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Cerebellar atrophy in temporal lobe epilepsy

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Abstract

Purpose. The goal of this work was to determine the presence and degree of cerebellar atrophy in chronic temporal lobe epilepsy, its clinical seizure correlates, and its association with general cortical atrophy.

Methods. Study participants were 78 persons with temporal lobe epilepsy and 63 age- and gender-matched healthy controls. All subjects underwent high-resolution MRI with manual tracing of the cerebellum. Clinical seizure features and history were obtained by structured interview and review of medical records.

Results. The epilepsy group exhibited significant abnormality in cerebellar volume, with mean reductions ranging from 4 to 6.6% depending on adjustments. Significantly more individual subjects with epilepsy exhibited cerebellar atrophy compared with controls across all operational definitions or thresholds of abnormality including $z \leqslant -2.0$ (13% TLE, 3.4% controls) and $z \leqslant 1.5$ (22% TLE, 3.4% controls). Clinical seizure features reflecting both neurodevelopmental (history of initial precipitating injuries) and severity of course (longer duration, increased number of lifetime generalized tonic–clonic seizures) factors were associated with cerebellar atrophy. Atrophy of the cerebellum could be observed independent of more general (cerebral) atrophic processes.

Conclusions. The presence of cerebellar atrophy is a reflection of the extratemporal abnormalities that can be observed in localization-related temporal lobe epilepsy, which may be due, at least in part, to factors associated with epilepsy chronicity.

Keywords: Cerebellar atrophy; Temporal lobe epilepsy; Quantitative magnetic resonance imaging

1. Introduction

Cerebellar atrophy, a neuropathological abnormality not uncommonly noted among patients with chronic epilepsy, was carefully described and characterized prior to the introduction of phenytoin. Cerebellar atrophy was reported in neuropathological investigations of institutionalized epilepsy patients dating back to 1825 [1], and the profound loss of Purkinje cells, preservation of basket cells, granule cell damage, and associated (Bergmann's) gliosis were characterized by neuropathologists early in the last century [2]. While occasional investigators viewed this neuropathology as unassociated with epilepsy [3], it was more generally believed to be a direct consequence of chronic epilepsy, although opinions varied regarding the exact mechanism of effect [1,4–6].

Following the development [7,8] and release [9,10] of phenytoin, it soon became evident that acute intoxication was associated with signs of cerebellar dysfunction [11]. Withdrawal or reduction of phenytoin often, but not always, resulted in resolution of symptoms. Reports appeared noting that some chronically treated patients exhibited persisting signs of cerebellar dysfunction, leading to interest in the role of phenytoin in the etiology of cerebellar atrophy [12–14]. Further supporting the view that treatment factors could contribute to or cause

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cerebellar atrophy were observations that this neuropathology could be induced in animals by phenytoin toxicity [15–17], as well as findings that cerebellar atrophy could be observed in humans without epilepsy [18–21] or in humans with very well-controlled epilepsy [13,22], following exposure to acute or chronic toxic doses of phenytoin.

Dam and colleagues refocused interest on the role of frequent and severe seizures and the contribution of seizure-induced hypoxia in the etiology of cerebellar atrophy, marshalling both animal and human data to support this view [23–27]. Further suggestion of direct seizure-related mechanisms came from investigations of patients with frequent partial seizures in whom hypoxia was uncommon, yet who exhibited cerebellar atrophy [28,29]. Considered less often were the potential effects of initial etiological insults and early neurodevelopmental factors in the etiology of epilepsy-related cerebellar atrophy [29,30]. Debate regarding the relative contribution of drugs (phenytoin), seizures, and other factors continues to the present [31].

Through the years, cerebellar atrophy has been investigated not only by histopathological analysis, but by evolving neuroimaging techniques including pneumoencephalography [14,32,33], computed tomography (CT) [13,21,22,34,35], and magnetic resonance imaging (MRI) [18,19,29,36,37]. The availability of quantitative MRI volumetric techniques offers to characterize more precisely the presence, degree, distribution, and predictors of cerebellar atrophy in patients with chronic epilepsy.

As summarized in Table 1, six quantitative MRI volumetric investigations have addressed the problem of cerebellar atrophy in epilepsy [38–44]. As is true of the larger literature, there is variability across these studies with respect to the populations studied, with only two investigations focusing specifically on temporal lobe epilepsy. Only one investigation examined children with epilepsy [41], and the abnormalities in cerebellar volume identified in that investigation indicate that neurodevelopmental factors are contributors to cerebellar atrophy. This emerging quantitative MRI literature contains investigations with varying image acquisition and volumetric processing procedures, as well as nonoverlapping primary outcome measures [e.g., comparison of group means, derivation of percentage reduction in cerebellar volume, determination of the degree of cerebellar atrophy (mild, moderate, severe)], making it difficult at times to compare results across studies and populations. The clinical seizure variables examined as predictors of cerebellar atrophy are variable across studies, with only one factor (duration of epilepsy) consistently examined. Few of the investigated clinical epilepsy variables are reliably associated with cerebellar atrophy across studies, but variations in methodology likely contribute to this problem.

The purpose of this investigation is threefold. The first aim is to characterize the presence and degree of cerebellar atrophy using various definitions of cerebellar atrophy to determine the rate and reliability of findings across various definitions of pathology. This is undertaken with respect to both group data (mean percentage volume loss) and individual data (proportion of subjects exhibiting cerebellar atrophy of varying severity). The second aim is to identify which of a number of clinical epilepsy factors are associated with cerebellar pathology. The clinical factors of interest here reflect the etiology, course, and treatment of epilepsy and were selected especially to reflect potential adverse neurodevelopmental as well as progressive effects of epilepsy on the cerebellum. The latter analyses control for the known effects of normal aging on brain structure to identify the unique impact of duration of disorder on cerebellar structure. The final aim is to determine the degree to which atrophy of the cerebellum occurs independent of atrophy of the cerebrum. These issues are examined in a large cohort of subjects with localization-related temporal lobe epilepsy and healthy age- and gender-matched controls spanning a very broad age range (14–60 years).

2. Methods

2.1. Subjects

Participants included 78 patients with a diagnosis of temporal lobe epilepsy and 63 healthy controls. The subject selection process has been described in detail previously [45]. Briefly, initial selection criteria for epilepsy subjects included: (1) chronological age from 14 to 60 years, (2) localization-related temporal lobe epilepsy, (3) no MRI abnormality other than atrophy on clinical reading, and (4) no other neurological disorder. Epileptologists reviewed patients' medical records including seizure semiology and previous EEG and neuroimaging reports, and rated each patient as having seizures of definite, probable, or possible temporal lobe origin. *Definite* temporal lobe epilepsy was defined by continuous video/EEG monitoring of spontaneous seizures demonstrating temporal lobe seizure onset; *probable* temporal lobe epilepsy was determined by review of clinical semiology with features reported to reliably identify complex partial seizures of temporal lobe origin versus onset in other regions (e.g., frontal lobe) in conjunction with interictal EEGs, neuroimaging findings, and developmental and clinical history. Only patients meeting criteria for *definite* and *probable* temporal lobe epilepsy proceeded to recruitment for study participation, patients with *possible* temporal lobe epilepsy were excluded.

Selection criteria for healthy controls included: (1) chronological age from 14 to 60, (2) either a friend or family member of the patient, (3) no current substance