DENTATORUBRAL-PALLIDOLUYSIAN ATROPHY (DRPLA) AND MIDLATENCY AUDITORY EVOKED RESPONSES

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Abstract: The human 'P1' middle latency evoked potential is postulated to be generated in the thalamus by a cholinergic component of the ascending reticular activating system. To test the midbrain function of dentatorubral-pallidoluysian atrophy (DRPLA), recording of middle latency response to click stimuli were carried out in a DRPLA family which was detected with the aid of molecular diagnosis. Comparisons between the DRPLA members and the normal members indicated normal Pa responses but P1 component is abnormal in DRPLA. This P1 abnormality suggests that the midbrain cholinergic cells in DRPLA may be dysfunctional.

Index Terms

midlatency auditory evoked responses, DRPLA, molecular diagnosis, P1 abnormality

INTRODUCTION

Dentatorubral-pallidoluysin atrophy (DRPLA) (MIM 125370)[1] is an autosomal dominant neurodegenerative disorder characterized by anticipation and variable combination of symptoms including progressive myoclonus, epilepsy, cerebellar ataxia, choreoathetosis and dementia[2]. Although this condition was first described in a sporadic case without family history in the United States[3], familial cases with an autosomal dominant trait have been found predominantly in Japan[4]. Recently, DRPLA families were detected in Europe with the aid of molecular diagnosis[5].

DRPLA has been shown to be due to unstable expansion of a CAG-trinucleotide repeat of a CTG-B 37 gene[6] on chromosome 12 p[7,8]. The normal range of repeats, 7-23, was expanded to 49-75 repeats in DRPLA patients. A correlation between age of onset, severity and repeat size was observed. Expansion of an unstable trinucleotide repeat has also been implicated as the molecular mechanism in other diseases including spinal and bulbar muscular atrophy (SBMA)[9], fragile X syndromes (FRAXA[10] and FRAXE[11]), myotonic dystrophy (DM)[12-14], Huntington's disease (HD)[15] and spinocerebellar ataxia type 1 (SCA 1)[16].

Although middle latency response (MLR) abnormalities in DRPLA subjects have not been reported, one of the MLR components, P1, changes significantly as function of state[17] and is abnomal in schizophrenics[18]. This potential has been related to generator substrate within the

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ascending reticular activating system and its thalamic projections[19]. Thus, MLR recordings of DRPLA subjects appeared to present an opportunity to assess an earlier and perhaps simpler series of potentials than the longer latency event-related potentials (ERPs) with at least one potential, the P1, shown to be intimately related to arousal-attentional mechanisms.

We present a kindred with DRPLA containig fourteen affected individuals in four generations, and also present the clinical and molecular findings and MLR abnormalities in these cases and their available families.

PATIENTS, MATERIAL, AND METHODS

Patients

Patient Y. K. - The proband (Fig. 1) was born in full term by spontaneous labor. She is the first child of nonconsanguineous parents. Her physical and mental development was normal until she was 8 years old when her mental retardation was noticed. Ataxia occurred at the age of 12, she fell down when she was walking. Tonic-clonic convulsion attacked her for the first time at the age of 13, after her menarche. In spite of psychopharmacotherapy including anticonvulsants, her mental retardation, cerebellar ataxia and convulsion had been gradually

