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Therapeutic response of absence seizures in patients of an epilepsy clinic for adolescents and adults

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Summary. Responses of seizures to therapy is one of the most important prognostic factors in epilepsy. Absences are among the seizure types with a good response to antiepileptic drug treatment and, usually, remission before adult age. Absence patients attending an epilepsy clinic for adults can be expected to represent a group with negative bias because they have not yet remitted. Furthermore, the majority have additional generalized tonic-clonic seizures, which is a recognized negative factor in prognosis. We studied 229 adolescents and adults who were under our care for at least 2 years, and divided them into three groups according to their becoming absence free for at least 1 year: (1) responders to simple therapy (one anti-absence drug in doses not exceeding 2 g/day); (2) responders to complex therapy (one anti-absence drug in higher dose or combination of anti-absence drugs); (3) non-responders. Groups 1 and 2 can be considered jointly as responders as opposed to the non-responder group. Similarly, groups 2 and 3 can be considered jointly as a group with poor as opposed to good therapeutic response. It was found that significant differences exist between good and poor responders, and 15 factors which had a negative effect on therapeutic response could be identified. No single factor or combination was responsible for non-response, but non-responders had the highest score of negative factors. Patients with complete absence control had a 93% chance of total seizure control, and, with constant medication, relapses after 1 year of control were very infrequent. The conclusion of this study is that complete absence control is of great prognostic importance for patients having this seizure type. With active treatment using, if necessary, high doses of succinimides or valproic acid alone or in combination, excellent results can be achieved even in a patient group biased towards a poor prognosis.

Key words: Absences – Prognosis – Therapy response

Introduction

Absences are counted amongst the most benign types of epileptic seizures. With correct treatment, complete control is expected in up to 95% of patients with absences as the only seizure type [6]. It is generally accepted that this excellent prognosis is considerably worsened by the occurrence of generalized tonic-clonic (GTC) seizures [1, 5, 7, 12, 14, 15].

Some authors, however, deny this [2] and believe that only one or two GTC seizures will not affect the prognosis [9] or state that their negative effects depend on their number [1]. This is, however, not generally believed [5].

Patients who only have absences usually stop having seizures before adulthood, owing to the early age of onset and benign course of this disorder. It might therefore be expected that absence patients attending an epilepsy clinic for adolescents and adults represent a selected group with less favourable prognosis. An investigation of their therapeutic response may shed more light on factors influencing prognosis and therapy of absences.

Material and methods

This study considered all outpatients with a diagnosis of absence (alone or together with other seizures) who were under our care for at least 2 years during the period from 1 January 1974 to 31 March 1983. They may have entered our care before that period. Most patients were already on some medication when we first saw them, but only those were included who still had absences when starting treatment in our unit. This includes the possibility that a patient whom we had started to treat before 1974 was already absence free on 1 January 1974. If he had remained in our care for at least 2 years thereafter, he was included.

There were 229 patients (116 female and 113 male), 208 of whom also suffered from GTC seizures.

Absence subtypes. The diagnosis of absence subtypes have been based on routine video recordings since 1975. In those patients of this study who ceased having absences before that time, the subtypes were diagnosed from the reports of witnesses. Absences with impairment of consciousness only were diagnosed in 101 patients (44%), absences with mild clonic components in 91 (40%) and absences with automatisms in 27 (12%). The remaining subtypes of the International Classification of Epileptic Seizures [3] were infrequent and will not be considered. Apart from the subtypes contained in the international classification, attention was paid to the type of movement occurring during an absence seizure. It was found that the retroversive movement of the head typical of pyknolepsy or childhood absence [10], was present in 30 patients (13%).

In 122 patients (68 females and 54 males) the absence recurrence was pyknoleptic (i.e. several to many times every day (for more detailed discussion of absence recurrence and

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its significance see Janz [10]). In 107 patients (48 females and 59 males) absences occurred less frequently than every day (non-pyknoleptic absences). The differences in sex distribution are not significant.

