CURRENT TOPIC

Typical absence seizures and their treatment

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Typical absences (previously known as petit mal) are generalised seizures that are distinctively different from any other type of epileptic fit.¹ They are pharmacologically unique²⁻⁵ and demand special attention in their treatment.⁶

The prevalence of typical absences among children with epilepsies is about 10%, probably with a female preponderance.⁶ Typical absences are easy to diagnose and treat. Therefore, it is alarming that 40% of children with typical absences were inappropriately treated with contraindicated drugs, such as carbamazepine and vigabatrin, according to a recent report from London, UK.⁷

The purpose of this paper is to offer some guidance to paediatricians regarding diagnosis and management of typical absence seizures. This is also important because of the introduction of new antiepileptic drugs. These are mainly tested in partial (focal) epilepsies and

there are inappropriate generalisations regarding their use in the treatment of other epilepsies.

Typical absence seizures

Typical absence seizures are defined according to clinical and electroencephalogram (EEG) ictal and interictal expression.^{1,6} Clinically, the hallmark of the absence is abrupt and brief impairment of consciousness, with interruption of the ongoing activity, and usually unresponsiveness. The seizure lasts for a few to 20 seconds and ends suddenly with resumption of the pre-absence activity, as if had not been interrupted. Although some absence seizures can manifest with impairment of consciousness only, this is often combined with the following:

- mild clonic jerks of the eyelids, corner of the mouth, or other muscles
- atonic components leading to drooping of the head, slumping of the trunk, dropping of the arms, and relaxation of the grip
- tonic muscular contraction causing head retraction or arching of the trunk
- automatisms that are common and range from lip licking and swallowing to fumbling with clothes or aimless walking
- autonomic components, such as pallor, and less frequently flushing, sweating, dilatation of pupils, and incontinence of urine.¹

EEG is pathognomonic. In more than 90% of these children, absence seizures are documented mainly during hyperventilation. Normal EEG results from a child suspected for absence seizures makes this diagnosis unlikely. The ictal EEG is characteristic, and usually has regular and symmetrical generalised discharges of 3-4 Hz "spike and slow" wave complexes, and may also have multiple spike and slow wave complexes (fig 1).¹ The background interictal EEG is usually normal. However, it should be stressed that asymmetries of the ictal discharge and focal abnormalities of mainly functional spikes are common.^{6,8,9} These should not be interpreted as evidence of focal epilepsy with secondary generalisation, which could cause errors in treatment.⁷

Epileptic syndromes manifested with typical absence seizures

The term typical absences does not refer to a stereotype symptom but to a cluster of clinico-EEG manifestations, which might be syndrome related.^{6,10}

Figure 1 Top: part of a video EEG recording of patient 1 at age 14 years before adding small doses of lamotrigine to adequate doses of sodium valproate. Numbers annotate breath counting, which stopped after the onset of the discharge. Bottom: part of a video EEG recording of patient 2 at age 8 years before changing from syrup to tablets of sodium valproate.

Four epileptic syndromes with typical absences have been recognised by the International League Against Epilepsy, namely¹⁰: childhood absence epilepsy, juvenile absence epilepsy, juvenile myoclonic epilepsy, and myoclonic absence epilepsy. The first three are genetically determined idiopathic generalised epilepsies; that is, they occur in patients with normal physical and mental states. Myoclonic absence epilepsy is categorised among the cryptogenic/symptomatic generalised epilepsies. Idiopathic refers to syndromes without an underlying cause other than a possible hereditary predisposition.¹⁰ Symptomatic epilepsies are the consequence of a known or suspected disorder of the nervous system.¹⁰ Cryptogenic epilepsies are presumed symptomatic epileptic syndromes of an unknown, hidden, or occult aetiology.¹⁰

Childhood absence epilepsy (pyknolepsy) is the archetypical epileptic syndrome of typical absence seizures with onset usually before the age of 10 years and a peak at 5–6 years. Absences are frequent (tens or hundreds each day) manifesting with sudden, severe, and brief impairment of consciousness. As a rule, absences are the only type of seizure. They usually respond well to ethosuximide or sodium valproate and remit within 2–5 years from onset.^{6–10}

