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EEG abnormalities among "normal" applicants for phase I clinical trials of an agent that could possibly act on the central nervous system

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Objective: To investigate the rate of EEG abnormalities among men who had applied to participate in the screening process of phase I clinical trials of an agent that could possibly act on the central nervous system held at the Kitasato University East Hospital.
Methods: All the applicants were admitted to our ward for 1 week and were investigated. Routine diurnal EEGs were recorded as part of the screening. All paper EEG recordings were visually inspected by clinical neurophysiologists certified by the JSCN (Japanese Society of Clinical Neurophysiology).
Results: Among the 296 applicants (aged 20－44 and 65－85.5 years), 51 men (17.2%) showed abnormalities in basic EEG activity, and 64 men (21.6%) showed epileptiform discharges.
Conclusion: Our results suggest that a considerable number of the applicants for phase I trials could have EEG abnormalities. Recording EEGs may be useful to rule out applicants with possible or concealed underlying brain diseases from phase I clinical trials.

Key words: central nervous system, electroencephalogram, epileptiform discharge, phase I clinical trial

Abbreviations: BETS, benign epileptiform transients of sleep; CNS, central nervous system; ECG, electrocardiogram; ED, epileptiform discharge; EEG, electroencephalogram; fMRI, functional magnetic resonance image; JSCN, Japanese Society of Clinical Neurophysiology; MRI, magnetic resonance image

Introduction

Kitasato University has one of the largest facilities for clinical trials in Japan, with various types of trials, including phase I clinical trials, currently underway. By definition, volunteers who are enrolled in phase I trials must be healthy and must have passed appropriate screening examinations. The inclusion/exclusion criteria and the characteristics of the enrolled participants have been described in previous papers reporting phase I trials.[1,2]

However, little has been reported about the applicants for phase I trials. In recent years, data on applicants for phase I trials held at the Kitasato University East Hospital have been collected. These data reveal unexpected findings regarding the applicants' social, physical, and neurological status. Here, we report the social status and electroencephalogram (EEG) abnormalities of applicants for Kitasato's phase I clinical trials. To our knowledge, this report is the first of its kind to examine the characteristics of applicants who were selected to take part in phase I clinical trials of an agent that could possibly act on the central nervous system in this type of applicant pool.

Methods

Subjects

All subjects were men who had volunteered to participate in phase I clinical trials held at the Kitasato University

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East Hospital. The trials were aimed to test an agent that could possibly act on the central nervous system (CNS). All the subjects lived in the south Kanto area, including Tokyo and Kanagawa, and were recruited via advertisement. None of the subjects reported any histories of head traumas, neuropathies, or psychiatric disorders, or any other chronic CNS diseases or disorders. None of the subjects was using any illicit drugs during the screening period.

All procedures used in this study were conducted in accordance with the World Medical Association's ethical principles[3] and the Japanese Good Clinical Practice Guidelines. All trials were approved by the institutional review board. All subjects were fully informed of the procedures of the clinical trial to which they had applied. A total of 303 volunteers provided written informed consent prior to the commencement of the study. Later, 7 subjects rescinded their consent. Here, we report on data obtained from the remaining 296 subjects.

Methods

All the pre-screening volunteers were admitted to our ward for 1 week and were investigated. Their social, medical, and trial-attendance histories and status were obtained by interview. Physical and neurological examinations and routine urine and blood tests, including tests for drug screening, were also performed. Electrocardiograms (ECGs) and routine diurnal EEGs were recorded.

EEG recordings were obtained from 18 or 21 electrode locations, according to the international 10－20 system, using silver cup electrodes placed with an electrolyte paste and a digital EEG instrument (Neurofax EEG-4518; Nihon Kohden, Tokyo; reference-free recording system with 16-bit A/D [analogue-to-digital] conversion, 256 samples per second). The time constant was set to 0.1 or 0.3 seconds. A bandpass filter (0.3－60 Hz) was used, and electrode impedances were kept below 10 kOhm. The EEG data was stored on a magneto-optical disk. All paper EEG recordings were visually inspected by clinical neurophysiologists certified by the JSCN (Japanese Society of Clinical Neurophysiology).

The background activity in the resting, wakeful, and eyes-closed states in each record was identified by visual inspection; the amplitude and frequency were subsequently measured using the FOCUS software accompanying the EEG equipment. The amplitude and frequency of alpha activity were measured at O2. Activities, other than alpha activity, were visually located, and then the amplitude and frequency measured at the identified peak electrode site. Epileptiform discharges (EDs) were located and typed, and the peak electrode sites were identified. Any abnormalities during eyes-open/close manipulations, photic stimulation, hyperventilation, or sleep were also identified.

