

# Natural History of Absence Epilepsy in Children

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**ABSTRACT:** Absence seizures may be seen in a variety of epileptic syndromes in childhood. Identification of the specific syndrome is important to determine medical prognosis. With childhood absence epilepsy, approximately two thirds of children can be expected to enter long-term remission, while in juvenile absence epilepsy, seizure control is often achieved, however, lifelong treatment is usually required. Other absence syndromes have a poorer prognosis, with lower rates of seizure control and remission. Psychosocial outcome is often poor, even in patients with more benign forms of absence epilepsy. Remission of epilepsy does not preclude psychosocial morbidity.

**RÉSUMÉ:** L'histoire naturelle des absences chez les enfants. Des crises d'absence peuvent être observées dans différents syndromes épileptiques de l'enfance. L'identification du syndrome est importante pour déterminer le pronostic médical. Dans l'épilepsie de type absence de l'enfant, on peut s'attendre à une rémission à long terme chez à peu près les deux tiers des enfants. Chez les adolescents, bien qu'on puisse généralement contrôler les crises, un traitement à vie est habituellement nécessaire. Certains syndromes d'absence épileptique comportent un pronostic plus défavorable et le taux de contrôle des crises et de rémission sont plus faibles. Les répercussions psychosociales sont plus lourdes même chez les patients qui présentent des formes plus bénignes d'absence épileptique. La rémission ne prévient pas nécessairement la morbidité psychosociale.

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Absence seizures are characterized by brief impairments in consciousness that occur without warning and abate suddenly without postictal changes. Several syndromes with absence seizures have been described,<sup>1</sup> however, and, in determining the prognosis for a given patient, one needs to identify not only the seizure type but also the seizure syndrome. Although this paper will focus on the natural history of typical absence seizures associated with the various idiopathic generalized epilepsy (IGE) syndromes, other subtypes of absence epilepsy will be briefly discussed (Figure 1).

One must first differentiate between atypical and typical absence. Clinically, atypical absences occur in children with neurodevelopmental delay, and co-exist with other generalized seizure types including myoclonic, atonic and tonic seizures. Most cases of typical absence seizures are seen in neurologically normal children and, depending on the epilepsy syndrome, may be the only seizure type. Electrographically, the spike wave discharge in atypical absences is slower than 2.5 Hertz and the background is usually abnormal. The prognosis for seizure control, remission of epilepsy and neurodevelopmental outcome is poor with atypical absence seizures.

Rarely, partial seizures of mesial frontal origin can clinically resemble typical absences. These seizures present with behavioural and speech arrest, diminished or lost consciousness, and may have associated minor head or eye turning and automatisms. They are usually brief, lasting 10-30 seconds, but

may have a longer postictal period before complete recovery. Frontal lobe absences may evolve into secondary generalized seizures.

Typical absences may be seen in cryptogenic/symptomatic generalized epilepsy, such as in myoclonic absence epilepsy.<sup>2</sup> Absences in this syndrome are accompanied by prominent, rhythmic, bilateral myoclonias, and a tonic contraction is often associated. Absences are very frequent, occurring multiple times per day and tend to be slightly longer in duration, lasting between 10-60 seconds. Other seizure types often are seen, including generalized tonic-clonic (GTC) and atonic seizures. Although some cases experience remission of seizures, prognosis for seizure control is often poor. Cognitive impairment is frequently present before or at the time of onset of myoclonic absences, and some patients may show mental deterioration during the course of their epilepsy. The prognosis is worse if there are associated GTC or atonic seizures, and in those with frequent seizures.