Similarly, absences in juvenile absence epilepsy are severe, frequent, and the main seizure type. However, onset is often later, after the age of 10 years, and regularly generalised tonic clonic seizures and random myoclonic jerks occur. Treatment may be life long.^{6–10}

Conversely, in juvenile myoclonic epilepsy, absences occur in only one third of the patients and they are usually mild without concurrent myoclonic jerks or automatisms.^{6–10} Juvenile myoclonic epilepsy is a common idiopathic generalised epilepsy characterised mainly by myoclonic jerks after awakening and generalised tonic clonic seizures. Myoclonic jerks start in mid-teens but these may be predated by absences. Juvenile myoclonic epilepsy is often mild and responds well to treatment. However, appropriate medication, usually with sodium valproate may be needed, even many decades after cessation of seizures.

Myoclonic absence epilepsy occurs mainly in children with learning difficulties or other neurological deficits. Absences are associated with rhythmic myoclonic jerks of the facial muscles, head, and limbs. The prognosis is poor.^{6–10}

Other epileptic syndromes can be associated with typical absences, such as eyelid myoclonia with absences (Jeavons syndrome), perioral myoclonia with absences, stimulus sensitive absence epilepsies, and others awaiting further studies and confirmation.⁶ Of these syndromes, eyelid myoclonia with absences consists of pronounced eyelid myoclonia followed by brief and mild absence. Main seizure precipitants are eye closure and photosensitivity. Onset is in childhood and seizures usually persist into adult life, often with infrequent generalised convulsions.⁹

Absence seizures may also manifest with subtle clinical manifestations during the typical 3 Hz spike wave discharges. These are inconspicuous to the patient and imperceptible to the observer (phantom absences). In these cases, medical consultation is sought only after a generalised tonic clonic seizure, probably long after the onset of absences.¹¹

Symptomatic typical absences mainly as a result of frontal lesions are well established but these are extremely rare.¹²

Biological basis

Absences are provoked by an abnormal thalamo-cortical circuitry that activates abnormal oscillatory rhythms, generating the generalised 3 Hz spike and wave discharges of typical absence seizures.^{2–5} The basic cellular mechanisms involve low current T calcium channels; ethosuximide exerts its anti-absence effect by blocking these channels.

GABA_B is the neurotransmitter that appears to play the most prominent role. GABA_B agonists, such as baclofen, aggravate and GABA_B antagonists suppress absences.^{2–5} Vigabatrin¹³ and tiagabine¹⁴ are GABA-ergic drugs, which interfere with degradation or re-uptake of GABA, and thus induces absences and absence status epilepticus.

Differential diagnosis

The differential diagnosis of typical absence seizures with severe impairment of consciousness in children is relatively easy, although such seizures can be missed if they are mild, or in babies, if they are not associated with myoclonic components.⁶ Their brief duration with abrupt onset and termination, their daily frequency, as well as their nearly invariable provocation with hyperventilation makes them one of the easiest types of seizures to diagnose. Automatisms, such as lip smacking or licking, swallowing, fumbling with clothes, or aimless walking, are common and should not be taken as evidence of complex partial (focal) seizures, which require entirely different management. In practical terms, a child suspected of having typical absences should be asked to over-breathe for three minutes while standing, counting his/her breaths, and with hands extended in front of him/her. This will provoke an absence in as many as 90% of affected individuals.