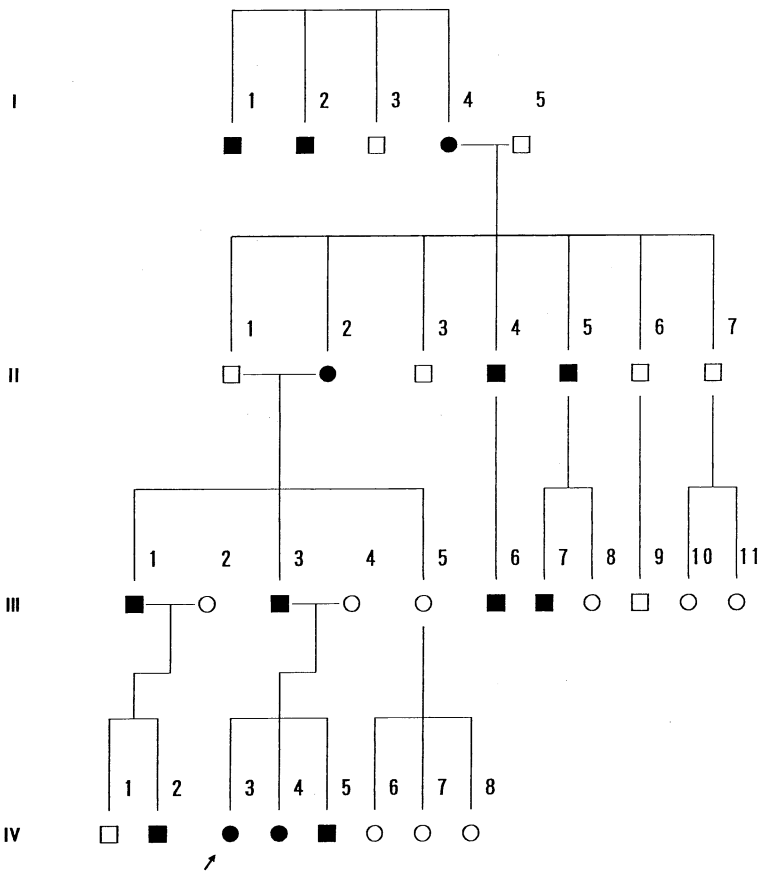

Fig. 1. Pedigree of Y. K. (IV-3). The proband is indicated by an arrow. Ten members of this pedigree were investigated.

progressing in severity. Her younger sister was also in a similar state, her younger brother was suffering from diabetes insipidus and showed abnormalities of electroencephalogram (EEG), and her father had ataxic gait. Serum levels of lactic acid and pyruvic acid were 14.9 mg/dl (normal range : 4-16 mg/dl), 0.63 mg/dl (0.3-0.9 mg/dl), respectively, negating the possibility of myoclonus epilepsy with ragged-red fibers (MERRF). Magnetic resonance imaging did not show nucleus dentatus at the level of fourth ventricle (Fig. 2). Therefore her disorder was strongly supposed to be DRPLA.

Molecular analysis

We investigated this family by amplification of the DRPLA CAG repeat (CTG-B 37) using primers and conditions previously descrided[7]. Prior to this investigation, all subjects signed informed consent. III-1 & 3, IV-1, 2, 3, 4, & 5 had expanded alleles containing above 60 repeats (Fig. 3). IV-1 was asymptomatic who had been originally diagnosed as unaffected. We diagnosed this kindred as having DRPLA.

Clinical inventigation

Present age, sex, age of onset, duration of course, clinical symptoms, Mini Mental State Examination (MMSE), EEG, latency of P300 of ERPs, and MLR P1 recording were investigated.

Auditory ERPs were recorded from Cz with reference on linked ear lobes. The auditory stimuli were 70 dB SPT tone bursts delivered binaurally at a rate of once every 2 sec. Based

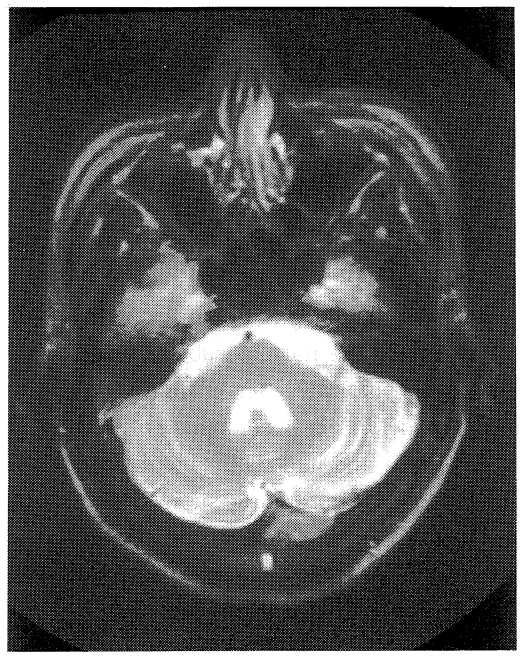

Fig. 2. Magmetic resonance imaging (T2) of IV-3 shows typical image of dantatorubral pallidoluysian atrophy.