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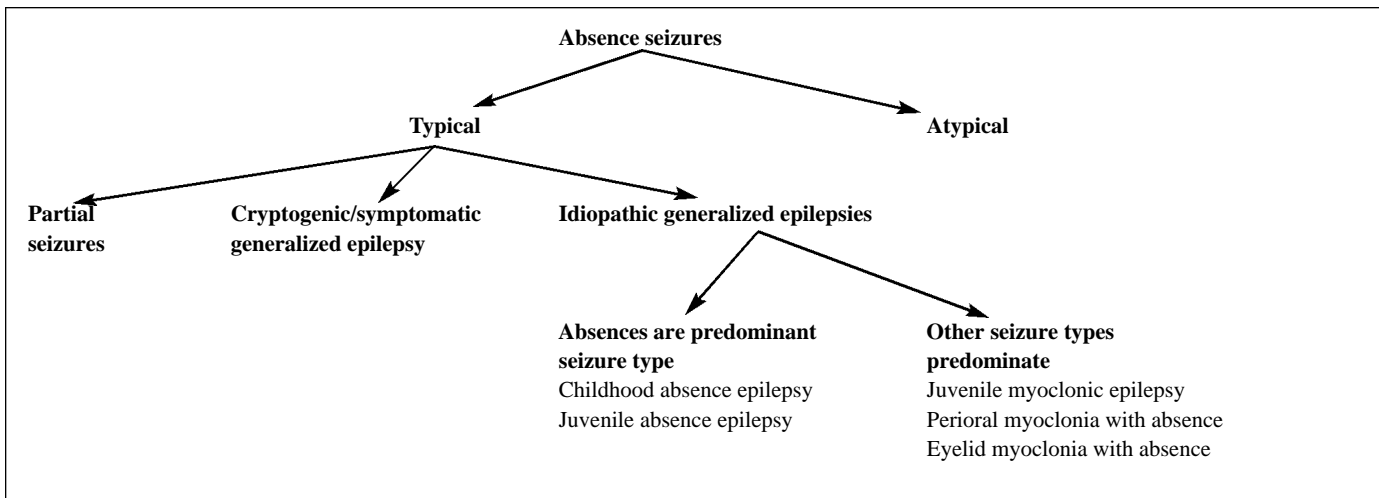


Figure 1: Classification of absence seizures

The IGEs in which typical absences occur can be divided into those where other seizure types predominate (juvenile myoclonic epilepsy [JME], perioral myoclonia with absences [PMA], eyelid myoclonia with absences [EMA]) and those in which typical absences are the predominant seizure type (childhood absence epilepsy [CAE], juvenile absence epilepsy [JAE]).

Juvenile myoclonic epilepsy usually presents in adolescence with prominent myoclonic jerks, that characteristically occur in the morning, and GTC seizures.<sup>3</sup> Seizures are exacerbated by sleep deprivation and alcohol. Typical absences may also be seen but are very brief and usually infrequent. Photosensitivity is common. The EEG shows fast, generalized polyspike and spike wave discharge. Although this epilepsy type typically responds well to low dose valproic acid or lamotrigine, lifelong treatment is usually required.

Other rarer seizure syndromes associated with typical absences which probably fall under the IGE umbrella, but which have not yet been recognized by the International League Against Epilepsy include PMA and EMA.<sup>1</sup> As suggested by their names, these syndromes have associated myoclonia of either the orbicularis oris and depressor anguli oris leading to rhythmic twitching of the lips and mouth, or rhythmic jerking of the eyelids and eyeballs. Generalized tonic-clonic seizures usually co-exist, and prognosis for both seizure control and remission of epilepsy is poor.

The vast majority of patients who present with typical absence seizures however, have either CAE or JAE.

#### MEDICAL PROGNOSIS IN CHILDHOOD ABSENCE EPILEPSY AND JUVENILE ABSENCE EPILEPSY

Childhood absence epilepsy typically has its onset in early to mid childhood, with a peak age of five to six years.<sup>4</sup> Typically, a child presents with multiple absences per day. Although GTC seizures may ultimately develop in up to 40% of cases, their onset is usually delayed until adolescence. Seizure types other than typical absence are rare at the time of presentation.

Electrographically, generalized spike wave at 3-4 Hertz is seen ictally, and discharge usually lasts longer than four seconds. Posterior delta activity is frequently seen.