Typical absence seizures of idiopathic generalised epilepsies are also easy to differentiate from atypical absences that occur only in the context of mainly severe symptomatic or cryptogenic epilepsies of children with learning difficulties, who also suffer from frequent other types of seizures such as atonic, tonic, and myoclonic seizures.^{1–10}

The EEG should confirm the diagnosis of typical absence seizures in more than 90% of affected children, with ictal recordings mainly during hyperventilation.^{1–10} Focal spike abnormalities and asymmetrical onset of the ictal 3–4 Hz spike wave discharges are common,^{6–8} and may be a cause of misdiagnosis, particularly in resistant cases.⁷ Ideally, all children with absence seizures should have video EEG

recordings in an untreated state because these might reveal features favouring a specific epileptic syndrome and, therefore, determine long term prognosis and management.⁶ If this is not possible, I suggest that it is mandatory that the clinical manifestations of the seizures are documented with camcorders by the parents or the treating physicians. I advise them to videotape the absences while the child is overbreathing for three minutes, holding his/her hands in front, and counting his/her breaths. This might be particularly useful if absences are resistant to treatment, other seizures develop, or for future genetic advice.

Treatment

Ethosuximide and sodium valproate are equally effective as monotherapy in controlling the absences of more than 80% of children and there appears to be no clear benefit in measuring plasma concentrations.¹⁵ Many clinicians prefer sodium valproate because this drug, as opposed to ethosuximide, also controls myoclonic jerks and generalised tonic clonic seizures, but this might not be of concern in the pure form of childhood absence epilepsy, which is not complicated by other types of seizures.^{6 10 15} Monotherapy should not be abandoned before making sure that the maximum tolerated dose has been achieved if smaller doses have failed. There is also an anecdotal report,² which I have confirmed (fig 1), whereby children might not respond to syrup of sodium valproate, despite adequate concentrations, but seizures stop if this is replaced by tablets of sodium valproate. It is also anecdotal experience that when seizure cessation has been achieved, sodium valproate can safely be reduced to more moderate doses without relapses.

If monotherapy fails or unacceptable adverse reactions appear with sodium valproate or ethosuximide, replacement of one by the other is the alternative. More than half of the cases resistant to monotherapy do well when these two drugs are combined.¹⁵

A new extraordinary development in the management of typical absence seizures came from our open studies documenting the dramatic beneficial effect of extremely low doses of lamotrigine, added to adequate doses of sodium valproate (fig 1).^{16 17} Although this has important practical and theoretical implications it is often not cited and may lead to failures and unacceptable side effects if not well understood.

We found^{16 17} that:

- absences stopped in nearly half of the patients immediately after small doses (25–50 mg) of lamotrigine were added to adequate doses of sodium valproate (fig 1)
- patients would relapse if sodium valproate was reduced, despite increasing doses of lamotrigine
- patients who did not respond to small doses did not benefit by increasing lamotrigine. This beneficial effect of lamotrigine was maintained in 4–5 years of follow up. It is also our experience that some other patients we saw after these reports relapsed when

lamotrigine was increased, despite the initial good response when it was first introduced in small doses. It should be of concern that no benefit was achieved in some by reducing lamotrigine again. This is probably the result of a pharmacodynamic interaction of small doses of lamotrigine with adequate doses of sodium valproate.^{16 17} Lamotrigine is either ineffective,^{5 18} or has a weak anti-absence effect¹⁹ in animal models.

Based on our experience, our approach for the management of cases resistant to sodium valproate is to escalate lamotrigine according to clinical response and not to recommended “therapeutic” doses. We ask the patient to add 25 mg lamotrigine (10 mg for a child 5–10 years old) to the existing regimen with sodium valproate. If seizures stop, we discourage any other modification. If in two weeks no significant change occurs or seizures improve, we add another similar dose of lamotrigine and give the same advice as above. According to their response, similar increments at the same intervals may be advised for a higher total dose of lamotrigine, or until unwanted adverse effects occur.

Acetazolamide²⁰ and benzodiazepines²⁰ might also be tried in the few remaining cases of failure with the above three drugs. Clonazepam, sometimes in small doses, might be particularly effective as “add on” in the treatment of absence seizures with myoclonic components, such as eyelid myoclonia with absences or myoclonic absence epilepsy.⁶ Felbamate was probably a good drug for absences but it has been withdrawn because of serious adverse reactions.

