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Non-Convulsive Status Epilepticus after Abrupt Withdrawal of Hypnotic-Sedative Drugs

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Summary. Four patients with severe addiction to sedative-hypnotics and with acute withdrawal symptoms of these drugs are described. They developed latent confusional states with characteristic EEG patterns (bilateral slow and sharp waves of high amplitude). Following small doses of benzodiazepines the EEG became normal together with a reduction in the clinical symptoms. It is suggested that the confusional states were of an epileptic nature.

Key words: Withdrawal of drugs and alcohol – Acute confusion – Non-convulsive status epilepticus – Benzodiazepine therapy.

Introduction

Convulsive seizures, delirium and acute confusional states of non-delirious types are well-known following abrupt withdrawal of sedative-hypnotic drugs [11, 14, 15, 26, 33, 34]. Convulsive seizures and confusional states usually pre-date delirium [7, 15, 16, 23, 25, 26, 31]. As early as 1891, a close relationship between epileptic cloudy states and delirium was suggested [18]. Similarly it was assumed that delirium could be an equivalent of an epileptic fit [8] and that "convulsive seizures as well as psychosis following withdrawal of barbiturates and other drugs are probably caused by the same mechanism" [15]. The cardinal manifestations of withdrawal of sedative-hypnotic drugs (delirium, convulsive seizures and non-delirious confusional states) were even considered to be an epileptic triade [13].

In the past 2 years we have observed four patients in whom acute prolonged confusional states following abrupt withdrawal of sedative-hypnotic drugs (mainly barbiturate-alcohol-benzodiazepine type) were suggestive of being epileptic in nature, i.e. representing a non-convulsive ictal phenomenon.

Case Reports

Case 1. This was a 58-year-old woman with a history of severe abuse of sedative-hypnotic drugs (mainly benzodiazepines) and alcohol for 5 years. She had had no previous seizures, and there was not epilepsy in the family. Benzodiazepines such as lorazepam and diazepam had been withdrawn 3 weeks prior to her admission, and replaced by amitriptyline and dibenzepine. On the day prior to admission she suddenly became confused, was frightened, had several episodes of loss of speech interrupted by inadequate answering and behaviour and complained of a rising gastric sensation followed by headache. On the day of admission the loss of speech recurred, this time with urine incontinence and vomiting. General examination was normal, pulse 76/min, blood pressure 135/80 mm Hg. Neurological examination was also unremarkable. She was awake, but intermittently disorientated as to place, she performed poorly on tests of abstract thinking, recent and remote memory and was unable to follow complex instructions. In the evening she could not sleep, showing automatic behaviour and marked motor and verbal perseverations. CT-scan showed mild cortical atrophy. Blood count and chemistry including glucose, creatine and electrolytes and urine examination were normal, VDRL and TPHA were negative, liver enzyme were slightly increased. The EEG recorded on the day after admission, showed continous bilateral synchronous, 2 cps rhythmic delta activity with a frontal and medial predominance, paroxysmally with steep ascending phases (Fig. 1A). Photic stimulation and nasopharyngeal recordings were unremarkable. Under EEG monitoring 1 mg clonazepam was given i.v. abolishing all the generalized, rhythmic activity within a few minutes and leaving diffuse, low amplitude beta activity (Fig. 1B). Clinically she became alert, responded adequately and spoke more spontaneously. The control EEGs in the following days showed a mixed alpha-beta activity with no paroxysmal components. A worsening with confusion and automatic behaviour again improved after clonazepam injection. On the 3rd day after admission a delirious syndrome with visual hallucinations, paranoid ideas, agitation, sleeplessness and a mild tremor appeared together with a slight fever, tachycardia, nausea, vomiting and pollakiuria. Under distraneurin these symptoms decreased within 72 h and disappeared completely within 5 days.

