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Absence seizures with myoclonic seizures as an early manifestation of dentato-rubro-pallido-luysian atrophy (DRPLA): a follow-up clinical course of twelve years

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Abstract

Typical absence seizures and isolated myoclonic seizures are both classified as age-related generalized seizures and are considered to be benign neurological manifestations. Concomitance of the two types of seizure is considered benign if it does not accompany other types of seizures or other neurological problems. We followed up a ten-year-old girl with isolated absence and myoclonic seizures whose family history of mental and neurological signs was initially not disclosed. After several years, the family history of neurological and mental problems was finally disclosed, and the diagnosis of dentato-rubro-pallido-luysian atrophy (DRPLA) was confirmed. The patient's clinical course was slowly progressive, and by age 21 she was in a nearly vegetative state. We would like to alert clinicians to consider DRPLA when diagnosing patients with absence and/or myoclonic seizures, even when they present the clinical features of benign epilepsies in the early stage.

Key words: Myoclonic seizure; astatic seizure; absence; Doose syndrome; DRPLA.

Introduction

An epileptic brief spell of unconsciousness with generalized spike-and-wave complexes on EEG is called an absence seizure (Commission on Classification and Terminology of the International League Against Epilepsy, 1981; Valentin *et al.*, 2007). Although absence seizures appear in a variety of epilepsies and epileptic syndromes, they are considered to be a hallmark of benign nature if they appear independently without other neurological manifestations such as mental retardation, ataxia, paresis, involuntary movements, or frequent convulsion (Commission on Classification and Terminology of the International League Against Epilepsy, 1997).

We followed the clinical course of a 10-year-old girl with absence seizures accompanied by myoclonic seizures for 12 years. As epileptic seizures were the main clinical problem for the first several years of treatment, we made an initial diagnosis of generalized epilepsy. Later, neurological deterioration appeared and gradually progressed until she reached a nearly vegetative state. Here we report the clinical course and present pitfalls in diagnosing and determining the prognosis for patients with absence seizures.

Case report

A girl was referred to our outpatient clinic at age 10 for control of frequent brief spells of unconsciousness accompanied by generalized muscle jerks with a likelihood of falling when walking. A family history of epilepsy, epileptic seizures, ataxia, involuntary movement, myoclonus, or other involuntary movements was denied by her mother at that time, with the sole report of a cousin who was mentally retarded, without precise information provided. The pregnancy had been uneventful, and the girl was borne at 38 weeks with normal delivery at 2950 gr. Her initial growth was only slightly delayed, with virgin gait at 15 months and initial speech at 24 months. At preschool age she was reported to have normal motor development with slight intellectual and language delay. Although she was admitted to normal elementary school, her school record was bad and she was referred to a special class for mentally retarded students at grade 2. Her subsequent school life was spent in the special class. There was

