THE FETAL ANTICONVULSANT SYNDROME IN AN ADULT MALE: A RARE EXAMPLE OF VIOLENT BEHAVIOUR IN THE CONTEXT OF EPILEPSY-RELATED DISORDERS

Willem M.A. Verhoeven, Jos I.M. Egger, and Siegfried Tuinier†

Abstract

Objective: Despite the relatively high prevalence of epilepsy, the existing literature is inconclusive with respect to the association between violent or aggressive behaviours and epilepsy related disorders

Method: The present paper describes two male adult siblings with fetal anticonvulsant syndrome and a history of felonies and misdemeanours. In addition, the main epilepsy related conditions that may coincide with aggression, such as postictal psychotic states, hypothalamic hamartoma and use of anti-epileptics, are briefly reviewed.

Results: For epilepsy related aggressive behaviours, brain disorders, contextual parameters, and the interictal period, as well as the behavioural pharmacology of antiepileptics and their teratogenic effects with prenatal exposure, are much more important than the epileptic fit itself.

Conclusions: The clinical neuroscientist should be equipped with specialized knowledge about psychopathology related to epilepsy and anticonvulsants. Of special importance for the clinician is the awareness during the diagnostic process that prenatal exposure to anti-epileptics may be associated with prolonged behavioural disinhibition as a long-term consequence.

Key Words: Fetal anticonvulsant syndrome, neuropsychiatry, epilepsy, aggressive behaviours.

Declaration of interest: None

Willem M.A. Verhoeven,1,2 Jos I.M. Egger1,3 and Siegfried Tuinier†

1 Vincent van Gogh Institute for Psychiatry, Centre of Excellence for Neuropsychiatry, Venray, The Netherlands
2 Erasmus University Medical Centre, Department of Psychiatry, Rotterdam, The Netherlands
3 Radboud University Nijmegen, Behavioural Science Institute / Department of Clinical Psychology, Nijmegen, The Netherlands

Corresponding Author:
Prof. Dr. Willem M.A. Verhoeven
Director of Residency Training, Vincent van Gogh Institute for Psychiatry
Stationsweg 46, 5803 AC Venray, The Netherlands
Phone:+31.478527339, Fax:+31.0478527119, E-mail: wverhoeven@vvgi.nl

Introduction

Epilepsy is a common disorder affecting up to one percent of the population. There is an ongoing debate on the association between aggressive behaviours and epileptic phenomena. The existing literature indicates that well-directed violent behaviour against humans is largely restricted to postictal psychotic states (Kanemoto et al. 1999; Schachter 2001), to the rare condition of hypothalamic hamartoma (Weissenberger et al. 2001), as a side effect of the use of certain antiepileptic drugs (AED) (Besag 2004; Weintraub et al. 2007), and possibly also as a result of prenatal exposure to antiepileptic drugs (Moore et al. 2000).

Epilepsy is a very heterogeneous disorder with respect to both etiology and phenomenology and is nowadays always treated with a variety of AED’s. Patients with epilepsy and disturbed and/or disinhibited behaviours are primarily treated in medical settings so that acts of violence that do occur are most likely not judicially labelled. The incidence of these non-labelled acts, however, is rather low (Mackay et al. 2006). Although it is well known for more than a century that there is a substantial psychiatric comorbidity in epilepsy (review: LaFrance et al. 2008), so far no clear consensus in the psychiatric taxonomy exists about the psychopathological symptoms and syndromes that may emerge in the context of epilepsy. Therefore, the International League Against Epilepsy (ILAE) proposed a nosology of epilepsy-specific psychiatric syndromes (Brodie et al. 1997; Malmgren et al. 2003). The latest version of this proposal presents a clinical and descriptive system of the classification of epilepsy-specific disorders (Krishnamoorthy et al. 2007).

In this paper an adult male with a fetal anticonvulsant syndrome is presented who had a long lasting history of severe disinhibited behaviours. Before describing the key elements of this syndrome, the clinically most relevant other epileptic conditions that may be associated with such behaviours will be shortly described.
Psychoses

In community studies, the prevalence of epilepsy associated psychiatric disorders is low whereas in specialized centres this figure can rise to 20 to 50 percent (LaFrance et al. 2008). Interictal behavioural changes in epilepsy remain controversial and difficult to define, mainly because they may be related to various causes such as epilepsy itself, possible brain lesions, the AED’s prescribed, and contextual factors, the latter not to be underestimated (Torta and Keller 1999).

