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# The clinical and neurobehavioral course of Down syndrome and dementia with or without new-onset epilepsy

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ABSTRACT

*Background:* Adult patients with Down syndrome (DS) are at higher risk of developing Alzheimer-type dementia and epilepsy. The relationship between developing dementia and the risk of developing seizures in DS is poorly characterized to date. In addition, treatment response and medication tolerability have not been rigorously studied.
*Methods:* We identified 220 patients with a diagnosis of DS and dementia. Those without a history of developing seizures (DD) were compared to patients with new-onset seizures (DD + S) after the age of 35. Electronic records were reviewed for demographics, seizure characteristics, cognitive status, and psychiatric comorbidities.
*Results:* Of the patients included for analysis, twenty-six out of 60 patients had new-onset seizures or developed seizures during the follow-up period (the DD + S group) with a median onset of 2.0 years after the dementia diagnosis. Generalized tonic–clonic seizures were the most common seizure type (61.5% of DD + S). Sixteen (61.5%) patients were reported to have myoclonus. Levetiracetam was the most commonly used initial medication, with the majority (73%) of patients treated achieving partial or complete seizure control. The DD + S patients tended to have a similar burden of new-onset neuropsychiatric symptoms compared to the DD group.
*Discussion:* New-onset epilepsy seems to occur early in the course of dementia in DS patients. Patients generally respond to treatment. A great burden of neuropsychiatric symptoms is seen. Future studies need to explore the relationship between β-amyloid accumulation and epileptiform activity and attend to the care and needs of DS patients with dementia and seizures.



## 1. Introduction

Down syndrome (DS), or trisomy of chromosome 21, is the most common known genetic cause of developmental delay and intellectual disability. In addition to recognizable physical features, patients with DS have intellectual disabilities including learning, memory, and language impairment [1] and a well-known predisposition to develop early-onset dementia of the Alzheimer's type. Prevalence rates of clinical Alzheimer disease (AD) are as high as 75% in DS patients over age 60 [2], and nearly all brain autopsies of DS patients over age 40 demonstrate characteristic pathological features of AD [3]. The life expectancy of patients with DS has increased considerably over the past years, mostly due to advances in the management of cardiac malformations and advancements in health care [4]. This rise in life expectancy increases the clinical importance of better characterizing dementia in DS including its course and co-morbidities.

Alzheimer's disease is an independent risk factor for developing seizures. Interestingly, the rate of developing seizures in AD is markedly higher among patients with early-onset AD, and those with more severe dementia [5]. In patients with both DS and AD, as many as 84% will develop seizures, although the details of epilepsy in this population are poorly characterized within the literature [2].

In the current study, we characterized seizures in patients with DS and dementia and assessed treatment response and medication tolerability which to date have not been rigorously studied. We also described the clinical and neurobehavioral characteristics of DD in patients developing seizures (DD + S) compared to those without seizures (DD).

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## 2. Patients and methods

### 2.1. Selection

This study was a retrospective chart review using the Research Patient Data Registry query tool (RPDR) [6] to search Partners Healthcare records. Patients carrying diagnosis codes consistent with Down syndrome (758.0) *and* Dementia (294.20 and 294.21)/mild cognitive impairment (331.83) who first presented from 2004 to 2014 were selected. Records with inadequate data, improper coding, or childhood-onset seizures were excluded. Provoked seizures were not included in this data search. Only patients over the age of 35 were included for review.

### 2.2. Collection of variables

The study was approved by the Partners Healthcare Internal Review Board (IRB). Charts were reviewed for demographics, seizure characteristics, cognitive status, and psychiatric comorbidities when available. We collected data relating to seizure characteristics, treatments, and treatment response by reviewing documentations by the treating neurologist. We also included any standardized batteries completed around the time of dementia diagnosis including the Dementia Questionnaire for the Mentally Retarded DMR [7] (a 50 item questionnaire scored by a caregiver with scores for each item ranging from 0 = no deficit to 2 = severe deficits). The sum of cognitive scores from the DMR includes short-term memory, long-term memory, and orientation. Other batteries included category Verbal Fluency (food, animals), Modified Zung Depression Inventory Score (total score of 60, higher scores indicative of depressive moods) [8], and the Test of Severe Impairment [9] (score is out of 24 with higher scores indicating better cognitive performance).

### 2.3. Statistical analysis

Continuous data were summarized in means and standard deviations while categorical data were summarized as percentages. Fisher's exact test was used to compare categorical variables between both groups. Data from cognitive batteries between patients with and without seizures were plotted and compared using Wilcoxon rank-sum as a non-parametric measures test using R statistical package [10].