Case 2. This 61-year-old retired man had been consuming large amounts of sedative-hypnotic drugs (benzodiazepines and barbiturates) in combination with analgesics for 6 years because of severe headaches and progressive depression caused by a disabling car accident. There was no personal or family history of epilepsy. On 9 January 1984 he attempted suicide by taking 60 mg of flunitrazepam. On admission, he was somnolent, and following stomach lavage he was transferred to the psychiatric ward. There, the physical and neurological examination, laboratory findings including total blood count, electrolytes, liver ezymes, VDRL and urine analysis

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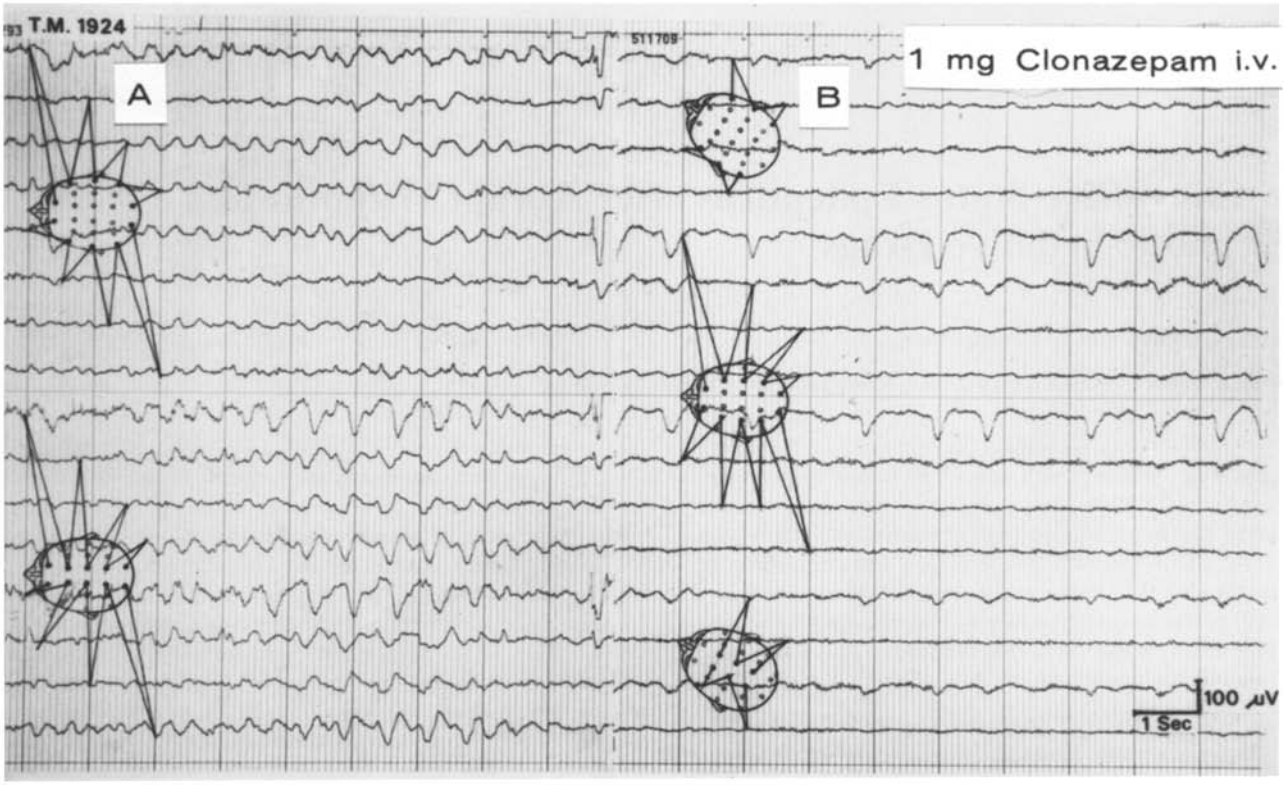

Fig. 1. EEG recordings from case 1 before (**A**) and immediately after (**B**) the injection of 1 mg clonazepam i.v. Note the high voltage rhythmic slow waves with steep ascending phases and bifronto-medial preponderance (**A**) which are abolished totally after the administration of clonazepam (**B**)