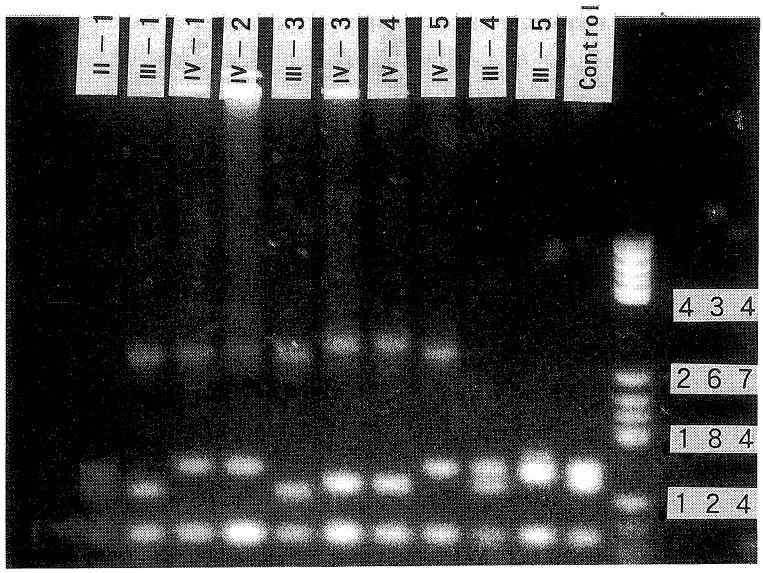

Fig. 3. Analysis of the PCR amplified products containing the CAG repeat in a DRPLA kindred. PCR products amplified with the CTG-B37 primer were analysed in 2% agarose gel. Individuals are identified by letters above each lane. Sizes are estimated by Molecular Wedight Markers, i.e. "267, 437" are corresponding to 50, 113 of number of repeats, respectively.

on oddball paradigm, two tones frequencies were used: 2000 Hz and 1000 Hz, and 80 percentages at 1000 Hz. Each tone burst was 50 msec in duration. Thirty-two sweeps were recorded and averaged for 2000 Hz. For MLR recordings, click stimuli (0.1 msec duration, 70 bB) were delivered binaurally throught earphones at every 1 sec. Stimuli were presented, and responses were averaged in 500 trials.

RESULTS

Fig. 4 shows contrasting effects of stimuli on P300 and P1 of the normal subject (III-4) and the DRPLA asymptomatic subject (IV-1). Latency of P300 of the DRPLA subject was prolonged compared with the normal subject. P1 component of the DRPLA subject was not clearly seen, while P1 component of the normal subject was recognized around 50-65 msec. Table 1 summarizes the results of this study. According to the classification by Naito[4], III-1 & 3 belonged to late onset type, and IV-3 & 4 belonged to juvenile type. IV-2 & 5 who were suffering epilepsy showed no ataxia and had no problems in daily life. All the subjects with expanded CAG repeat including a asymptomatic subject showed prolonged latency of P300. There was no correlation between P300 latency and MMSE score. Also, absence of P1 components was found in all the subjects with expanded CAG repeat including the asymptomatic subject.

DISCUSSION

P300, which is an endogenous component of ERPs, is considered to indicate the higher