## 3. Results

### 3.1. Patient demographics

We reviewed 220 patient charts from the database search; 60 cases with complete clinical documentation were identified. Forty patients had at least one measured cognitive score. Table 1 summarizes the demographic and baseline data characteristics. Twenty-six out of 60 patients with DS and associated diagnosis of AD carried a diagnosis of a new-onset seizure disorder at the time of diagnosis or developed a seizure disorder during the follow-up period. Within this group, none had a history of childhood seizures, known structural brain abnormality, history of encephalitis or stroke, or had a known family history of epilepsy. Only two patients had a reported history of head trauma with loss of consciousness.

**Table 1**
Demographics and baseline characteristics of patients.

| | DD | DD + S |
|---|---|---|
| N (M/F) | 34 (18/16) | 26 (13/13) |
| Follow-up duration, mean years | 3.75 (1.64) | 3.25 (1.69) |
| % classical trisomy 21 | 71% | 81% |
| Estimated age at dementia onset[a], mean (SD) | 52 (6.1) | 50.6 (5.9) |
| Age at seizure onset[a], mean (SD) | N/A | 53.3 (7.0) |
| Time to first seizure from dementia onset[a,b] | N/A | 2.0 (−7 to 12) |

DD, Down syndrome and dementia; DD + S, Down syndrome, dementia, and seizures.
[a] Data from 5 patients omitted due to uncertain onset.
[b] Only in one patient seizure predates dementia.

### 3.2. Diagnosis of dementia predated seizure onset in the majority of patients

Among the 26 patients in the DD + S group, seizure onset predated the dementia diagnosis in only one patient. The time from dementia diagnosis to first seizure ranged from −7 to +12 years (interquartile range 0–2, median 2 years; Fig. 1). (See Fig. 2.)

### 3.3. Seizure semiology was variable

The most common seizure semiology was reported as a generalized tonic–clonic seizure (GTCS) in 16/26 (61.5%) of patients. Six patients presented with focal seizures with dyscognitive features (23.1%). Sixteen (61.5%) patients developed myoclonus 10 of whom also had GTCS fulfilling criteria for LOMEDS (late onset myoclonic epilepsy in Down's syndrome) although not all of them had EEG available to confirm the epileptic nature of the myoclonus. In two patients, the information was lacking to characterize the initial seizure type. Most of the patients had more than one seizure semiology: 19/26 patients (73.1%) when including myoclonus as a separate semiology, and 6/26 patients (23.1%) when excluding myoclonus, including one with tonic and one with atonic/drop attacks. Twenty-four patients had at least one EEG study as part of their work-up, and two other patients did not have any EEG on record. Two patients had an additional long-term video-EEG monitoring study. Four patients (16.6%) were reported to have epileptiform abnormalities in their EEG, and myoclonus was documented in one patient. The rest of the EEG findings revealed diffuse, moderate to severe delta slowing in (25%), and in 14 patients the EEG showed either mild slowing or was normal.

### 3.4. Both patient populations have a significant burden of neuropsychiatric disorders

Table 2 summarizes the neuropsychiatric features in the DD and DD + S groups at the time of dementia diagnosis.

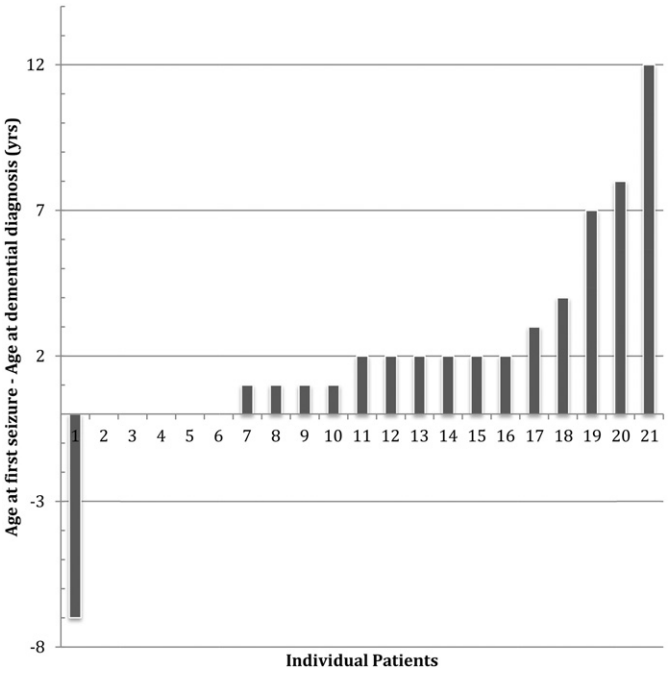


**Fig. 1.** Graphical representation of the latency of the onset of the first seizure from the diagnosis of dementia in individual patients.