All data were stored and analyzed at the Kitasato University East Hospital and AstraZeneca, Tokyo. The utilization of data for purposes other than pharmaceutical development was prohibited prior to 2011. All statistical analyses were performed using JMP10 (SAS Institute, North Carolina, USA).

Results

Table 1 shows the age-stratified data for the total number of subjects, number of subjects who had participated in previous clinical trials, employment status, and social use of alcohol and/or tobacco (Table 1).

Table 2 shows the quantity and type of each abnormal or variant (unusual but benign) finding among the 296 EEG records. Briefly, among the 296 applicants, 51 (17.2%) showed abnormalities in background EEG activity (i.e., slow alpha activity, focal or diffuse bilateral theta or delta activity during wakefulness), and 64 (21.6%) had epileptiform discharges. The classification of EEG findings was adopted from Ebersole and Pedley.[4]

Applicants with either slow alpha activity (n = 3), focal theta (n = 3), or localized delta (n = 1) had no epileptiform discharge. There were 12 of 24 applicants who showed diffuse bilateral arrhythmic theta during wakefulness and had epileptiform discharges. Most of the EDs appeared during drowsiness or sleep. An example of spikes without after-going slow waves is shown in Figure 1. A 3 Hz spike-and-slow wave complex (n = 4) appeared during wakefulness (n = 1), drowsiness or sleep (n = 3), and hyperventilation (n = 2). Neither wicket spikes nor psychomotor variant rhythms were observed. Eyes-open/closed manipulations or photic stimulation yielded no abnormal EEG patterns, and no photoparoxysmal responses or photoconvulsive responses were observed. Age, smoking habits, drinking habits, or employment status were not significantly associated with any of the EEG abnormalities. Applicants with any EEG abnormalities were not enrolled in the phase I clinical trials held at our facility.

Discussion

Our data on the pre-screening applicants for phase I clinical trials raises the question of the adequacy of the selection criteria for enrolling persons in normative studies. Boutros et al.[5] comprehensively described the

criteria that are required to show that the subjects are neurologically normal and that the EEGs of those subjects could be regarded as normative. As the basis for their review, they chose 7 criteria that are commonly used in contemporary neuropsychiatric research for selecting healthy subjects. They reported that none of the studies they reviewed met all 7 criteria for the selection of normal subjects, and concluded that the boundaries for "normal" analog EEG are not well defined for neuropsychiatric clinical purposes or research.

The rate of apparently "abnormal" EEG findings in "normal" subjects has been reported to be around 0.9% −2.9%. Gibbs et al.[6] reported that 0.9% and 1.1% of 1000 normal adult controls (who met 2 of Boutros et al.'s 7 criteria[5]) showed paroxysmal discharges and very abnormal basic activities, respectively. Among Rossen and Gordon's 70 subjects[7] who had had no overseas duty (and who met 3 of Boutros et al.'s 7 criteria[5]): 2 subjects

Table 1. C linical features of applicants in phase 1 clinical trials, stratified by age

Age	20−24	25−29	30−34	35−39	40−44	65−69	70−74	75−79	80−
Number of applicants	90	37	36	46	19	36	14	16	2
Employed	52	29	30	41	16	14	2	3	0
Unemployed	9	6	6	5	3	22	12	13	2
Students	29	2	0	0	0	0	0	0	0
Drinkers	56	21	28	35	9	23	9	9	1
Smokers	10	3	3	6	2	5	1	0	0
Previously took part in another trial	24	14	21	27	4	18	10	11	1

Table 2. Variant and abnormal EEG findings of the 296 applicants for phase 1 clinical trials

Age	20−24	25−29	30−34	35v39	40−44	65−69	70−74	75−79	80−
Number of records	90	37	36	46	19	36	14	16	2
Benign variants									
Asymmetry in alpha amplitude (20−50%)	1	1	0	0	2	0	0	0	0
Slow alpha variant rhythm	0	0	1	0	0	0	0	0	0
Midline theta during wakefulness	2	3	2	1	0	0	0	0	0
Benign patterns with an epileptiform morphology									
14 & 6 Hz positive bursts	4	3	0	1	0	0	0	0	0
Benign epileptiform transients of sleep	0	0	1	0	0	2	1	0	0
Phantom spike and wave	5	1	1	1	0	0	0	0	0
Abnormal patterns									
Slow alpha activity	0	0	1	0	0	0	0	2	0
Abnormal slow activity during wakefulness									
Focal theta activity	0	0	0	0	0	1	0	2	0
Diffuse bilateral arrhythmic theta activity	11	2	4	0	0	4	2	1	0
Localized arrhythmic delta activity	0	0	0	0	0	0	0	1	0
Diffuse bilateral arrhythmic delta activity	0	1	0	0	0	0	1	0	0
Epileptiform discharges									
Spike or sharp waves alone	10	7	2	6	1	12	2	6	1
3-Hz spike and slow wave complexes	2	1	0	1	0	0	0	0	0
Irregular spike and slow wave complexes	3	1	0	1	0	0	0	2	0
Polyspike and slow wave complexes	1	0	0	0	0	0	0	0	0
Sharp and slow wave complexes	5	1	2	3	1	3	0	2	0

The classification of findings was adopted from Ebersole and Pedley.[4] "Spike or sharp waves alone" indicates spike or sharp waves without a following slow wave.