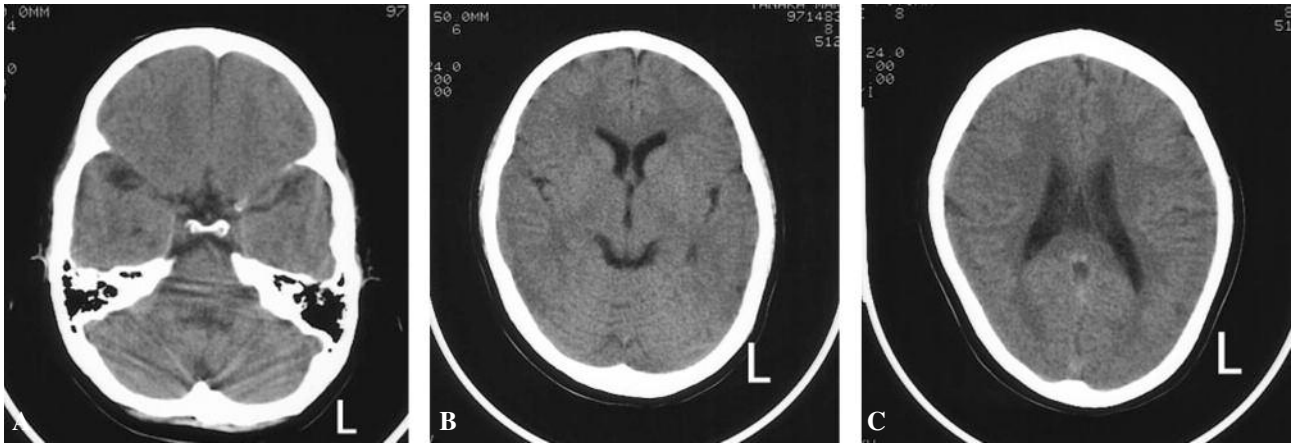

FIG. 1. — A, B, C. CT with axial sequences at age 10 showing equivocal atrophy of cerebral white matter without definite abnormality in the brainstem or cerebellum.

no history of febrile convulsions or febrile seizures. Her initial seizures (age 6) were loss of consciousness with duration of not more than a few seconds, which occurred more than ten times a day. She was diagnosed with childhood absence epilepsy (pyknolepsy) (Commission on Classification and Terminology of the International League Against Epilepsy 1989), and valproic acid was started. The valproic acid was effective, and she became seizure free; however, 9 months later, absence seizures reappeared and generalized myoclonic seizures dominant in the upper extremities appeared and gradually increased, sometimes evolving into generalized tonic-clonic convulsions. At age 9, atonic seizures of the lower extremities and neck appeared in addition to the increased absence and myoclonic seizures, even when zonisamide was administered.

At age 10, the girl was brought to our clinic. At first arrival, although she exhibited mild mental retardation, she had no ataxia or involuntary movements. Cranial CT showed slight dilation of the fourth ventricle, without definite cerebral or cerebellar atrophy (Fig. 1A, B, C). EEG showed frequent spells of uniform 4-Hz spike-and-wave complexes with duration of 1 to 8 seconds (Fig. 2). We diagnosed the patient as having cryptogenic or symptomatic generalized epilepsy and continued drug control against epilepsy.

The girl's clinical course showed gradually progressive physical and mental deterioration. Besides epileptic seizures, which became more frequent, speech disturbance, dysphagia, choreic involuntary movements, cerebellar ataxia, and gait disturbance appeared and made gradual progression. At age 13, the patient's mother revealed the patient's family history: the patient's father (husband of her mother) had died in a psychiatric hospital because of dementia, psychosis, dysarthria, and gait ataxia, and her cousin was mentally retarded with ataxic gait. We performed genetic analysis and confirmed that the girl's disease was dentato-rubro-pallido-luysian atrophy (DRPLA). At age 17, total laryngostomy was performed due to recurrent aspiration pneumonia. At age 18, the patient's left leg was resected because of osteomyelitis and gangrene. At age 21, she was in a nearly vegetative state, with eyes open. Occasional myoclonic seizures in her face and limbs, and clonus in her legs still existed, but there was no response to stimulation. MRI showed progressive generalized brain atrophy (Fig. 3 A, B, C), and EEG showed diffuse suppressed activity with sporadic mixture of dysrhythmia (Fig. 4). Within several years of determining the patient's genetic diagnosis, the diagnosis of DRPLA was confirmed genetically in her father and cousin. In addition, her father's younger sister presented clinical manifestations three years ago and was genetically confirmed as having DRPLA. Figure 5 shows the family tree. The patient is now age 22 and staying at home under the care of her mother, home helper, visiting nurse, and visiting doctor.

Discussion

Absence seizures, which are characterized by brief spells of unconsciousness with generalized 3- to 4-Hz spike-and-wave complexes, are classified as generalized seizures and are associated with generalized epilepsy or epileptic syndrome. Myoclonic seizures are also classified as generalized seizures. Isolated absence seizures or absence seizures accompanied by myoclonic seizures without neurological