The prevalence of psychoses in epilepsy is estimated to be 2 to 7 percent of which a quarter is postictal and 10 to 30 percent interictal (Nadkarni et al. 2007). According to Adachi et al. (2002), no clear association can be found between psychoses and the location of epilepsy. Apart from postictal psychoses, especially interictal psychoses might have disinhibitory behavioural complications because their symptomatology may be dominated by a purely delusional state, visual hallucinations and behavioural dyscontrol such as irritability and aggressiveness (Gaitatzis et al. 2004). Since it is suggested that postictal psychoses develop over time in interictal psychoses (Sachdev 2007; Oyebode 2008), the focus of interest should be extended primarily to postictal psychoses. With respect to the latter, it is reported that the psychopathological picture in about 25% of the patients may be dominated by outward directed violent behaviours (Kanemoto et al. 1999).

Of particular interest is the so called ‘alternative psychosis’ or ‘forced normalization’ that describes a clinical state in which patients become psychotic when their seizures are under control and their psychosis resolves with return of seizures. The clinical presentation of ‘forced normalization’ includes not only the obligatory psychotic symptoms but may also present with challenging behaviours like aggression and agitation (Trimble and Smith 2007, Sachdev 2007).

In the here mentioned psychotic disorders related to epilepsy, the concomitant behavioural problems can be effectively treated by optimising the AED treatment regimen, the prescription of psychotropics, or by non-pharmacological interventions (Faroq and Sherin 2009).

Hypothalamic hamartoma

The hypothalamic hamartoma (HH) is a rare developmental malformation containing atypical proportions of neuronal tissue elements (Berkovic et al. 1988). The clinical picture is dominated by a variety of epileptic phenomena including episodes of inappropriate laughter, the so-called gelastic seizures. This congenital disorder is associated with a varying degree of aggression, rage and hyperactivity (Arita et al. 1999, Weissenberger et al. 2001, Kanner 2004).

With respect to the type of aggression, patients with HH exhibit unpredictable aggressive behaviour that is only partially context dependent, unplanned and irrespective of the consequences of self-harm or damage to property (Veendrick-Meeke et al. 2007). This type of offensive aggression is the result of stimulation of the hypothalamus and resembles that of the hypothalamic stimulated aggression paradigm in animal experiments (Haller and Kruk 2006). HH’s are associated with intellectual disability, developmental delay, treatment refractory epilepsy and a variety of psychiatric comorbidity that warrant hospitalisation at an early age.

Behavioural side effects of AED’s

As can be inferred from Table 1, nearly all AED’s have the potential to induce, mostly reversible, psychiatric side effects including confusion and behavioural disinhibition. Most reports deal with levetiracetam (Dinkelacker et al. 2003; Weintraub et al. 2007) and topiramate (Mula and Trimble 2003). The relative uncertainty about the risk of behavioural side effects of AED’s is the result of the lack of systematic and methodologically sound large scale studies so that the information has to be collected from case reports and small series (Besag 2004). As underlined by Trimble (1996) and Besag (2002), the most important confounding factors in interpreting the data on behavioural syndromes associated with AED’s are: 1. the ‘alternative psychosis’ that can be precipitated by any drug that controlled the seizures, 2. the ‘release phenomenon’ which refers to patients who have been disabled by severe epilepsy and become more to misbehave when the seizure control is improved and 3. drug interactions between AED’s that may evoke behavioural disinhibition as a result of changes in plasma concentrations.

In the following paragraph a forensic psychiatric case is described in which maladaptive behaviours and cognitive deficits were most probably related to prenatal exposure to AED’s.

Case report

The patient is a nearly 40-year-old Caucasian male, born from non-consanguine parents with normal intelligence. There are two younger siblings, one male and one female. During the pregnancies, the mother was treated with an identical combination of AED’s for epilepsy. According to her information, it concerned carbamazepine and phenytoin as well as phenobarbital. No other potentially teratogenic drugs were used. Pregnancy and delivery were uncomplicated. She was free of seizures during pregnancy. The patient’s birth weight was about 3000gr and he had a hypospadias. Motor and language development were markedly delayed. At the age of 5, his flap-ears were surgically corrected. He attended a special primary school for children with learning and behavioural difficulties. At the age of 10 it became apparent that his abstract thinking was weak and that he had poor social communication skills. From the age of 12 his behaviour deteriorated showing deceitfulness and serious violations of parental rules e.g., staying out at night and running away from home that resulted, four years later, in an institutionalisation for two years because of burglary and misdemeanours. He underwent several surgical corrections for his hypospadias between the age of 14 and 17. From that time on, the patient showed
periods with wandering, drug abuse, exhibitionism, sexual harassment and fire setting for which he was convicted at the age of 23 and consequently committed to a forensic psychiatric hospital. Forensic psychiatric examination at that time showed a mild intellectual disability and diagnoses of a Personality Disorder NOS with antisocial, narcissistic and borderline characteristics, and a Pervasive Developmental Disorder NOS were established. Based on his history with impulsive behaviours, the forensic psychiatrist concluded that there was a high risk for recidivism he and therefore advised institutionalisation in the chronic department of a forensic psychiatric state hospital. In the course of subsequent hospitalisation years, the patient stayed in a highly structured clinical environment where he did not show severe problematic behaviours, except for short leaves during which he relapsed in his wandering and sexually aberrant habits. As a consequence, risk assessment repeatedly showed a high recidivism risk resulting in a hospitalisation for almost two decades. At the age of 36 he was referred to the outpatient department of neuropsychiatry for extensive re-evaluation.