were unremarkable. His mental state was normal with the exception of a depressive mood; he was oriented in all three spheres and had no hallucinations. Over the following 3 days he seemed normal, had slept well and was cooperative. On 12 January 1984 he experienced two convulsive seizures within 5 h, following the second seizure he became agitated but had no hallucinations. On the next day a fracture of the humerus was diagnosed and the patient was transferred to the surgical department. There, he appeared awake but was disoriented as to time and place, spoke slowly and incoherently using single words, having a blank, staring and expressionless face. The motor performance and spontaneity were also reduced, his gait was slow and unsteady. There were frequent face twitchings and to a lesser extent in the extremities. Pulse was 84/min, regular, blood pressure 180/100 mm Hg. The EEG showed an alpha-beta-theta background activity interrupted by frequent paroxysms of bilateral synchronous and generalized high voltage 5 cps theta groups maximal in the occipital region. Photic stimulation provoked a photoconvulsive reaction. During EEG monitoring 5 mg midazolam was given i.v. The generalized paroxysmal activity was immediately replaced by a fast spindle-like alpha rhythm and the patient became alert with adequate responses. The EEG recorded 1 month later was normal and the clinical state unremarkable.

Case 3. This 43-year-old woman had severe polytoxicomania due to a 15-year history of alcohol and several hypnotic-analgesics (mainly barbiturates) abuse. There was no history of epileptic seizures, and the family history was unremarkable. Disulfiram therapy was started 2 months prior to admission, during which her alcohol consumption continued. This therapy was stopped because of progressive worsening of her mental state. Treatment with flupenthixol and thioridazine was introduced and her alcohol consumption still did not cease. In the following days she became confused, showed an infantile behaviour, lack of spontaneity and eventually incontinence of urine. On admission she was in a coma and showed skew deviation of the eyes. On suspicion of a Wernicke-Korsakoff syndrome, thiamine therapy was instituted. The next day she awoke, was atactic but fully orientated. The laboratory findings were normal, and CT scan showed a mild cortical atrophy. She had a grand-mal seizure 7 days later, followed by a cloudy state: the patient had a blank staring, expressionless face, replied monosyllabically using single words in a monotonous fashion, had marked echolalia and verbal and motor perseverations with widespread muscle twitching. On the next day, still in the same state, the EEG showed generalized, bilateral synchronous high voltage slow waves, frequent paroxysmal bursts of sharp waves and sharp slow waves, predominating in the fronto-medial leads. An i.v. dose of 500 mg diphenylhydantoin was given with no clinical improvement. The next day, with the EEG still showing the same activity, 5 mg midazolam was injected i.v. Within a minute the bilateral synchronous high voltage sharp waves disappeared and the slow background activity was replaced by a fast beta activity (Fig. 2). Simultaneously, the patient became fully alert as if awakening from a dream and asked what was happening. Her alertness improved further but the following day some other symptoms developed: during the night she became hyperactive, complaining about nightmares and visual hallucinations, she had vegetative signs such as tachycardia, a mild fever, hypotonia and sweating. She recovered fully during the next few days under benzodiazepines.