Reported remission rates for CAE vary widely, ranging from 33-79%.<sup>5-11</sup> A number of factors explain this variation. Firstly, remission rates vary with the duration of follow-up. Although the majority of children will have their typical absence seizures controlled, and will be able to wean off anti-epileptic drugs (AEDs), approximately 30-40% will ultimately develop GTC seizures, usually in their adolescent years.<sup>4</sup> Hence, subjects must be followed into young adulthood before one can determine whether their epilepsy has remitted. Secondly, remission rates may vary depending on the population being studied. Most studies have identified cases through epilepsy clinics, and these series are more likely to contain higher numbers of refractory patients. Thirdly, many studies have not clearly demarcated between patients with CAE and other types of typical absence. Inclusion of subjects with syndromes other than CAE will bias the results toward a less favorable outcome.

We studied a large, population-based group with CAE and followed them up in young adulthood, to determine how many had remission of their epilepsy and how many progressed to JME.<sup>11</sup> Potential cases of CAE were identified by review of all pediatric EEG records for the province of Nova Scotia over a nine year period. Patients with typical 3 Hertz generalized spike and wave discharge on EEG, who met criteria for CAE as defined by Loiseau,<sup>4</sup> were included. The mean age of our 72 cases at follow-up was 20.4 years and mean follow-up from seizure onset was 14.1 years. Overall, 65% of subjects had remission of their epilepsy, meaning that they were seizure-free and off AEDs at follow-up. A further 7% were seizure-free on medication (4/5 of these had previously failed a trial off drug therapy). Seventeen percent had discontinued AED treatment but had definite or suspected ongoing seizures (42% had absences only, 8% had GTC seizures only, and the remainder had absences in combination with GTC and/or myoclonic seizures). Eleven percent had continuing seizures despite medication (38% had

absences alone and the remainder had a combination of generalized seizure types). Significant prognostic factors for lack of remission of CAE on univariate analysis were *absence status* (relative risk [RR] 3.2, 95% confidence interval [CI] 2.3-4.6,  $p < 0.005$ ), *myoclonus while on AEDs* (RR 3.3, 95% CI 2.0-5.5,  $p < 0.0002$ ), *GTC seizures while on AEDs* (RR 2.9, 95% CI 1.8-4.8,  $p < 0.01$ ), *EEG background slowing* (RR 2.4, 95% CI 1.2-4.6,  $p < 0.01$ ), *family history of generalized seizures in a first degree relative* (RR 2.4, 95% CI 1.3-4.2,  $p < 0.01$ ) and *cognitive difficulties at presentation* (RR 1.9, 95% CI 1.1-3.6,  $p < 0.05$ ). Significant factors on multivariate analysis were *myoclonus while on AEDs*, *absence status*, *family history of generalized seizures in a first degree relative*, and *EEG background slowing*. Using these four factors, a classification tree could predict against remission with an overall sensitivity of 64% and specificity of 94% (Figure 2).

Overall, 15% of the total cohort had progressed to JME at follow-up. Significant factors predicting progression to JME were *lack of response to AEDs within the first year* (RR 5.6, 95% CI 1.4-21.6,  $p < 0.01$ ), *absence status* (RR 3.8, 95% CI 1.2-12.0,  $p < 0.05$ ), *EEG background slowing* (RR 3.5, 95% CI 1.0-12.2,  $p < 0.04$ ) and *family history of generalized seizures in a first degree relative* (RR 3.6, 95% CI 1.3-10.4,  $p < 0.02$ ). Development of both GTC and myoclonic seizures were used to define JME and therefore could not be used as predictors of its development. However, only 1/7 (14%) who developed GTC seizures and 4/12 (33%) who developed myoclonic seizures while on AEDs did not progress to JME.