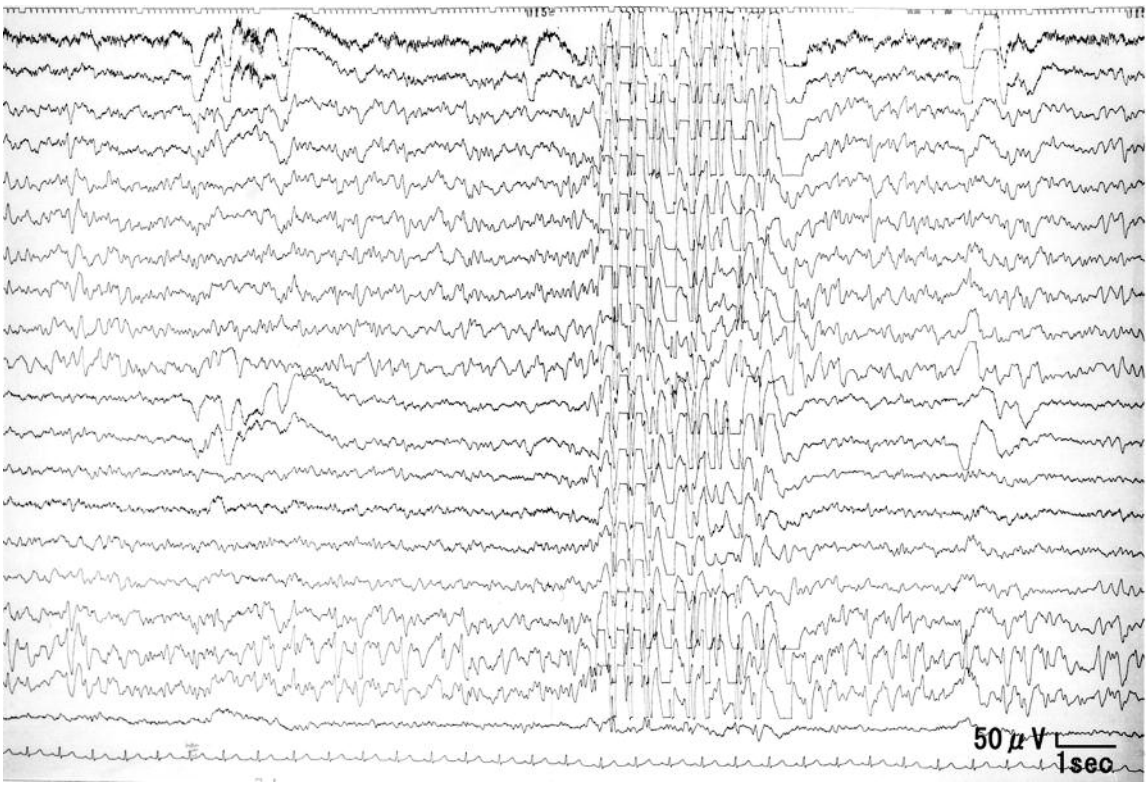

FIG. 2. — EEG at age 10 showing continuous strong epileptic activity

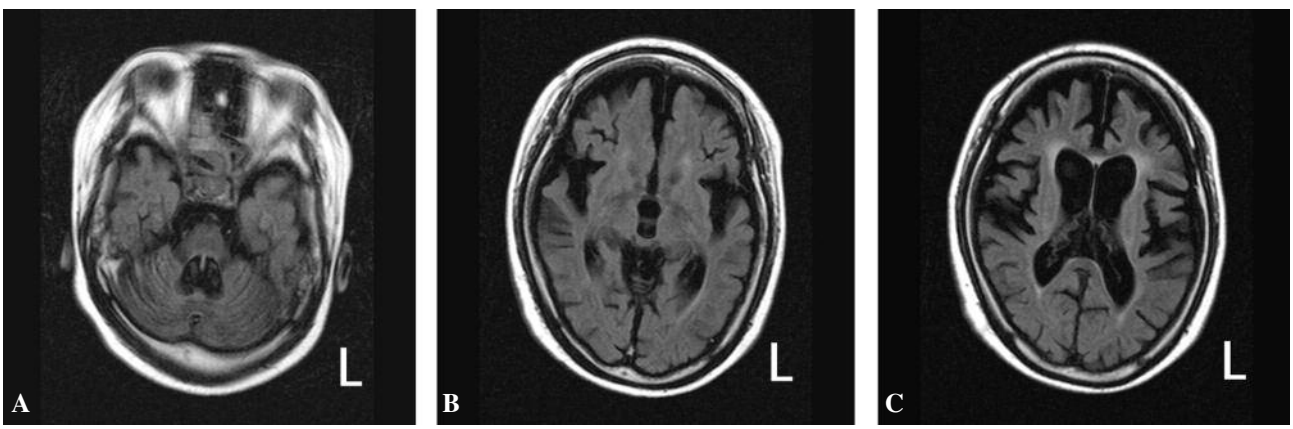

FIG. 3. — A, B, C. MRI with axial sequences at age 21 showing diffuse brain atrophy including the cerebrum, brainstem, and cerebellum.

abnormality tend to accompany 3- to 4-Hz spike-and-wave complexes, and are associated with favorable outcome (Valentin *et al.*, 2007). In the classification of epilepsies organized by the International League Against Epilepsy, absence seizures with or without myoclonic seizures are cordial manifestations of benign, childhood onset, idiopathic generalized epilepsies such as childhood absence epilepsy, juvenile absence epilepsy, and juvenile myoclonic epilepsy. In contrast, absence seizures with or without myoclonic seizures accompanied by other types of seizures (especially partial seizures), involuntary movements, or ictal or inter-ictal neurological abnormalities are called atypical absence seizures and usually show a less favorable clinical course with poorer response to antiepileptic agents. Such cases are classified as generalized cryptogenic or symptomatic epileptic syndrome, which included diseases such as Lennox-Gastaut syndrome (Dulac and N'Guyen, 1993), epilepsy with myoclonic