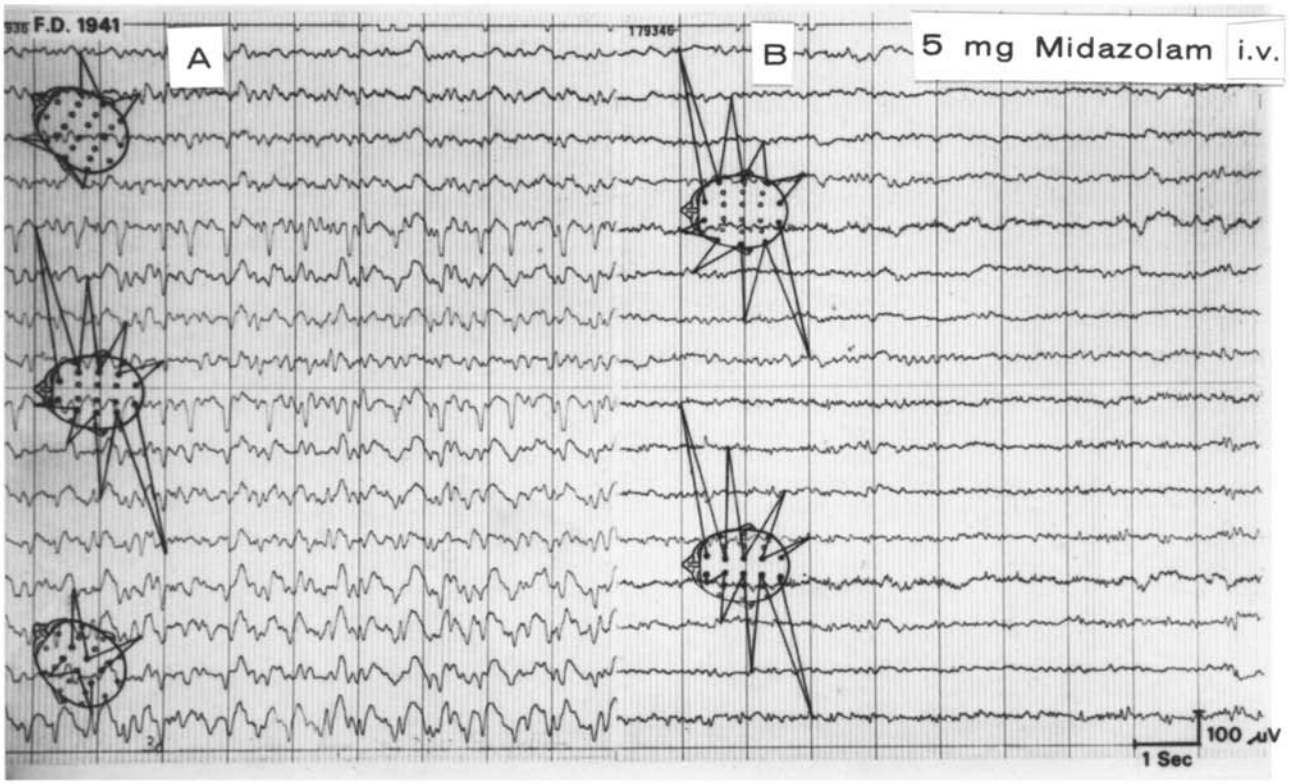

Fig. 2A, B. EEG recordings from case 3. Similar to Fig. 1, prior to the administration of midazolam, high voltage, partly rhythmical slow sharp waves, best recognisable in frontal leads, were observed (**A**), which were replaced through fast beta activity after the injection (**B**)

Case 4. This 40-year-old waitress had been an occasional drinker but became a severe alcoholic following the death of her husband 2 years previously. In the months prior to admission she had had nausea and vomiting, lack of appetite and tremor in the morning with no hallucinations. There was no personal or family history of seizures. She had fainted at work 1 week prior to admission and on the day of examination she had been abstinent for about 24 h. The neurological examination was normal except for a slight tremor of the hands and a mild excitability. The EEG was inconspicious with a normal background activity. However, on photic stimulation, bilateral synchronous 2–2.5 cps spike wave activity occurred, maximally in the occipital leads, persisting for 190 s after the cessation of the photostimulation. During this activity the patient became confused, following simple commands sluggishly and in a distracted way. She was disoriented to time and place, had a blank, staring, expression and showed verbal and motor perseverations. She recovered in 5 min with no therapy and was amnesic for this period.

Discussion

The common features of these four patients were severe addiction to sedative-hypnotic drugs such as benzodiazepines, barbiturates and alcohol and an abrupt withdrawal. Three of them had a prolonged confusional state of spontaneous, sudden onset, in two preceeded by a grand-mal seizures. In three patients the confusional state was promptly interrupted by a small dose of i.v. benzodiazepines. The fourth patient showed a similar state during photic stimulation which improved spontaneously 5 min later. All had similar EEG changes with bilateral, synchronous high amplitude slow and some sharp waves (Table 1).

The primary clinical picture did not show the characteristic signs of a delirium. There was no tremor, restlessness, vegetative signs, hallucinations or psychomotor agitation. They were merely confused and their psychomotor activity was clearly reduced. The clinical manifestations with impaired consciousness, lack of initiative, verbal perseverations, disorientation, lack of spontaneous speech, monosyllabic answers, infantile behaviour, incontinence, amnesia, clumsy motor performance corresponded to those of petit-mal status reviewed by Andermann and Robb [1]. Furthermore, two of these patients with longer latency developed a typical delirium tremens which was successfully treated with distraneurin after interruption of their primary confusional state. Contrary to this clear clinical differentiation from delirium, in the two patients with preceding grand-mal seizure a post-ictal confusion cannot be excluded with certainty. However, the sudden improvement after small doses of benzodiazepines without falling asleep makes this unlikely. In delirium tremens the administration of benzodiazepines or barbiturates is known to be effective [31], but generally large doses are needed, initiating sleep for several hours [6, 8, 33]. On the other hand, the dramatic response to relatively *small doses* of i.v. benzodiazepine, has been described in patients presenting with isolated petit-mal status de novo in middle age [29] and in "acute prolonged confusion in later life as an ictal state" [3].

