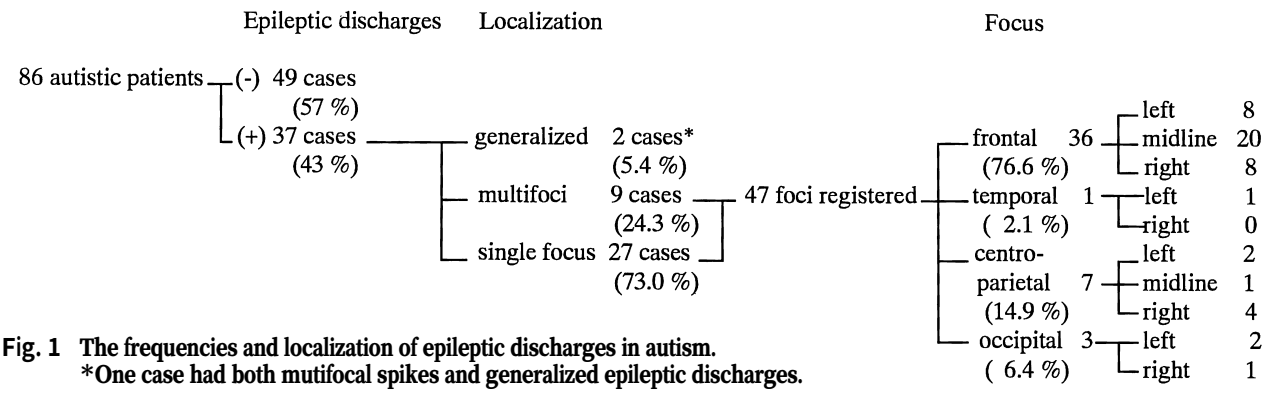

Fig. 1 The frequencies and localization of epileptic discharges in autism.
*One case had both mutifocal spikes and generalized epileptic discharges.