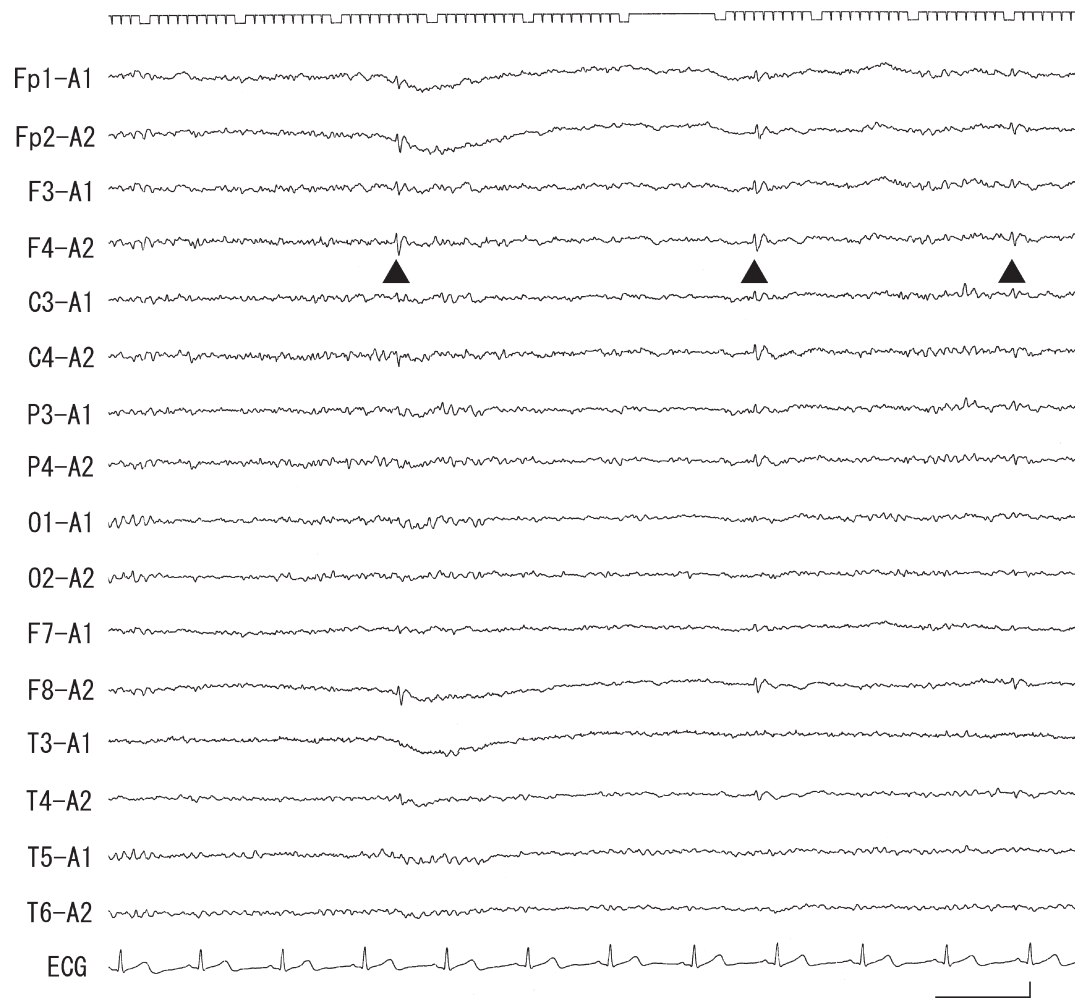

Figure 1. Electroencephalogram of an applicant

An example of spikes (▲) recorded during the first transition from wakefulness to sleep in a 22-year-old man who applied to take part in a phase I clinical trial. These spikes have low amplitude (less than 50 microvolts) and have no after-going slow wave. The peak distribution of the spikes does not change from spike to spike. No polarity change between the hemispheres can be seen.

(2.9%) showed grossly abnormal EEGs, and 8 (11.4%) showed slightly abnormal EEGs. Rodin[8] reported that 1 subject (2.5%) of 40 "normal" subjects (who met 3 of Boutros et al.'s 7 criteria[5]) showed long periods of 5－6-Hz activity in the resting state; this was described as definitely abnormal. Finally, Bennett[9] reported that 16 of 1965 flying personnel (who met 2 of the 7 criteria of Boutros et al.[5]) had spike-wave abnormalities.