The mean age of onset of *absences* in the pyknoleptic group was 8.3 ± 4.5 years (range 2–27), in the non-pyknoleptic group 14.8 ± 8.3 years (range 2–47).

Mean age of onset of *epilepsy* was 8.1 ± 4.5 years (range 1–27) in the pyknoleptic group, and in the non-pyknoleptic group 13.4 ± 7.0 years (range 1–47). Thus, the frequency of recurrence seemed to distinguish clearly between childhood and juvenile absence epilepsies (U-test, $P < 0.001$).

According to the therapeutic response, each patient was assigned to one of three classes: responders to simple therapy, responders to complex therapy, and non-responders. A responder was a patient who became free of absences for a minimum of 1 year during the study period. Non-responders were patients whose absences could not be controlled for 1 year. "Simple" therapy was defined as therapy with only one drug for absence, valproate (VPA) or ethosuximide (ES), in a daily dose not exceeding 2 g. Twelve patients whose treatment had started long before the onset of this investigation period had been treated with mesuximide (6 responders). A daily dose of this up to 1.5 g was considered to represent "simple" therapy. "Complex" therapy was defined as monotherapy with a higher dose of one of these drugs or a combination of various anti-absence drugs. Additional drugs for other seizure types (such as phenytoin, carbamazepine, or phenobarbitone, used for 155 patients) were not considered to represent combination therapy for the purpose of this study. Possible therapeutic actions of such drugs on absences were, thus, disregarded. As the dose limit for simple therapy is rather high, patients in the group of complex therapy were indeed difficult to treat.

Statistical treatment of the material included comparisons of

a) all three response groups;

b) the combined groups of responders versus the non-responders;

c) responders to simple therapy with the combined groups of responders to complex therapy and non-responders ("good responders" versus "poor responders").

The statistical techniques used were chi-square test and U-test.

Each mode of therapy led to absence control in one-half to two-thirds of the patients who received it (Table 1). The average number of modes of therapy applied per patient was 1.3. Medication previous to our therapy was not considered.

Serum drug levels are not considered in this study because in most patients they were only available in the later phases of treatment.

Table 1. Methods of absence therapy and their efficiency

Treatment	n	Complete absence control
VPA only	126	63%
ES only	82	60%
MS only	12	50%
VPA + ES	60	65%
Other	14	57%

Combination with antiepileptic drugs other than anti-absence drugs is not taken into account. Unsuccessful modes of therapy were replaced by others. In 134 patients (58.5%), the first therapy controlled the absences; 79 patients received between two and four modes of therapy with an average of 2.3. The remaining 16 had only one mode of therapy, and their absences remained uncontrolled.
VPA = valproate; ES = ethosuximide; MS = mesuximide

Table 2. List of variables tested

Clinical
Sex
Age of onset of epilepsy and absences
Age of onset of our therapy
Hereditary predisposition
Febrile convulsion (simple or complicated)
Developmental delay
Mental retardation
Abnormal neurological findings
Abnormal CT findings
Absence frequency (pyknoleptic–non-pyknoleptic)
Combination with other seizure types
Frequency of accompanying GTC seizures
Diurnal distribution of GTC seizures (awakening, sleep, random)
History of GTC or absence status
Focal signs in GTC seizures
Absence subtypes
EEG
Spike-wave complex
mono-SW or poly-SW
frequency (< 3, 3–3.5, > 3.5/s) (stable or unstable)
regular or irregular
symmetric or asymmetric
accentuation (F–C, P–O, T, none)
maximal duration (< 5, 5–10, > 10 s)
appearance (spontaneous or provoked by hyperventilation or photic stimulation)
Photosensitivity
Focal epileptic discharges
Background activity

Results

Of the patients, 188 (82%) became absence free for at least 1 year, but 41 (18%) patients did not. Of the absence free patients, 123 or two-thirds responded to simple, 65 or one-third to complex therapy. The three response groups were studied in relation to clinical and EEG findings (Table 2).