At neuropsychiatric examination, the patient showed a strabismus convergens of the right eye, a broad forehead, infraorbital grooves, a broad nasal bridge, dysplastic ears and slightly hypoplastic digits. No further somatic or neurological abnormalities were present. Cytogenetic analysis demonstrated a normal XY karyogram and no fragile-X. MRI scanning of the brain did not show structural abnormalities.

Psychiatric evaluation revealed emotional flattening, a relative deficiency in the recognition and verbalization of emotions, low self-esteem and an infrequent eye contact. His level of intelligence seemed to be subnormal with, however, good verbal capacities. He showed an automatic and shallow insight in his own functioning. There was no development of contact and in the forensic psychiatric hospital the patient had only minimal social interactions. He had no expectations or plans for the future. No major psychiatric symptoms could be demonstrated. During his long stay in the institute with a structured day program, the patient never showed behavioural abnormalities or infractions of the institutional rules. No formal psychiatric diagnosis was made.

Neuropsychological assessment using an extensive test battery revealed a total IQ of 56 indicating a mild intellectual disability (Kaufman Adolescent and Adult Intelligence Test; KAIT). He displayed increased distractibility, a fluctuating level of attention and high sensitivity for interference. Executive functioning (EF) was characterized by a lack of self-regulation and an impulsive and unsystematic strategy. He showed perseverations and low flexibility. Although capable of learning new strategies on EF-training tasks, and consequently able to develop rule-governed behaviour, a marked deficit in rule automation was assessed as well as a relative insensitivity for future consequences of behaviour. Emotional recognition of self and others was slightly impaired. His personality profile showed elements from the paranoid-emotional and schizoid cluster.

Both his sister and his brother were known with intellectual impairments. His sister lived in a sheltered house and was in need for social support. She was born with dysplastic ears and an atrial septal defect (ASD) that were both surgically corrected. His brother was also permanently committed to a forensic psychiatric hospital because of felony. His phenotypic characteristics comprised broad forehead and nasal bridge, dysplastic ears, slight digital hypoplasia, a total IQ of 75 (Wechsler Adult Intelligent Scale; WAIS-III) and problems in executive functioning, similar to those demonstrated in his brother. The children grew up in a fairly normal, middle class family without antisocial characteristics.

Given the combination of mild intellectual disability in all three siblings, the exposure to AED’s during the pregnancies, the clear dysmorphias in the two brothers, the hypospadias in the presented case and the ASD in his sister, a diagnosis of fetal anticonvulsant syndrome was made that was confirmed by an independent clinical geneticist.

The fetal anticonvulsant syndrome

Approximately one third of people receiving AED’s are of a reproductive age. In about 1:250 pregnancies, the foetus is exposed to AED’s that are known to possess teratogenic properties and can also act as a behavioural teratogen. The fetal anticonvulsant syndrome constitutes a real clinical entity that includes developmental delay and cognitive impairments with or without dysmorphisms (Adab et al. 2001, Gailit et al. 2004, Kini et al. 2006). Several large-scale studies in different countries investigated AED teratogenesis (Samrén et al. 1999, Wide et al. 2004, Meador et al. 2006, Battino and Tomson 2007, Tomson and Battino 2008). The general outcome was that AED’s have a differential teratogenic effect with the highest risk for valproic acid (Artama et al. 2005) and the lowest for lamotrigine (Shor et al. 2007). In case of valproic acid, the risk of major malformations and cognitive impairment increases with polytherapy and higher dosages. It has been suggested that minor facial dysmorphias may be specific for certain AED’s (Moore et al. 2000, Dean et al. 2002, Adab et al. 2004a).

