THE IMPORTANCE OF NEUROPSYCHOLOGICAL SIDE EFFECTS OF ANTIEPILEPTIC TREATMENT FOR THE QUALITY OF LIFE IN EPILEPTIC CHILDREN AND ADOLESCENTS

IMPORTANȚA EFECTELOR SECUNDARE NEUROPSIHOLOGICE A TRATAMENTULUI ANTIEPILEPTIC PENTRU CALITATEA VIEȚII LA COPIII ŞI ADOLESCENȚII CU EPILEPSIE

H. Mayer, Ph.D.,
Epilepsiezentrum, Klinik für Kinder u. Jugendliche, 77694 Kehl-Kork, Landstrasse, Germany

Rezumat

Funcțiile neuropsihologice şi comportamentale pot fi afectate la pacienții epileptici, mai ales în copilărie, când aceste funcții se dezvoltă. Un grup important de factori de risc îl reprezintă efectele secundare neuropsihologice şi comportamentale ale tratamentului antiepileptic. Pentru o perioadă lungă , investigațiile asupra efectelor secundare cognitive şi comportamentale au jucat doar un rol nesemnificativ în cadrul literaturii ştiințifice. De asemenea, în practica clinică psihologică efectele secundare au fost subevaluate.

În ultima perioadă, înțelegerea din partea noastră a impactului medicației antiepileptice clasice asupra funcționării neuropsihologice şi comportamentale a crescut considerabil. Până acum a existat o lipsă a experimentelor şi studiilor clinice controlate.

Lucrarea prezintă date empirice despre efectele secundare ale medicamentelor antiepileptice clasice şi mai noi.Se va demonstra că impactul major al efectelor secundare implică procesare şi viteza mentală. Aceste funcții sunt puternic implicate în cadrul funcțiilor developmentale şi a performanței şcolare. Tratamentul antiepileptic poate fi privit ca o intervenție de succes, dacă şi numai dacă găsim un echilibru între profitul eliberării de crize şi prețul, care trebuie să fie plătit pentru aceasta în ceea ce priveşte efectele secundare şi neajunsurile care se răsfrâng asupra calității vieții.

Cuvinte cheie: copii şi adolescenți epileptici, tratament antiepileptic, efecte secundare neuropsihologice, calitatea vieții

Abstract

Neuropsychological and behavioral functions are at risk in epileptic patients, especially in childhood, when these functions are developing. An important group of risk factors are the neuropsychological and behavioral side effects of the antiepileptic treatment.

For a long time investigations into cognitive and behavioral side effects have played only an unimportant role in the scientific literature. Also in the clinical practice psychological side effects were undervalued. During the last decade our understanding of the impact of the classical antiepileptic drugs on neuropsychological and bevavior functioning has considerably increased. Until now there has been a lack of controlled experimental and clinical studies.

The paper presents empirical data on neuropsychological side effects of classical and newer antiepileptic drugs. It will be demonstrated, that major impact of side effects concerns mental processing and speed. These functions are strongly involved in developmental functions and school performance. Antiepileptic treatment can be regarded as a successful intervention, if and only if we find a balance between the profit of freedom from seizures and the price, which has to be paid for as side effects and impairments in life quality.

Key-words: epileptic children and adolescents, antiepileptic treatment, neuropsychological side effects, quality of life

Introduction

Problems of learning and behavior are overrepresented in children and adolescents with epilepsy (Aldenkamp et al., 1990; Mayer & Christ, 1992), because the development of neuropsychological and behavioral functions are at risk in these patients. Three groups of risk factors are empirically evidenced (Hermann & Whitman, 1996). At first central nervous system dysfunctions such as congenital or aquired brain damages or dysfunctions have to be mentioned, also ictual and interictual neurophysiological disorders. The second class of risk factors comprehends social and emotional factors like overprotection by the familiy and the relatives or psychological handicaps such as low self esteem and self confidence, feelings of inferiority and depression. Last not least the antiepileptic treatment and their neuropsychological cognitive and behavioral side effects have to be considered as risk factors, because AEDs are not only powerful anticonvulsants they also have strong psychotropic effects (Fenwick, 1992). For a long time investigations into cognitive and behavioral side effects have played only an unimportant role in the scientific literature (Mayer, 1989).In the clinical practice psychological side effects were undervalued as well. This situation is stressed with the statement, that some children suffer more from side effects than from seizures (Stores, 1978). Undoubtedly that is an exaggeration, but it underlines the problem. During the last decade our understanding of the impact of antiepileptic drug treatment on neuropsychological and behavior functions has considerably increased Numerous papers have been published as professionals have become more and more aware that antiepileptic treatment may have adverse effects on cognition and behaviour (Mayer, 1989, Mayer Heinemann.