Unexpectedly, there seemed to be only minimal differences between responders to complex therapy and non-responders. The differences, if any, separated both these groups (poor responders) from responders to simple therapy (good responders). The following factors proved relevant (Table 3).

Patients with non-pyknoleptic recurrence of absence responded better than those with pyknoleptic recurrence. Absences with mild clonic components had a poorer response than all others. Absences with impairment of consciousness only seemed to respond better than average. The reliability of this finding, however, is doubtful, as discussed below.

All patients who had no GTC seizures were responders to therapy although sometimes only to complex therapy (Table 4). A small number of GTC seizures had no significant effect, but more than 10 GTC seizures were clearly correlated with poor response to therapy ($P < 0.001$). If the GTC seizures occurred during sleep or in random distribution, the response

Table 3. Factors relevant for response to therapy

		Good responders	Poor responders		$P <$
		Responders to "simple" therapy	Responders to "complex" therapy	Non-responders	
All patients	(229)	123	65	41	
Pyknoleptic recurrence	(122)	56	41	25	0.02
Absence with impairment of consciousness alone	(101)	64	27	10	0.01
Absence with mild clonic components	(91)	39	28	24	0.01
GTC seizures, $n > 10$	(123)	53	40	30	0.001
GTC in sleep or at random	(32)	10	14	8	0.02
History of absence status	(87)	38	26	23	0.02
History of GTC status	(14)	3	8	3	0.02
Developmental delay	(20)	5	7	8	0.01
Mental retardation	(19)	4	6	9	0.001
Slow EEG background activity	(65)	27	22	16	0.05
Spike-waves unprovoked	(117)	54	38	25	0.05
Spike-wave bursts of >5 s	(101)	38	36	27	0.001
Asymmetry of spike-waves	(96)	44	32	20	0.05

All statistical differences are between good and poor responders (χ^2–test, two-tailed); GTC, generalized tonic-clonic

Table 4. Influence of GTC seizure frequency on response to therapy of absences

	"Simple" responders	"Complex" responders	Non-responders
No GTCS	15	6	0
≤10 GTCS	55	19	11
>10 GTCS	53	40	30

Intermediate frequencies of ≥3, and ≥5 GTC seizures were also tested but dit not differ from ≥10

to therapy of absences was poorer than with GTC seizures occurring on awakening, the type much more common in these patients ($P < 0.02$).

The association with other seizure types (mainly myoclonic) in 42 patients had no negative effect.

Histories of either grand mal or absence status and signs of organic brain damage were indicators of poor response to therapy. Of the many epileptic EEG parameters studied only three had a negative bearing on response to therapy: asymmetry of spike-wave (SW) discharge, unprovoked SW discharge, and SW discharge of more than 5 s duration.

Focal clinical signs were not encountered, but 27 patients had focal interictal EEG abnormalities (11 epileptic, 16 non-specific). Of these, 14 responded to simple therapy (4 epileptic, 10 non-specific). Focal epileptic abnormalities could perhaps prove to be a negative factor if more patients were studied, but were not shown to be so in this study.

Earlier onset of epilepsy but not of absences, later onset of therapy, and longer duration of absences at onset of therapy were negative factors (Table 5).

Therapeutic non-response could be the consequence of an accumulation of negative factors. To test this, we looked at how many of the 15 significant negative factors derived from Tables 3–5 (Table 6) were present in each individual, and compared the average scores thus obtained for every response group. It turned out that there were indeed significant differences between the three groups, the non-responders presenting the highest average of 7.1 negative factors (Table 7).

Significance of 1-year absence control. In 154 (91%) of the 169 patients with more than one seizure type and complete control of absences, not only the absences but all seizure types were controlled. Thus, 173 (76%) of all patients became completely seizure free.