Obviously, our study was not a normative study. However, our pre-screening applicants met 4 of Boutros et al.'s 7 criteria[5] (i.e., historical or current absence of: 1. systemic disorders with CNS involvement; 2. neurological disorders, including traumatic brain injury, childhood neurological disorders, and dementia-related illnesses; 3. alcohol and drug abuse or dependence; and 4. receiving CNS-active medications, including any psychotropics). Moreover, these volunteers were observed on an inpatient ward for 1 week. Therefore, before this study, we expected that less than 2.9% of our volunteers would show abnormal EEG findings.

Surprisingly, the volunteers of the present study showed a strikingly higher rate of EEG abnormalities: 17.2% (51 of 296) showed abnormal basic EEG activity, and 21.6% (64 of 296) showed EDs. Although it is difficult to fully explain the high rate of EEG abnormalities among these participants, some possible factors could be considered.

First, some of the benign epileptiform transients of sleep (BETS) could have possibly been mistaken as spikes. The occurrence rates of BETS are reported to be 14% in patients with complex partial seizures and 25% in normal controls[10]; whereas, only 4 (1.4%) of 296 applicants showed BETS. Among some of the applicants, the localized spiky-looking transients that repeated only

a few times (Figure 1) with an amplitude of 50 microvolts or less, without a sharp wave or relevant focal slow background activity, were not recognized as BETS but as spikes because such transients did not occur in varying electrode sites like BETS. However, it is sometimes hard to distinguish BETS from low-amplitude spikes repeating only a few times.

Second, we suspect that some of our participants were actually patients with epilepsy with low frequency or in remission. Applicants 65－80 years showed more sharp-and-slow wave complexes (5 of 68, 7.4%) than did applicants 20－44 years (12 of 228, 5.3%; Table 2). There is a relationship with sharp and slow wave complexes and epilepsy and seizures.[11] In addition, compared with younger individuals, elderly people are more likely to develop seizures, whether provoked by acute illness or without an obvious precipitating cause.[12,13] These facts support our views that we could not completely be sure that we did not select any patients who were unaware that they had epilepsy or any patients who were trying to conceal their epilepsy only by obtaining self reports of past neurological and psychiatric histories and inward observations in only a 1-week period.

Third, a few participants might have been in a prodromal state of epilepsy and may possibly develop seizures after the completion of this study. Actually, in the 142 "normal" patients of Zivin and Marsan[14] who showed EDs, 20 (14.1%) were reported to have developed seizures after the initial detection of EDs.

Fourth, some of our participants could have had neurological but non-epileptic disorders with very few or no symptoms. Non-epileptic patients after cranial operations, non-epileptic patients with congenital or perinatally aquired brain abnormality, brain neoplasms, neuroectodermal dysplasias, antineoplastic agents, mental retardation, or biochemical disorders were reported to have significantly higher occurrence rates of EDs than were "normal" patients.[14] In another study, non-epileptic patients with cerebral infarction, progressive dementia, hypoxic encephalopathy, and enlarging brain tumor, among other aflictions, were reported to show EDs.[15] As shown in Table 2, applicants aged 65－80 years showed more "spike or sharp waves alone" (21 of 68, 31%) than did applicants aged 20－44 years (26 of 228, 11%). Taken together, we could have possibly failed to exclude some elderly volunteers with asymptomatic brain tumor or dementia in the early stage before the EEG screening.

Fifth, withdrawal from barbiturates or benzodiazepines should be taken into account.[11]

Lastly, if EDs are detected in persons without seizure histories, they often occur infrequently on EEG recordings and may not be observed in subsequent recordings.[16] Although 3 Hz spike and slow wave complexes are strongly related to epilepsy,[11] 4 cases of Zivin and Marsan,[14] who had no seizure histories and had "typical" 3 Hz spike and slow wave complexes (2 with family histories of epilepsy), were reported to have developed no seizures in the follow-up study. Therefore, it could be possible that 3 of our applicants with a 3 Hz spike and slow wave complex might not have epilepsy and only have family histories of epilepsy.

This study has certain limitations, e.g., a follow-up study and a neuroimaging study, as a brain MRI (magnetic resonance image) or an fMRI (functional MRI), is lacking. The distribution of the applicants' ages is also limited. However, our data could be regarded as an alert that a considerable number of applicants for phase I trials might have had EEG abnormalities. Recording EEGs could be useful to eliminate any applicants with possible or "concealed" underlying brain diseases from phase I clinical trials of agents that could act on the CNS. And, if any kind of EEG abnormality was discovered, we would recommend that the applicant consult a clinical neurologist to clarify the significance of the finding.

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