From a theoretical point of view that had to be expected, because AEDs are psychotropic drugs, which have a powerful influence on excitatory and inhibitory processes in the brain. These processes exert influence on the neuroregulation of behaviour, too.

Antiepileptic treatment can only be regarded as a succesfull intervention, if we find a balance between the profit of freedom from seizures and the price, which has to be paid for (as) side effects and impairments in life quality.

It is important to stress, that side effects of AED can be considered as the unique impact factor on cognition and behaviour which can be changed in the short term in contrast to many of the other, often unchangable contributory risk factors.

Phenobarbitone (PB / PRM)

Phenobarbitone belongs apart from Bromide to the oldest antiepileptic compounds. Among the well established antiepileptic PB has the greatest potential for behavioural toxicity. In nearly 50% of children irritability, hyperactivity, restlessness and difficulty in getting to sleep are reported (Herranz et al. 1988; Mayer, 1989; Devinsky, 1995). Also PB has been cited for its potential cognitive effects, nevertheless the empirical support for this assumption is not so clear (Mayer, 1989). For it may be that these effects are a result of known behaviour disorders, which were described above.

Various other studies merely show subtle cognitive effects, which are detectable only by careful examination. More and more the impact on developmental functions of children is discussed, but not clearly elucidated. In order to answer these questions long-term follow-up studies are needed. Sulzbacher (1999) believes to prove a long-term decrease in cognitive functions of children. Such similar effects (likely) have to be expected because prenatal exposure to PB may cause neuronal deficits in neuronal proliferation and migration.

Side effects of Primidone are alike. (Diener & Mayer,1996).That can be expected because of the similarity in the chemical structure of both compounds. Some studies only show, that the incidence rate of adverse side effects of PRM are higher than with PB (Mayer & Diner, 1995; Herranz et al., 1988)

Phenytoin (PHT)

PHT is one of the most used anticonvulsant in the world. Especially the absence of sedation is one of the most cited property . Many studies in the last decades have shown adverse effect on cognition. It is not clear if this effect is a unique property of PHT or the consequence of a lower rate of information processing (Green, et al. , 1992). Impressive behaviour disorders as a consequence of PHT are known as progressive PHT-Encephalopathy (Trimble & Reynolds, 1976). These changes can be explained only by special idiosyncratic reactions of some patients. Also behaviour changes, which are described with PB are known. (Herranz et al., 19982; Mayer, 1989). Indeed the incidence rates are significant smaller than with other AED´s of the choice.

Carbamazepine

Undoutedley CBZ has significantly fewer rates of side effects (Devinsky, 1996). In studies which compare CBZ with PR, PB or PHT, it consistently out-performed these other drugs on tests of attention and concentration. On the other side impacts on psychomotor performance and mental speed are described, too (Gallassi, et al, 1988). Empirical data stresses the good properties of CBZ concerning cognition and behaviour (Aldenkamp, 1993) For all that it is important to assert, that for a small group of patients CBZ is not the anticonvulsant of first choice because of significant behaviour changes (Diener & Mayer, 1996)

Valproate (VPA)

Early clinical studies postulate a benefit psychotropic effect. In the meantime a lot of papers report that VPA may impair all day living activities, because of tiredness and reduces arousal. Also impairments of school-performance in children are evidenced (Gallassi, et al, 1990). It is not excluded, that reduced arousal facilitates memory problems, which are reported by Baker et al. (1997) Mayer (1999) shows that a drug induced deceleration of mental speed in children can reduce the IQ-level, which was reversible after withdrawal of the drug. He could demonstrate, that side effects of VPA do not cause learning disabilities but can lead to an impairment of central arousal and mental speed. It is not surprising that in this case also school performance can decrease. Nevertheless in the majority of patients VPA has no significant impacts on behaviour or neuropsychological functions such as memory, concentration or motor speed.

Ethosuximide (ESM)

A variety of psychological and psychiatric disorders such as tiredness, drowsiness or anxiety have been reported. Incidence rates of side effects are comparable with CBZ or VPA (Mayer & Diener, 1995). Also acute paranoid episodes are described as well in children as adults. It can be stated, that considering other drugs of first choice ESM has not experienced enough scientific attention (Mayer, 1989). Furthermore the introduction of VPA in the antiepileptic treatment had limited the scientific interest in that drug.