Juvenile absence epilepsy presents in late childhood or adolescence.<sup>12</sup> Typical absences are less frequent, usually occurring less than daily. Co-existent GTC seizures occur in approximately 80% of subjects and random, infrequent myoclonic jerks are also said to be common. The ictal EEG is similar to that in CAE.

Juvenile absence epilepsy is less well-studied than CAE, but

is probably a life-long epilepsy syndrome. In many cases however, it can be controlled with medication. Three studies have been reported on prognosis in JAE.

Bartolomei et al<sup>13</sup> reported on 27 cases of JAE from an epilepsy center in France. The mean duration of epilepsy was 12 years, and subjects were followed for a mean of three years. Eighty-one percent had co-existent GTC seizures, and in 38%, these were the presenting seizure type. Overall, 56% had a complete response to valproic acid, with or without ethosuximide. Of those with continuing seizures on these medications, 33% had absences alone, 25% had GTC seizures alone, and the remainder had both persisting absence and GTC seizures. No significant prognostic factors were identified, although the presence of polyspikes on EEG tended to correlate with failure to achieve seizure control on medication ( $p = 0.06$ ). The authors did not comment on what proportion of refractory patients achieved seizure control on the newer drugs, such as lamotrigine, and whether any patient who became seizure free on medication was successfully tapered off their AEDs.

Obeid<sup>14</sup> reported on a small group of 15 patients with JAE, followed for between 12 and 66 months. The mean age at onset of absences was 11.4 years. Eighty percent had co-existent GTC seizures and the mean age at onset for these was 13.1 years. All cases were treated with valproic acid, and although all had their GTC seizures controlled, 40% continued to have rare absences. The author did not comment on whether other AEDs afforded control of these absences. The frequency of GTC seizures predicted outcome, with poorer seizure control being seen in subjects who had GTC seizures more frequent than monthly.

The largest study, and one with long-term follow-up was reported by Loiseau et al.<sup>15</sup> They followed 62 patients with JAE to a mean age of 30 years. The proportion with co-existent GTC seizures was 79%, similar to previous studies. The mean age at onset of absences was 12 years, and of GTC seizures was 17 years. All subjects received valproic acid, with or without other