The mean duration of follow-up for our patients was 7.3 ± 5.9 years (range 2–26), which allows some conclusions on long-term prognosis. With constant medication, a relapse after 1 year without absences was seen in only 5 patients. In 10, a relapse without change of the prescribed dose was due to non-compliance, and in 21 patients late relapse followed

Table 5. Influence of time factors on response to therapy of absences

	"Simple" responders (123)		"Complex" responders (65)		Non-responders (41)	
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range
Onset of epilepsy	11.3 ± 6.8	(1–47)	10.1 ± 6.2	(0–30)	9.0 ± 4.3	(2–18)
Onset of absences	11.9 ± 7.5	(2–47)	10.6 ± 6.2	(2–30)	10.7 ± 7.8	(2–40)
Onset of therapy	23.5 ± 11.3	(5–61)	25.5 ± 10.8	(6–54)	27.2 ± 11.4	(3–51)

Poor therapy response (responders to "complex" therapy plus non-responders) is correlated with earlier onset of epilepsy ($P < 0.05$), and with longer interval from onset of absences to onset of therapy at our unit ($P < 0.01$).

When the cohort was split at the mean ages of these factors, and the subgroups compared, epilepsy onset before age 11 years, persistence of absences beyond (i.e. therapy onset at our unit after) age 25, and absence persistence for more than 12 years (i.e. interval from onset of absences to onset of therapy at our unit) appeared as negative factors. These are used for Tables 6 and 7

Table 6. List of negative factors

1. Pyknoleptic recurrence of absences
2. Absence with mild clonic components
3. More than 10 GTC seizures
4. GTC seizures in sleep or at random
5. History of absence status
6. History of GTC status
7. Developmental delay
8. Mental retardation
9. Slow EEG background activity
10. Spike-waves unprovoked
11. Spike-wave bursts of more than 5 s
12. Asymmetry of spike-waves
13. Onset of epilepsy before age 11 years
14. Persistence of absences beyond age 25
15. Persistence of absences for more than 12 years

Table 7. Influence of accumulation of negative factors

Response groups	Mean scores ± SD	Range
Good responders (responding to simple therapy)	4.1 ± 1.8	(0– 9)
Poor responders		
Responders to complex therapy	6.1 ± 2.3	(2–12)
Non-responders	7.1 ± 2.0	(3–11)

Both the difference between good and poor responders ($P < 0.001$), and between responders to complex therapy and non-responders ($P < 0.05$) are significant (U-test)

reduction of the drug dose with the aim of terminating therapy. (In 15 patients, absence drugs have been stopped without relapse.)

Whereas control of GTC seizures was achieved in 93% of patients with complete absence control, this was true only for 25 (60%) of the 41 patients still having absences ($P < 0.0005$).

It can be concluded that efficient therapy of absences is paramount and 1 year of absence control is a good indicator of control of all seizure types as well as of excellent long-term prognosis on stable doses of medication.

Discussion

The therapeutic response in this group of adolescents and adults still having absences was better than expected with complete absence control in 82%. This demonstrates the efficacy of absence therapy with succinimides or valproate alone or in combination (accompanied in most cases by a drug for GTC seizures, phenobarbitone, primidone, phenytoin or carbamazepine) in patients considered to have a less favourable prognosis than those with absences alone [1, 5–8, 13, 15]. Therapy was difficult in many instances, and required rather high doses of medication.

Factors indicative of poor therapeutic response which could be identified in this study (Table 6) were not surprising, and were in accordance with the literature on prognosis of absences [1, 2, 4–9, 11, 13–15]. At variance with our findings, it has been suggested that short SW discharges [1, 5] and seizure onset after age 10 years [1] are negative factors, but this has not been confirmed by all investigators.

Some expected negative factors could not be demonstrated. Thus, slow spike-waves [4] were predominant in 20 patients, 10 of whom, however, responded to simple therapy. The clinical seizure type seems more important for therapy response than the frequency of the SW discharge.