Lamotrigine (LTG)

Lamotrigine has enjoyed a great deal of popularity in the last years. In contrast to the popularity only a few studies were carried out in order to determine rates and qualities of side effects. Until now one can say that only a small proportion of cognitive side effects have been described (Meador & Baker, 1997). In contrast to many other anticonvulsants, the older or the newer ones, no impressive change on motor and mental speed has been observed (Martin et al. 1999). The clinical experiences with this drug are consistent with the experimental and psychometric data (Cochrane et al. 1998). For this reason some authors believe in special favourable psychotropic effect of the drug. Assessments of parents and relatives seem to confirm the experimental and clinical data (Brodbeck et al, 2006)

Whether LTG has truly unique cognitive and behavioural properties has been discussed controversely up to now (Wallace, 2001). Also the impact on a combination with other drugs was not sufficiently evaluated. It is not surprising

that LTG can cause behaviour disorders in a polytherapy regimen (Beran, 1998). May be the thesis of a favourable psychotropic effect of LTG was provoked rather from marketing departments than from empirical data. Nevertheless and above all studies with comprehensive neuropsychological assessments are needed to fully delineate the impact of LTG on cognition and behaviour especially in children. Recent findings using qualitative evaluation is supporting LTG as an anticonvulsive drug with a profile suitable for the use in children (Brodbeck et al., 2006)

Topiramate (TPM)

In the meantime TPM has proved its potency in the control of seizures. Information on its use in children is limited. Indeed, there are a lot of reports about significant rates of adverse side effects on cognition and behaviour functions. Also a decline in memory and concentration functions has been reported (Kwan, & Brodie, 2001; Huppertz, et al., 2001; Martin et al. 1999). Some papers exist, which seem to demonstrate impacts of AED polytherapy including TPM on so called "executive functions" like verbal fluency, memory span and working memory (Kockelman et al., 2004). Further investigations, independently of interests of the pharmaceutical companies, are needed to explain these relationships especially in children.

In clinical settings tiredness, drowsiness, agitation and irritability are described, too (Dichter & Brodie, 1996).. Above all in combination with valproate there is a risk of stuporous encephalopathy (Latour et al.,2004).

Undoutedly comparing with other newer anticonvulsants TPM seems to be the compound with the highest rates of side effects on cognitive and behaviour functions, above in children (Gerber et al., 2000, Coppola et al. 2007). Also the assessment of parents and seem to confirm the neuropsychological and experimental findings (Bootsma et al., 2006)

Oxcarbazepin (OXC)

The antiepileptic properties of OXC has been proven in a lot of placebo-controlled double blind studies. There is no doubt that OXC can be considered as a possible alternative, when CBZ is not well tolerated. (Homberg, et al., 2001). Based on a similar chemical structure OXC has been considered as "CBZ" without side effect but with a favourable effect on cognition and behaviour (Kohler & Hofmann, 1998). In the meantime some few studies could not underpin these assumptions (Glauser, 2001, Franzoni et al. 2006; Tzitiridou, et al., 2005). Especially in children there are only limited data regarding optimal use and about the patterns of neuropsychological side effects.

Vigabatrine: (VGB)

Vigabatrine is one of the most extensively studied of the newer anticonvulsants, but side effects have been studied only to some degree until now. Only few mostly add-on studies were carried out in order to determine the pattern of side effects. These revealed only slight adverse impacts on cognition and behaviour. Also a dose related impact on mental and psychomotor speed is likely (McGuire, 1992).

Clinically the most common reactions were drowsiness and behaviour changes like mood instability or depression (Kwan & Brodie, 2001). On this base also cognitive side effects may develop.

Nevertheless there are no controlled studies in children to detect special impacts on learning or school performance. Caution should be exercised in patients with a history of psychosis (Sander et al, 1991) Vigabatrin can strenghten these behaviour dispositions. The most severe side effect, that has reduced significantly the use of Vigabatrine are specific patterns of visual field loss in nearly one third of patients, as well in adults as in children (Spencer & Harding, 2003). In the meantime these findings has been impressively confirmed. It is evident that the therapeutic benefit of VGB is counteracted by these severe side effects (Wild et al., 2007)

Bearing in mind empirical data presented above, the following surveys can be put together.The ratings following international standards: (www.swissepi.ch.,2004)

Fig. 1

	PB	PRM	PHT	CBZ	VPA	ESM
Cognition !	++	+	++	+	+	+
Speech	++	+	+	?	+	?
Memory	+	+	+	?	+	?
Attention	+++	++	++	+	+	+
Mental speed	+++	++	+	+	+	+
Motor speed.	+++	++	+	+	+	+
Behaviour	+++	+++	+	+	++	++