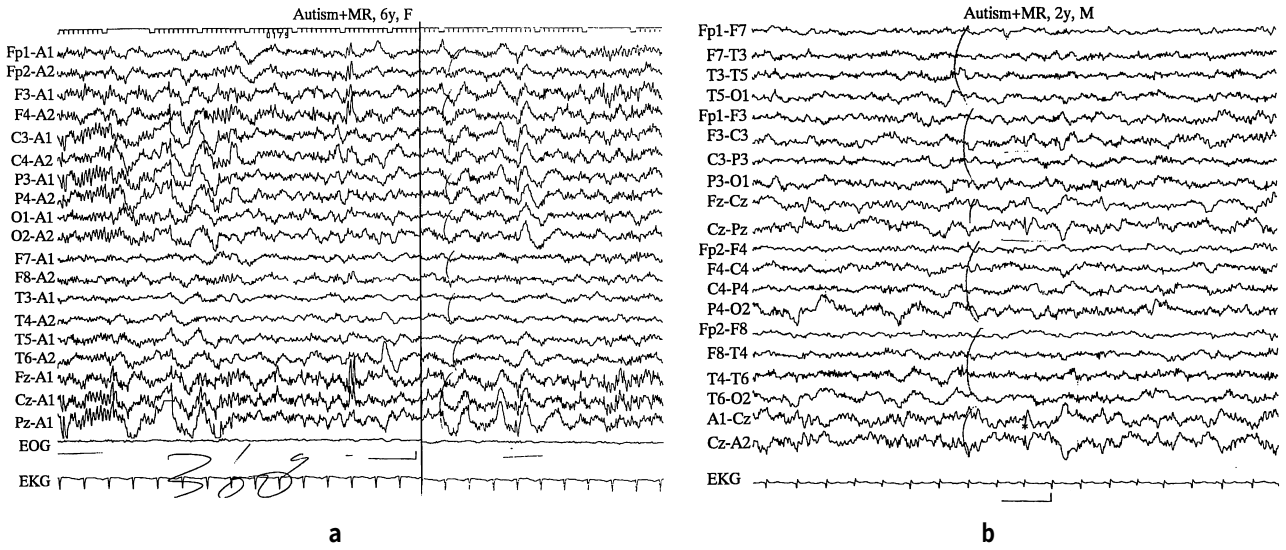

Fig. 2 Epileptic discharges observed in autism. a, 6-year-old girl. She has autism with mental retardation. Her EEG shows multifocal spikes at both Fz and Pz. b, 2-year-old boy. He has autism with mental retardation. His EEG shows focal spikes at Cz. Calibration, 3 cm/sec. and 50Ê V/5 mm.

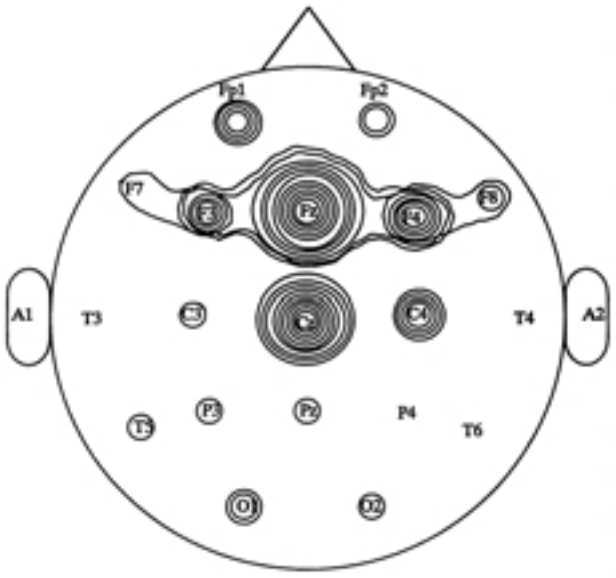

Fig. 3 Locations of the 47 registered epileptiform discharges. One ring shows one epileptic discharge focus. There are many foci at Cz and Fz in the midline region. There was no difference in the number of spike foci between the two hemispheres.

IIIs and Dipole Source Localization. Fig. 4a, b and c show a typical case with a frontal midline spike focus (Fz). Mapping of spikes at Fz was also performed. Spikes extended from Fz to F4 and Fp2. The dipole of these midline frontal spikes was in the deep frontal region at the midline and directed to the upper right anterior region.

DISCUSSION

In autism, EEG studies have revealed a high rate of epileptic EEG abnormalities. Small (14) documented a relationship between EEG and IQ, in that the incidence of mental retardation was higher in the group with EEG abnormalities. Kawasaki *et al*. (7) reported that there was a significant relationship between the presence of epilepsy and the occurrence of spikes. The backgrouds of the subjects in the present study were consistent with those of previously reported study subjects.

Although the focus of spike discharges has been reported to be the centro-temporal (8), temporal (15, 16), or frontal (7) region, there has been no consensus. Kawasaki *et al*. reported that spike discharges on EEG became focused to the frontal region with increasing age (7). The prevalence of this EEG abnormality became increasingly greater with the number of EEG recordings. In the present study abnormal spike discharges were observed in 43% of 86 cases with autism. This result was consistent with those previously reported (17.6 - 60.8%) (7, 17). In the present study, a normal control study was not performed. However, the incidence of epileptiform abnormalities observed on EEG in children without epilepsy has been reported to be 3.5-4.0% (18, 19). In comparison, 43% had spike discharges in the present study.