The most common major congenital malformations include heart defects, cleft palate and/or lip, limb defects, genito-urinary abnormalities and neural tube defects (Battino and Tomson 2007). In addition, ophthalmological abnormalities are rather frequent (Glover et al. 2002). It has been documented that genes in the folate pathway, especially a polymorphism in the MTHFR gene, may contribute to the teratogenic effects of AED’s (Dean et al. 1999, 2007).

The more subtle effects on the subsequent neurological and cognitive development have been poorly studied in children. Virtually no information is available about adults. In general, prenatal exposure to AED’s is associated with a lower intelligence that holds particularly for valproic acid (Christianson et al. 1994, Reinisch et al. 1995, Adab et al. 2004b, Vinten et al. 2005, Eriksson et al. 2005, Schnitz et al. 2006, Tüte et al. 2008). In animal experiments, exposure to phenytoine showed dose dependent developmental neurotoxicity expressed as hyperactivity and deficits

With respect to behavioural abnormalities in children, only one report suggests a behavioural phenotype that comprises poor social interaction and communication skills, insistence on routines and disinhibited behaviours (Moore et al. 2000). From the neuropsychiatric vantage point, autism spectrum disorders, mainly associated with valproic acid, have been reported (Rasalam et al. 2005).

In the Netherlands, each year about 700 children are prenatally exposed to AED’s that leads to about 50 children with major congenital malformations whereas the risk of the effect on cognition and behaviour is far less clear (Lindhout and Omptigt 1992). The risk for recurrence in a subsequent pregnancy is increased (Malm et al. 2002). Psychiatric cases in adults have not been published so far.

Discussion and concluding remarks

In this paper the main clinical conditions in which epilepsy may coincide with aggressive behaviours are presented, with special attention to the fetal anticonvulsant syndrome. Although the enigmatic nature of epileptic fits and postictal automatisms have stimulated ideas on the connection between violent crimes and epilepsy, the database underlying such a relationship is still rather limited (Brooke et al. 1996, Mackay et al. 2006, Reuber et al. 2008).

In order to enhance the understanding of epilepsy related behavioural disorders, it is essential to consider contextual parameters as equally important as the brain disorder per se. Increased attention should therefore be given to the functional and psychopathological parameters that can elucidate syndrome-specific dysfunctions (Egger et al. 2007). Here, the detailed analysis of executive functioning (EF) is obligatory. EF comprises such abilities as working memory, shifting between tasks or mental sets, and inhibition of dominant or prepotent responses, all of which mediate complex human behaviour (Miyake et al. 2000). In this respect, the so called contextual behavioural approach, in which executive processes are seen as a subset of rule-governed behaviour, is the most promising strategy for studying self-regulation and brain-context interactions (Hayes 1996, Barkley 2001). Thus, such a behavioural analysis indicates function and meaning of the behavioural act, which in turn determines the sociocultural acceptance or consequences.

In conclusion, behavioural disorders as a manifestation of interictal psychopathology may be epilepsy-related, even if there is no temporal relationship with ictal phenomena. Whether such behaviours may have a forensic impact depends on a variety of circumstances e.g., the clinical setting, the presence of handicaps like intellectual disability, and the social context. All this is best illustrated by the here reported adult male patient with late consequences of prenatal exposure to AED’s. Unfortunately, no psychiatric reports are available about the fetal anticonvulsant syndrome in adults and no forensic cases have been described.

Acknowledgments

-The authors are indebted to Mrs. Irma Hernandez-Dwarkasing, psychiatrist at the Forensic Psychiatric Clinic, De Rooyse Wissel, Oostrum, The Netherlands for referral of the patient and to Mrs. Ineke Van der Burg, clinical geneticist at the Radboud University Medical Centre, Department of Human Genetics, Nijmegen, The Netherlands for her contribution to the diagnosis.

-The experimental assessment of rule governed behaviour was performed by Mrs. Gwenny Janssen, M.Sc., Ph.D-student at the Behavioural Science Institute of the Radboud University Nijmegen, Nijmegen, The Netherlands.

-For publication of this case, written informed consent was obtained from the patient, his brother, the parents and the board of directors of the Forensic Psychiatric Clinic, De Rooyse Wissel, Oostrum, The Netherlands.

Table 1. Behavioural and psychiatric side effects of AED’s

<table>
<thead>
<tr>
<th>Compound</th>
<th>Psychosis</th>
<th>Depression</th>
<th>Confusion</th>
<th>Agitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pheno</td>
<td>__</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Phenytoin P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Carbamazepine P</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Topiramate</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Felbamate</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Adapted from Besag 2004, Schmitz 2006 and Weintraub et al. 2007.

References