CONTRAINDICATED DRUGS

Carbamazepine,⁷ vigabatrin,¹³ and tiagabine¹⁴ are contraindicated in the treatment of absence seizures, irrespective of cause and severity. This is based on clinical and experimental evidence.^{7 13 14} In particular, vigabatrin and tiagabine, which are GABA agonists, can be used to induce (not treat) absence seizures and absence status epilepticus. The error of prescribing these drugs in the treatment of absence seizures would be of the same magnitude as prescribing a gluten rich diet in the treatment of coeliac disease. Similarly, phenytoin, phenobarbitone, and gabapentin should not be used in the treatment of absence seizures because they are ineffective.⁵

ILLUSTRATIVE “RESISTANT” CASES WHO RESPONDED WELL TO MILD MODIFICATIONS OF THEIR DRUG TREATMENT

Figure 1 shows EEG ictal samples of typical absence seizures in two girls with intractable typical absences, who became free from seizures after adding small doses of lamotrigine to sodium valproate (patient 1) and changing from syrup to tablets of sodium valproate (patient 2).

Patient 1

This normal woman had onset of typical absence seizures at age 7 years. These lasted for 10–20 seconds each and occurred in tens or

hundreds each day, frequently with incontinence of urine. On video EEG at age 14 years, five clinical absences lasting from nine to 17 seconds were recorded. Clinically, there was severe impairment of consciousness, with consistent eyebrow rhythmic myoclonus, automatisms, and vocalisations. Ictal EEG consisted of high amplitude generalised spike/multiple spike and slow waves at 3 Hz (fig 1). Interictally, there were brief generalised bursts of spikes and multiple spikes as well as focal sharp waves occurring independently on both sides of the anterior brain regions.

Ethosuximide at age 7 was partially beneficial but was discontinued because of adverse effects. On referral, aged 14, she had three to 20 absences each day despite 1000 mg valproate daily. Increasing valproate to 1500 mg had partial benefit. The addition of 125 mg ethosuximide three times daily could not be tolerated. However, all absences stopped after the first dose of 50 mg lamotrigine every other day added to 1500 mg valproate. Absences reappeared when she stopped valproate, despite doubling the dose of lamotrigine. She has remained free from seizures in the past six years of follow up on 1000 mg valproate and 50 mg lamotrigine. Only twice, aged 15, she had a generalised tonic clonic seizure preceded by clusters of absences, after missing her medication.

Patient 2

This normal girl aged 8 years had uncontrollable typical absences from the age of 5 years. Absences were severe, of 8–15 seconds duration, and as frequent as tens or hundreds each day. Despite adequate doses of syrup of sodium valproate, ethosuximide, and lamotrigine, alone or usually in combination, she continued to have frequent daily absences. When she was first seen at age 8 she was on 600 mg syrup sodium valproate and 150 mg lamotrigine. On video EEG, seven clinical absences lasting from eight to 15 seconds were recorded at that stage. Clinically, there was severe impairment of consciousness, often with automatisms associated with high amplitude 3 Hz generalised spike and slow wave discharges (fig 1). All absences stopped within a week of replacing the syrup with tablets of 800 mg sodium valproate and reducing lamotrigine. One year later she remained seizure free on tablets of 600 mg sodium valproate and 50 mg lamotrigine.

Absence status epilepticus

Absence status epilepticus is a prolonged seizure lasting for more than half an hour, sometimes hours or days.^{21 22} Clinically it is characterised mainly by the continuous impairment of consciousness (absence) concurrent with EEG generalised discharges of spikes/polyspikes and slow wave discharges. Impairment of consciousness may be mild or severe and associated with other mainly motor disturbances, as described in the absence seizure. The symptoms can be continuous or repetitive without full recovery before the cessation of the status. The ictal EEG is characteristic, usually with regular and symmetrical generalised

discharges of 1–4 Hz spikes or polyspikes and slow waves. The background interictal EEG might be normal in idiopathic cases or abnormal in symptomatic cases. Like absence seizures, absence status epilepticus is categorised as typical of mainly idiopathic generalised epilepsies or atypical of symptomatic and cryptogenic generalised epilepsies. Furthermore, absence status epilepticus can be caused by the introduction or withdrawal of certain drugs (mainly diazepam), intoxication, or electrolyte disturbances. It may also be caused by severe brain anoxia or other brain damage as reported in adult populations.²²