The focus of spike discharges was mostly in the frontal region, especially at midline (Fz and Cz). The dipole of midline spike discharges present in the deep frontal midline region may represent the cingulate gyrus. The frontal dominance of spikes is consistent with the findings of Kawasaki *et al*. (7). It is important to note that 22/37 cases (59.5%) and

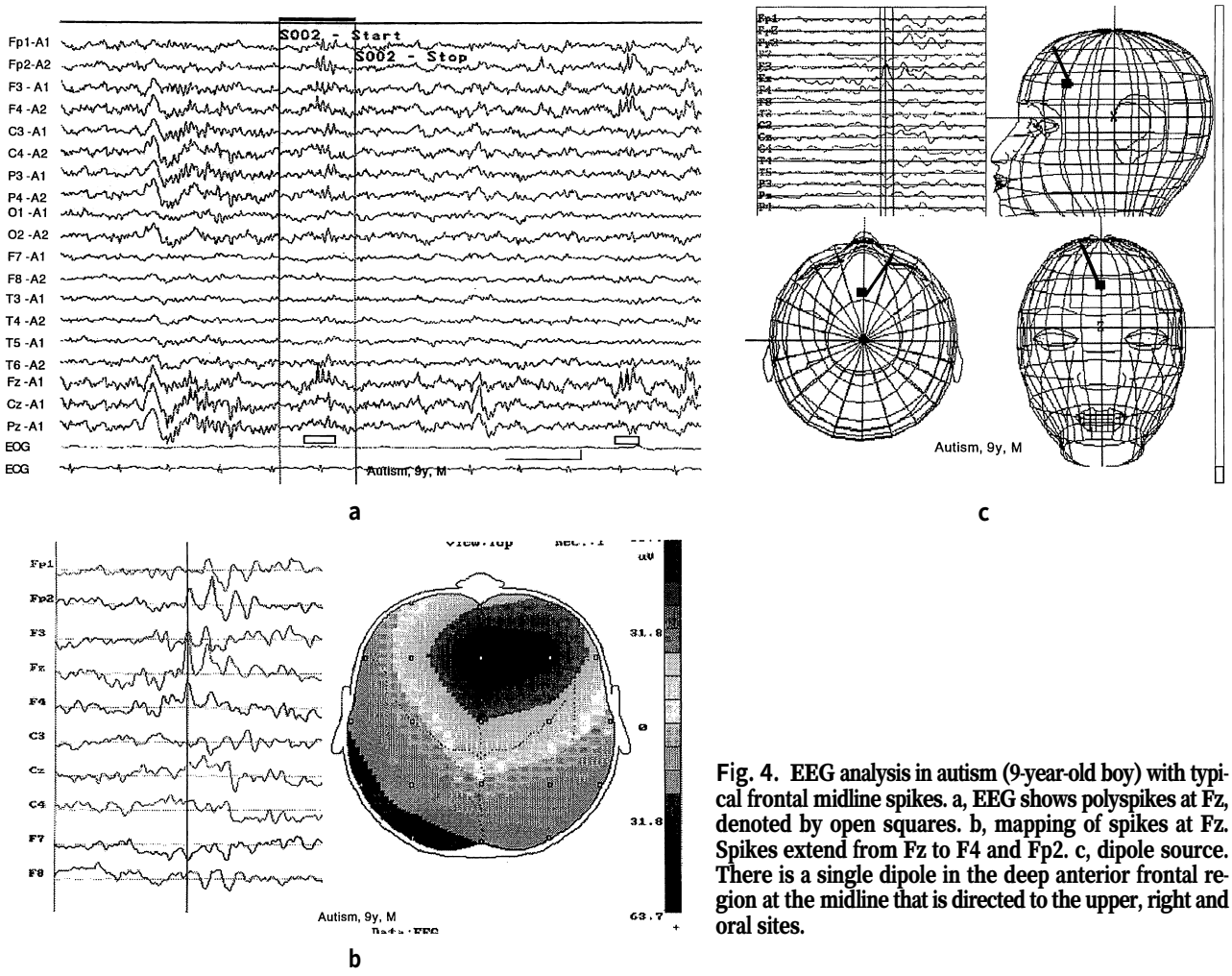

Fig. 4. EEG analysis in autism (9-year-old boy) with typical frontal midline spikes. a, EEG shows polyspikes at Fz, denoted by open squares. b, mapping of spikes at Fz. Spikes extend from Fz to F4 and Fp2. c, dipole source. There is a single dipole in the deep anterior frontal region at the midline that is directed to the upper, right and oral sites.