Absences with mild clonic components showed poorer response than others. The finding that absence with impairment of consciousness only responded better than other types has to be interpreted with some reservation: absences with impairment of consciousness only are more common in this series than in patient groups with subdiagnoses based on video analysis. In this study, the absence type in many cases is still based only on reported observations. In patients with complete absence control, the supposed absence type could not be reviewed by video study which could be done in patients still having absences. The apparent number of patients with absence with impairment of consciousness alone may therefore be expected to be unusually high in the group of therapy responders.

Other items that did not emerge as relevant were association with seizures other than GTC, spatial distribution of SW discharge and photosensitivity.

The most interesting finding was that significant differences were only occasionally between responders and non-responders but were mainly between responders to simple therapy and the combined groups of poor responders. No significant differences could be detected between responders to complex therapy and non-responders. Thus, the negative factors found indicate that there is a group of patients who are difficult to treat but not a separate group of cases resistant to therapy.

It is uncertain what differentiates the non-responders from other patients. One might wonder if non-responders have received the same kind of treatment. Of the 41 non-responders, 13 or one-third are confessed non-compliers: they have taken the drugs in doses lower than prescribed, irregularly, or not at all. For three reasons, however, one cannot assume that non-compliance is their sole or decisive reason for therapeutic failure. First, it is not known if there are fewer non-compliers in the two responder groups; many of them will not be detected as long as seizures are absent. Second, the reasons for non-compliance are not always clear; in some individuals, this seemed to be due to poor drug tolerance. Third, the negative factors for therapeutic response in this small group of 13 confessed non-compliers did not appear to be different from those of the other non-responders.

Comparison of the prescription of the anti-absence drugs in the groups of non-responders and responders to complex therapy revealed that monotherapy in non-responders had often not reached the dose of 2 g daily. Thus, in these cases it would appear that one cannot speak of drug resistance. The concept of drug resistance that applies for drugs like phenytoin, phenobarbitone or carbamazepine is that a patient is resistant to the drug if seizure control cannot be achieved without signs of toxicity, toxicity being defined as typical clinical toxic signs in the presence of drug levels above the "therapeutic range". This concept, however, cannot easily be applied to ES and VPA because these drugs have no toxic range in the conventional sense. Adverse reactions depending on individual drug levels may occur at concentrations which are low in comparison to those tolerated by other patients. In our patients who did not receive maximal doses of monotherapy, this was due to one of three reasons. In some patients, intolerable side-effects such as hiccups or forced normalization [16, 17] with ES, tremor, weight gain or hair loss with VPA occurred at moderate doses. In other patients, initial partial

response to the drug was not followed by further reduction of absence and SW discharges with increasing dose and serum levels, making further dose increase unreasonable. Finally, some patients did not accept higher doses for reasons which were not always clear, but at least some indicated that they developed symptoms of intolerance.

When combination therapy of ES and VPA is considered, a clearer picture emerges. We looked at the 61 patients who received this combination and arbitrarily considered high dose combinations, those where the dose of one drug exceeded 2 g, or that of each drug 1 g. Of the 39 responders, 17 took a low-dose combination; 18 of 22 non-responders received a high-dose combination. The difference is significant ($P < 0.05$) and indicates drug resistance in the conventional sense in this group of 18 patients who did not respond to high-dose combinations.

We conclude from these results that drug resistance is not a specific negative characteristic of some absence patients but that there is a continuum from very benign to very difficult cases. The patients most resistant to therapy are characterized as a group by having more of a series of negative factors, which together make therapy increasingly difficult, sometimes reaching a level with which our present drugs cannot cope.

Note added in proof

After termination of this manuscript, we received the recent article of Sato S, Dreifuss FE, Penry JK, Kirby DD, Palesch Y (1983) Long-term follow-up of absence seizures. Neurology (Cleveland) 33:1590–1595. The results of this important study, some in accordance and some different from our findings, could thus not be discussed.

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