Typical absence status epilepticus occurs in 10–30% of idiopathic generalised epilepsies with absences,^{21 22} and it might be incompatible with the pure form of childhood absence epilepsy.²²

TREATMENT OF ABSENCE STATUS EPILEPTICUS

The traditional treatment is intravenous diazepam or sodium valproate but this may be available only in hospitalised patients. Self administration of rectal preparations of diazepam as soon as the first symptoms appear may stop absence status, but this advice is often not followed. Some patients could avoid a generalised tonic clonic seizure by taking a substantial amount (usually double their daily dose) of sodium valproate at the onset of absence status. A new important development is that buccal application of midazolam may stop absence status and prevent the development of generalised tonic clonic seizures.^{23 24} Five to 10 mg (1–2 ml) of midazolam dissolved in 5 ml of peppermint (otherwise it smells and tastes awful) is swirled in the mouth for five minutes and then spat out. In uncooperative patients, the lips are parted and the same solution is squirted through a syringe around the buccal mucosa.^{23 24} Swallowing midazolam does not harm the patient. On preliminary evidence, I am of the opinion that this is probably the best practical treatment option in absence status epilepticus. However, the individuals involved should be informed that midazolam is not yet licensed for this type of treatment.

Withdrawing antiepileptic medication

This is syndrome related.⁶ In the pure form of childhood absence epilepsy, drug treatment can be withdrawn gradually (within 3–6 months) after 2–3 years free from seizures. In others, such as juvenile absence epilepsy, juvenile myoclonic epilepsy, or eyelid myoclonia with absences, treatment might be life long.⁶

Finally, it is my conviction that the management of epilepsies cannot be satisfactory unless the current theme of “how to treat epilepsy” is redirected to “how to diagnose and treat epilepsies”.⁹

Addendum

While this report was in press, a multicentre study was published on lamotrigine monotherapy in newly diagnosed patients with typical absence seizures.²⁵ The design was “responder enriched” with open label dose escalation followed by placebo controlled,

double blind testing of lamotrigine. A patient was considered "seizure free" only on hyperventilation and EEG (HV-EEG) documentation, which may not be an absolute criterion (see text). Whether the patients were also seizure free in their daily life was not considered and is not mentioned.

Forty two children and young adolescents completed the open label lamotrigine escalation phase. The patients had HV-EEG testing after each dose increment. If this failed to induce absences (a probability that is likely to increase with serial trials over time, reducing number of absences or both) the patient was considered seizure free and entered the second double blind phase. Thirty (71.4%) patients met this criterion with a median dose of 5 mg/kg/day. The earliest this was achieved was four weeks to probably longer than two months. However, for more than half of the patients the upper target dose was increased to 15 mg/kg/day (or a maximum of 1000 mg/day), which is double the recommended maximum dose, also demanding more HV-EEG trials.

The vulnerability of the "seizure free" criterion is shown when these patients were tested for a second time in the double blind phase. Five of 14 "seizure free" patients had absences despite receiving the same dose of lamotrigine. However, 11 of the 14 patients relapsed when lamotrigine was replaced by placebo, but three remained seizure free. The difference was significant ($p < 0.02$) providing that both groups had equal numbers of tests. In untreated or partially treated patients more HV-EEG tests are expected to be positive than negative, and the probability of having at least one negative trial is higher with increasing numbers of trials.

Therefore, according to these results lamotrigine as a single agent is effective in probably 50% of newly diagnosed patients with typical absence seizures. For valproate this is around 80% and the effect is within days to a few weeks because of insignificant escalation problems. However, sodium valproate may have unacceptable side effects particularly in women. Lamotrigine may be an alternative for these patients. A comparative study of lamotrigine versus sodium valproate is well overdue. We also need to understand better the interaction between these two drugs as detailed in the text.

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