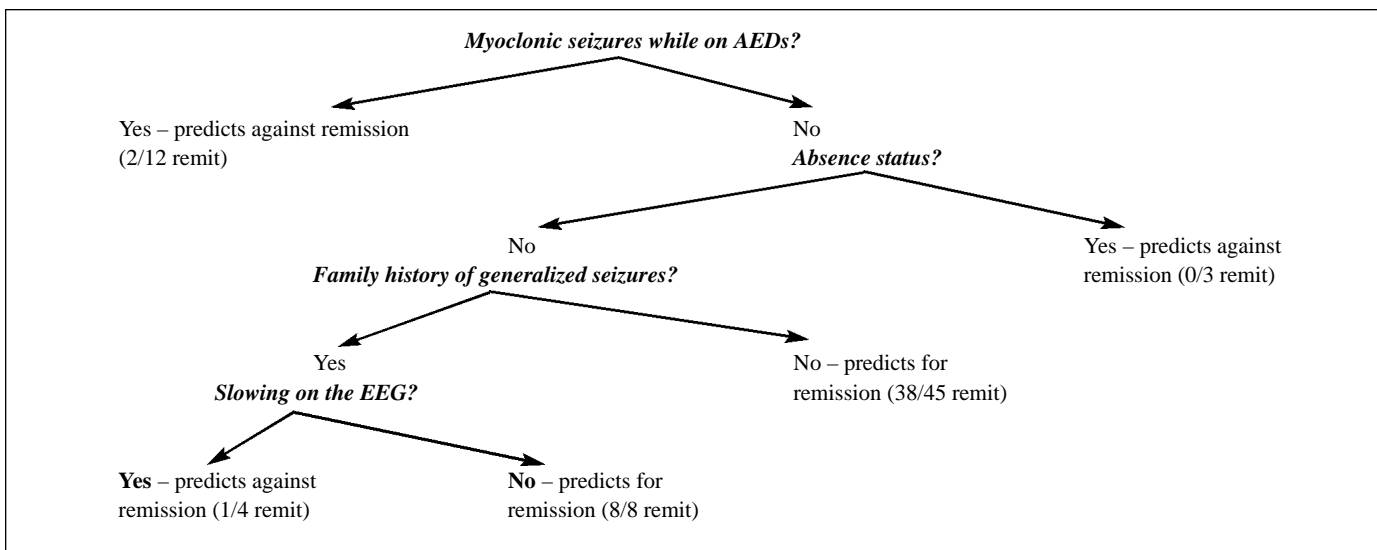


Figure 2: Classification tree predicting lack of remission of childhood absence epilepsy

AEDs and 47% achieved complete control of absence seizures. Although the authors comment that most cases had remission of their GTC seizures, actual numbers are not given in this paper.

A number of other studies have looked at prognostic factors in absence epilepsy. They did not, however, subdivide their cases into specific absence syndromes. Olsson et al,<sup>16</sup> in a population-based Swedish study of absence epilepsy, reported that early control of absences predicted against development of GTC seizures and for remission of epilepsy. Only 3% of children whose absences were controlled within six months vs. 33% of those with persisting absences after this time developed GTC seizures ( $p < 0.01$ ). Fifty-five percent of those with absences alone vs. only 6% of those with co-existent GTC seizures had remission of their epilepsy after a mean follow-up of five years. Sato et al<sup>17</sup> reported on prognostic factors for seizure freedom in 83 cases of typical absence epilepsy followed in an epilepsy centre to a mean age of 20.1 years. Forty-eight percent were seizure-free, and of these, 60% were off AEDs. Significant predictors for seizure freedom on multivariate analysis were  $IQ > 90$ , no hyperventilation-induced spike and wave, male sex and normal neurological examination.

We studied the prognostic significance of failure of the initial AED in our population-based cohort of children with typical absence epilepsy (75 CAE, 11 JAE) from Nova Scotia.<sup>18</sup> Overall, 60% achieved complete seizure control with the first AED, with the chance of response being higher with CAE (65%) than JAE (27%). Ethosuximide was usually the first AED used, which may explain the lower response rate in JAE. Terminal remission of epilepsy was more likely if the initial AED was successful than if it had failed (69% vs. 41%,  $p < 0.02$ ). Subjects whose initial AED had failed were more likely to progress to JME at follow-up (32% vs 10%,  $p < 0.02$ ) and to develop intractable epilepsy (17% vs 2%,  $p < 0.04$ ). Covanis et al<sup>19</sup> also noted that children who required two or more AEDs used consecutively to attain seizure control had a higher rate of relapse once medication was discontinued than those treated on monotherapy alone.

With the advent of the human genome project, there has been significant interest and some progression in our understanding of genes in epilepsy. However, most of the progress has been made in rarer epilepsy types with simple inheritance patterns. The inheritance of absence epilepsy is complex, probably both multigenic and multifactorial. Although a relatively restricted family of genes may cause various types of idiopathic generalized epilepsy, specific combinations of genes may lead to different absence subtypes. In CAE, several linkages (chromosome 8q<sup>20,21</sup> and chromosome 1<sup>22</sup>) have been reported, and one family has been found with a mutant GABRG<sub>2</sub>.<sup>21,23,24</sup> Clearly, absence epilepsy is genetically heterogenous and further advances in genetics may allow for more accurate prediction of medical prognosis.