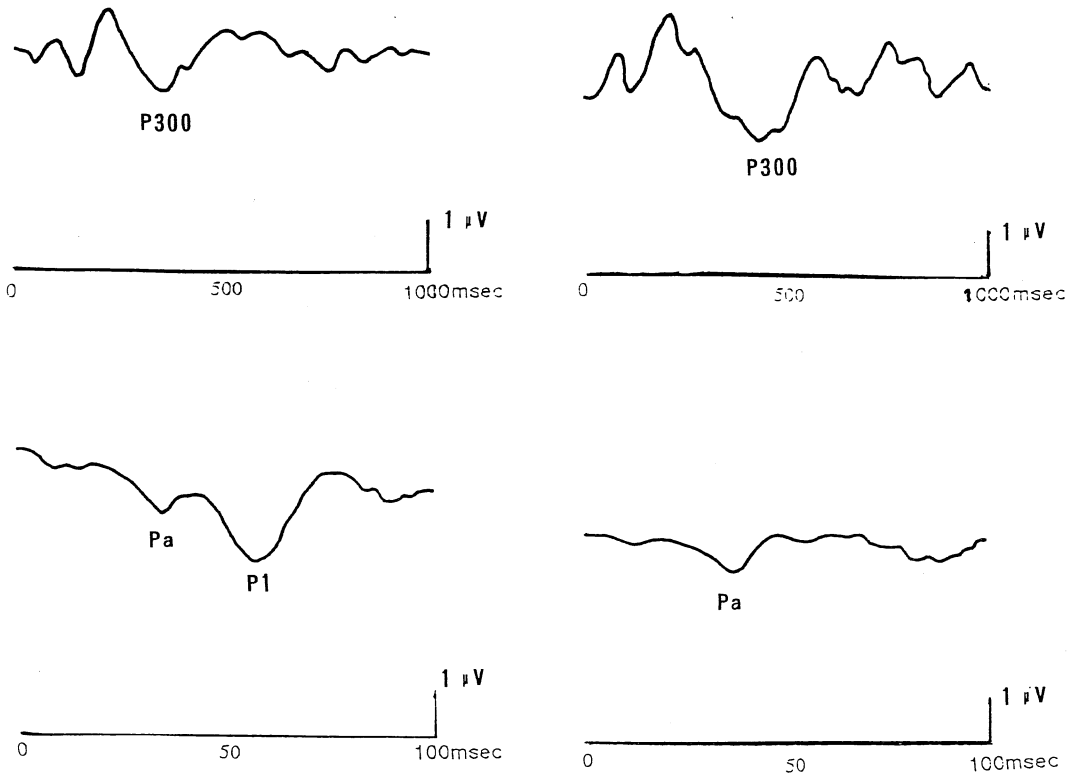

Fig. 4. Left, P300 & P1 of a normal subject of DRPLA family. Right, P300 & P1 of a DRPLA asymptomatic subject who had an expanded DRPLA gene.

Table 1. Summary of Investigation of 10 members of a DRPLA kindred

	Expanded allele	Age/Sex	Onset of age	Duration (ys)	Clinical symptoms	MMSE	EEG	P300 Latency	P1
II—1	−	74/M	—	—	—	28	Normal	364	+
III—1	+	49/M	44	5	P+A+1	19	F+S	365	−
III—3	+	46/M	36	10	P+A+1	25	F+S	366	−
III—4	−	46/F	—	—	—	29	Normal	311	+
III—5	−	45/F	—	—	—	21	n. a.	n. a.	n. a.
IV—1	+	25/M	—	—	—	26	S+P	362	—
IV—2	+	17/F	13	4	E+D	19	S+P	370	−
IV—3	+	25/F	12	13	E+M+D+A	8	S+P	366	−
IV—4	+	22/F	6	16	E+M+D+A	0	S+P	400	−
IV—5	+	17/M	13	4	M+E+P	25	S+P	398	−

Clinial Symptoms A : Ataxia E : Epilepsy M : Myoclonus
D : Dementia P : Personality change I : Involuntary movement
EEG findings F : Fast wave S : Slow wave P : Paroxymal wave n.a. : not available

cognitive functions in information processing in the brain and also to be maintained in certainly high levels in healthy subjects. It is widely accepted that there is a negative correlation between latencies of P300 and age[20]. The delay of P300 latency reflects the degree of cognitive decline

in demented patients[21]. Although MMSE score were within normal range (scoring above 23) in IV-1, 2, & 5, their latencies of P300 were prolonged. It might be the reason why the oddball task required the subjects to discriminate the tones and press the button, i. e., they would have some clinically unnoticeable motor retardation and could not respond or perform the task well. This result suggests that P300 based on oddball paradigm might not be a useful tool in order to evaluate the cognitive impairment in subcortical dementia such as DRPLA.

The absence of P1 in these DRPLA subjects dose not reflect an inability to hear the click stimulus. Pa component occurred at a normal amplitude and latency. As the DRPLA subjects were monitored by an observer throughout all recordings and consistently awake, with eyes open. P1 could not have disappeared because of sleep onset. Thus, we concluded that the P1 component is diminished or missing in the DRPLA subjects because its generator substrate is abnormal.

An animal model of the P1, which shares physiological and parametric features of the human potential, has been recorded and its generator substrate investigated. This response is permanently abolished by midbrain lesions which include the colinergic cells of the pedunculo-pontine tegmental (PPT) nucleus[22], a component of the reticular activating system (RAS) with ascending cholinergic projections to the thalamus[23]. Moreover, this response is reversibly blocked by scopolamine, a cholinergic antagonist and is reestablished by physostigmine, a cholinergic agonist[24]. The cat P1 model thus appears to require the activation of PPT cholinergic cells within the mesencephalic RAS, which project to and excite cholinergic-muscarinic receptors located on target thalamic cells.

Human P1 may require an RAS genetrator system similar to this one in the cat[24]. An intimate relationship between P1 and RAS is strongly suggested by the human data, a relationship more definitively established by the PPT lesion studies in the cat. The pharmacological data further suggest a dependent relationship between the human P1 and activation of muscarinic receptors to which cholinergic cell components of the RAS project[25].

The present data are the first demonstration that the P1 component is abnormal in DRPLA, i. e., the abnormality of P1 indicates a rather specific neural substrate dysfunction. We propose that this substrate system is a cholinergic component of the ascending RAS and its post-synaptic projection onto thalamic target cells. Although the present sample is small, the results suggest that marked P1 abnormality may provide a useful tool in conjunction with other neuropsychological indices of DRPLA.

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