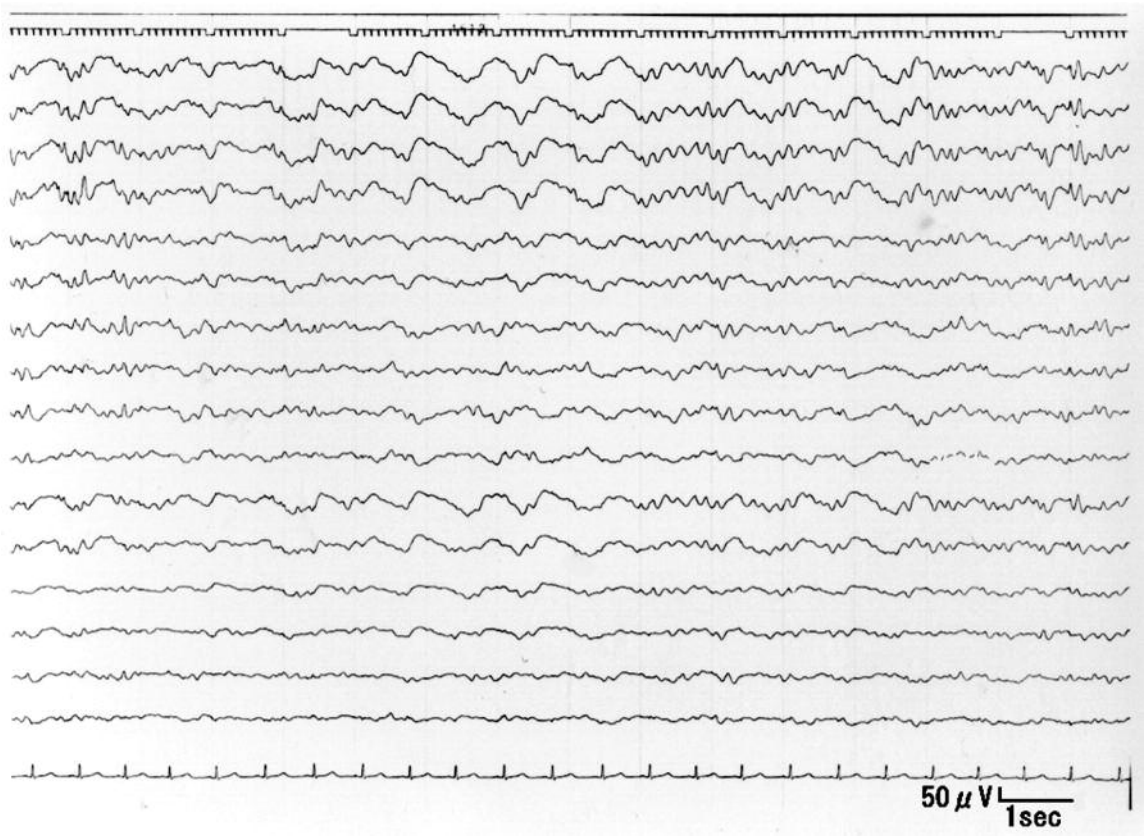

FIG. 4. — EEG at age 21 showing continuous, diffuse dysrhythmic and suppressed activity on EEG

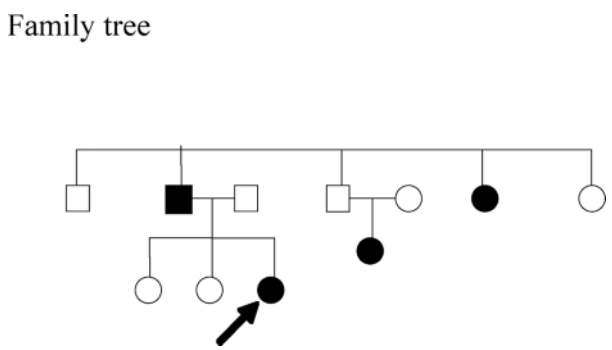

FIG. 5. — Family tree of the patient

astatic seizures (a syndrome described in detail by Doose, 1992), and epilepsy with myoclonic absences (a syndrome described in detail by Bureau and Tassinari, 2005).

As our case presented typical absence seizures with occasional myoclonic seizures with relatively regular 4-Hz spike-and-wave complexes, we at first suspected her illness was idiopathic generalized epilepsy or, in the worst case, cryptogenic generalized epilepsy adjacent to idiopathic generalized epilepsy, and we thus judged the prognosis to be not so bad. However, the patient presented intellectual and language delay, and her first cranial CT image showed ventricular dilatation not typical for her age. As these inferior qualities were not so marked, we at first did not pay them sufficient attention. Had we concentrated on these clues, it is possible we might have reached the correct diagnosis at that time. DRPLA is an autosomal dominant hereditary degenerative disease whose patients exhibit ataxia, intellectual deterioration, choreic involuntary movements, and epileptic seizures (Yanagisawa *et al.*, 1996). DRPLA is caused by CAG trinucleotide repeat expansions in the respective genes in the 12p13.31 locus (Wardle *et al.*, 2009; Wardle *et al.*, 2009; Yanagisawa *et al.