#### SOCIAL PROGNOSIS IN TYPICAL ABSENCE EPILEPSY

Although psychosocial difficulties are common in children and adolescents with epilepsy, typical absence epilepsy has often been considered a “benign” form of childhood epilepsy, with most cases outgrowing their epilepsy and having a favorable social outcome. However, several studies have documented poor psychosocial outcome in typical absence epilepsy, although in

some reports, difficulties appear to be restricted to those with ongoing seizures.<sup>8, 25-29</sup>

A Danish study by Hertoft<sup>25</sup> reported on 50 children followed in a tertiary center for absence epilepsy. Although absence subtypes were not documented, most cases were probably CAE, given the reported ages at onset. However, some cases appeared to have a more malignant absence epilepsy subtype, as there were several patients with very early onset of both absences and GTC seizures. Twenty percent of their group were found to have a “subnormal” IQ, defined as  $< 90$ . Sixteen percent were functioning in a “socially unacceptable” manner, meaning that they were either in a reform school for behaviour problems, or if they were out of school, were unable to provide for themselves.

In a more recent, population-based study from Sweden, Olsson and Campenhausen<sup>26</sup> compared psychosocial outcome in 58 young adults with persisting absences to normal controls without epilepsy. They did not include cases whose epilepsy had remitted. Those with absence epilepsy were more likely to hold a job requiring shorter training and to be overqualified for their job. They had fewer social outings, were less likely to have a close friend and to participate in sports activities.

To determine whether young adults in whom typical absence epilepsy had been diagnosed in childhood had greater psychosocial difficulties than those with a non-neurological chronic disease, we compared social outcome in our Nova Scotian cohort with typical absence epilepsy to controls with a history of juvenile rheumatoid arthritis.<sup>29</sup> The groups were comparable with regards to mean age at onset of disease and sex ratio, however, more patients with absence epilepsy had remission of their disease (absence – 57%, juvenile rheumatoid arthritis – 28%,  $p < 0.01$ ). The mean age at follow-up was 23 years for both cases and controls. A structured interview was used to survey academic achievement, recreational drug and alcohol use, social functioning with family and friends, psychological and emotional difficulties, employment and job satisfaction. Statistical factor analysis showed that the psychosocial outcome variables clustered into five categories: *academic-social* (comprising academic achievement, frequency of social outings with friends, unplanned pregnancy and psychological/emotional difficulties), *behaviour* (comprising behaviour problems, legal convictions and substance abuse), *employment-financial* (comprising employment status and financial independence), *family relations* (comprising frequency of activities with the biological family and degree of satisfaction with relationships among family members) and *personal relations* (comprising involvement in a personal relationship and frequency of social outings with partner). Cases with absence epilepsy had significantly poorer outcomes in the *academic-social* and *behaviour* categories ( $p < 0.001$  for both). Compared to the controls with arthritis, cases with absence epilepsy were more likely to drop out of high school (36% vs. 14%), to experience an unplanned pregnancy (34% vs. 3%) and to have a history of substance abuse (39% vs. 16%). Although most seizure-related factors did not correlate with psychosocial outcome, cases with persisting seizures had the worst prognosis, with 42% of this group reporting ongoing psychiatric/emotional difficulties. However, the poorer outcome in the epilepsy group could not be attributed solely to ongoing seizures, as even those with remission of epilepsy had significantly poorer outcomes in the

*academic-social* ( $p < 0.03$ ) and *behaviour* categories ( $p < 0.001$ ) than the cohort with juvenile rheumatoid arthritis.

## SUMMARY

In determining prognosis in absence epilepsy, one must identify not only the seizure type but also the seizure syndrome. The majority of cases of typical absence epilepsy will fall into either CAE or JAE. While approximately two thirds of children with CAE will enter long-term remission and can discontinue AEDs, those with JAE often achieve seizure control but usually require lifelong treatment. Better refinement of prognosis may come with greater understanding of the genes involved in these epilepsy syndromes.

Psychosocial outcome is often poor in many young adults with a history of typical absence epilepsy in childhood, particularly in areas involving school, social relationships, mental health and behaviour. Remission of the epilepsy does not ensure good outcome, although those without remission have a notably worse outcome and a high risk of ongoing psychiatric and emotional difficulties. Risk counseling and remediation for many types of problems are needed to allow children with absence epilepsy to become successful adults.

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