36/47 total registered spike foci (76.6%) showed a frontal spike focus. The frontal region is related to the theory of mind and executive function (9, 20). Baron-Cohen *et al.* hypothesed that in autistic patients the theory of mind is deficient (21). Happe *et al.* (9) found in a PET study that normal controls exhibited an increase in metabolism in the left medial frontal region (BA 8 and 9) during the theory of mind test, while Aspergar syndrome patients exhibited an increase in metabolism in the left frontal region (BA 10) in front of one of the controls. Haznedar *et al.* found, in studies involving MRI and PET, that autism exhibited decreased glucose metabolism activity and a volume loss in the cingulate gyrus (Broadman area 24') (22). In a PET study, Chugani *et al.* (6) found decreased serotonin synthesis in the left frontal cortex and thalamus in 5 of 7 boys, and in the right frontal cortex and thalamus in the remaining 2 autistic boys. In a neuropathological study of autistic brains, Bauman and Kemper observed an increased cell-packing density and reduced nerve cell size in the anterior cingulate gyrus, which comprises a major portion of the limbic system of the brain (3).

In an EEG study, Dawson *et al.* (23) found that compared with normally developing children, autistic children exhibited reduced EEG power in the frontal and temporal regions, but not in the parietal region, and that the differences were more prominent in the left than the right hemisphere. Harrison *et al.* (24) presented an adult autistic patient with results suggestive of left anterior deactivation and right frontal activation. His quantitative EEG findings revealed relative activation of the right frontal region corresponding to deactivation of homologous zones of the left frontal region.

In the present study, frontal epileptic paroxysms were highly frequent. Beun *et al.* (25) observed frontal sharp wave activity during drowsiness and/or light sleep in 41 of 60 healthy adult volunteers. We did not judge the sharp waves, which are shown in Figs. 1 and 2 of their publication, to be abnormal waves. Their subjects were adult in comparison to the children in the present study. On the other hand, a propensity for frontal propagation of paroxysmal discharges

during sleep has also been mentioned in relation to epileptic discharges (26). However, the present findings suggested that the spike discharges observed in the frontal region in autism represent a dysfunction of the frontal region, because autistic patients have some frontal lesion signs and/or symptoms such as perseveration, disturbances of creativity and executive function, attention disorders, and so on.

Although the focus of spike discharges has been reported to be the centro-parieto-temporal (8) and temporal (15, 16), in the present study there were few centro-temporal spike foci. Moreover, Lewine *et al.* (27) observed epileptic activity in the intra-perisylvian region using magnetoencephalography in children with regressive autism spectrum disorders. Although the reason for this discrepancy is unknown, several factors may contribute to it. One factor may have been that all chidren in the present study had been sedated with medication. The second factor is the difference in the recording methods. We included F7, F8 and Cz in the frontal region. Cz is anatomically in the posterior frontal region and so was included in the frontal region. Olsson *et al.* (16) reported EEG abnormalities in the temporal lobes of autistic children with epilepsy. However, only one case showed spikes at F8 in the present study, and this did not have an affect on our conclusion that F8 should be included in the temporal region. The third factor is the difference in subjects. In the present study, there were only a few patients with regression of symptoms. The final factor is that the brain dysfunctions in autism occur at several levels, including the brainstem, cerebellum, limbic system (especially amygdala and hippocampus) and association cortex (especially frontal lobe). The present cases may be a subgroup with frontal lesions. Anatomical studies of the autistic brain have shown deep medial temporal lesions including those in the hippocampus and amygdala. Although the reasons for the few temporal epileptic discharges are unknown, deep medial temporal lesions may be one reason. In future studies the use of sphenoidal electrodes may be needed.

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