*, 1996), and it has been confirmed to occur especially in Japanese, Caucasian, Italian, UK, or Portuguese populations (Martins, 2003). Knowledge of family history is sometimes unavailable, and ataxia and chorea do not always manifest in DRPLA, especially in the early stage (Commission on Pediatric Epilepsy of the International League Against Epilepsy, 1997). Because of the lack of correct information about the family history as well as the absence of ataxia and

Table 1

Differential diagnosis of myoclonic epilepsy

Benign
benign familial myoclonic epilepsy
Miscellaneous
Lance-Adams syndrome
Serious
DRPLA
Lafora disease
MERRF (mitochondrial epilepsy with ragged red fiber)
Unverricht Lundborg disease
neuronal ceroid-lipofuscinosis
Gaucher disease
sialidosis
galactosialidosis
Huntington disease
(so-called) Ramsay Hunt syndrome (progressive myoclonic ataxia)

chorea, we at first could not make the correct diagnosis of DRPLA in this case.

In addition to distinguishing benign epilepsies from symptomatic epileptic syndrome, it is important to differentiate benign myoclonic epilepsy from myoclonic epilepsy with subsequent regression. We showed other possible diagnoses we should be aware of in the Table 1. We would like to alert clinicians, when diagnosing patients, to consider DRPLA as one of the differential diagnoses when the inferior qualities mentioned above are observed even minimally, even when patients manifest the clinical features of benign epilepsies, especially in areas or populations known for a prevalence of DRPLA.

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