? = < 1%, + = > 1% ++ = >10%, +++ = > 30%

Fig.1 Survey of adverse side effects of the older AEDs

Fig.2

	LTG	TPM	OXC	VGB	Poly
Cognition !	?	++	?	?	++
Speech	?	+	?	?	+
Memory	?	+	?	?	++
Attention	+	+	+	+	+++
Mental speed	+	++	+	+	+++
Psymot. speed	+	++	+	+	+++
Behaviour	++	++	+	+	+++

? = < 1% , + = > 1% , ++ = > 10%+++ = >30%

Fig.2 Survey of adverse side effects of the newer AEDs

The question arises, which are the major basic impacts of antiepileptic drugs, if we do reveal side effects ? The delineated survey stresses adverse effects on mental speed, psychomotor and attention functions. More over impacts on behavior functions, which are needed in schooling and in daily life activities, are out of the question. Taking all these data into consideration one could argue, the major weak point of side effects is the speed of information processing and at least central arousal. AED´s can change the relationship between arousal, induced in the formation reticularis, and performance. which can be delineated as inverse U-shaped curve. That means we have an optimal performance level, when the level of arousal is in the middle range. By the special properties of the drugs a sup- or supraoptimal level can be produced. In each case the performance level is reduced. Now the irritation of that neuroregulatory process is a special risk for the development of cognition and behaviour (Sulzbacher et al., 1992; Dessens, et al. ,2000).

Fig. 3

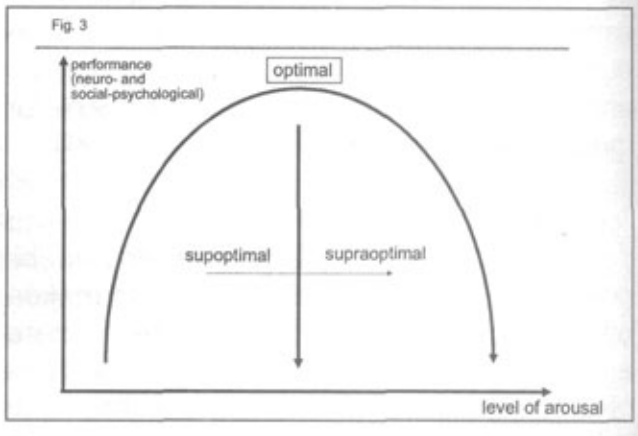

Fig 3 Relationship between level of arousal and performance

Moreover, also brain damage patients are at a special risk to develop side effects. These patients often have a very early onset of epilepsy, which means as a rule a long duration of therapy. Moreover they more frequently need a polytherapy regimen, which can rarely be avoided, especially in children.

Conclusions

There are a lot methological problems in studies to detect cognitive, neuropsychological or behavioural effects. They include selection factors but also questions how to measure side effects (Dodrill, 1992). In the literature one cannot find obliging methodological standards which are accepted by the most scientists (Mayer, 1989). For this reason it is difficult to compare the older and the newer compounds regarding the special pattern of side effects. All the same there is no doubt, that the older and the newer antiepileptic compounds can have detrimental effects on various cognitive and behavioural functions It is important to assess these patients who suffer more from side effects than epilepsy itself. Keeping this in

mind it is not unfair to emphasize, that the new anticonvulsants often lead to favourable results in case of moderate epilepsy. However they do not appear to change the conditions of the group of patients, who suffer from severe epilepsies. These patients are treated with complex AED regimens. Complex means higher drug load and poytherapy regimen and means higher rates of unfavourable side effects. I dare to argue, that this group is at a special risk to develop nearly similar rates of side like on polytherapy including the older AEDs.

The scientific knowledge about side effect of AED has lead to recommendations, how to handle a treatment supposing side effects (American Academy of Pediatrics: Committee on Drugs, 1995).

1.When AED is required the relative influence of each anticonvulsant agent on behavioral and cognitive functions should be considered, along with all the other potential adverse effects.

2. The physican should monitor the child's behaviour and academic progress through routine questioning of parents (teachers, when relevant) and observation of cognitive functions, mood, and behavior during follow-up visits.

3. If changes in the child's behavior or cognitive performance occur in relation to the initiation of AED, the need for AED and/or alteration of AED must be reassessed.

4. If school problems persist the physican should advocate a comprehensive evaluation of cognition and learning ability in order to plan for appropriate remediation or intervention

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