The EEG changes during abrupt withdrawal of barbiturates were first documented experimentally by Isbell et al. [14] and Wikler et al. [33]. The EEGs associated with withdrawal psychosis were mainly of the random slow, diffusely slow or paroxysmal 6–8 cps, type. However, no one-to-one correla-

Table 1

Age, sex	Abuse type/duration	Days after withdrawal	Previous seizure or family history	Clinical picture	Laboratory and Neurological findings and CT	EEG	Therapy and result	Course in advance
58 F	Alcohol, benzodiazepines for 5 years	? 20 days	–	Impaired consciousness, responsiveness disorientation, perseveration stereotyped movement, no vegetative symptoms no agitation	Neurologically normal, CT diffuse atrophy, laboratory findings normal	Bilateral synchronous 2–2.5 activity frontal predominance	Clonazepam 1 mg improvement	Delirium
61 M	Barbiturates, benzodiazepines for 6 years	4 days	–	Impaired consciousness, responsiveness disorientation, perseveration stereotyped movement, no vegetative symptoms no agitation	Neurologically normal, no CT laboratory, findings normal	Bilateral synchronous 5 cps activity occipito-medial predominance	Midazolam 5 mg improvement	Progressive improvement
43 F	Alcohol, barbiturates for 15 years	6 days	–	Impaired consciousness, responsiveness disorientation, perseveration stereotyped movement, no vegetative symptoms no agitation	Neurologically normal, CT diffuse atrophy, laboratory findings normal	Bilateral synchronous 2–4 activity fronto-medial predominance	Midazolam 5 mg improvement	Delirium
40 F	Alcohol, for 1 year	1 day	–	Impaired consciousness, responsiveness disorientation perseveration stereotyped movement, vegetative symptoms no agitation	Neurologically normal, no CT laboratory findings normal	Photostimula-bilateral synchronous 2–2.5 cps spike-wave, occipital predominance	Spontaneous improvement	Tremulous

tion between a particular clinical appearance and a specific EEG pattern was found. Similar changes have been observed by other authors [4, 19, 28] and in markedly milder forms also after alcohol withdrawal [24, 34]. No particular EEG pattern appeared to be associated with the mental changes which occurred during the abstinence period [34]. Nevertheless the EEG changes during delirium tremens itself were reported to be much less evident, most often consisting of low voltage, irregular fast activity [2, 9, 24], disapperance of the occipital alpha rhythms and without epileptic activity [34].

Referring to the observation that during delirium tremens the EEG changes are less evident, a semiological differentiation between confusions with agitation and thoses with psychomotor under-activity and reduced responsiveness, which would often be accompanied by EEG abnormalities, was suggested [2].

Generalized convulsive status epilepticus in non-epileptics following withdrawal of alcohol and hypnotic-sedative drugs is well-known [25, 26, 31]. Generalized status epilepticus expressed as a confusional state in non-epileptics triggered through external means, i.e. through i.v. pentyltetrazol [27] and camphor [20] have also been described. Gallenkamp [7] observed "psychomotor" seizures after withdrawal in two otherwise non-epileptic patients, and very rare "psychomotor" seizures following withdrawal have been mentioned by others [6]. Furthermore Kalinowsky indicated that chlorpromazine which improves the productive schizophrenic psychosis and is known to decrease seizure threshold, triggers and/or aggravates the withdrawal psychosis [16].

We conclude therefore that the clouded confusional states following withdrawal of sedative-hypnotic drugs, described in this paper represent epileptic phenomen. They are characterized clinically by cloudy consciousness with amnesia, automatic behaviour and perseverations, no vegetative signs or agitation, rapid improvement to an awakened state after a minimal dose of benzodiazepines and by continuous bilateral synchronous, partly rhythmic high voltage slow and frequent sharp waves in the EEG. The acute onset of a clinically and electrographically similar state in case four during photostimulation which ended abruptly and spontaneously 5 min later is also strongly indicative of an epileptic origin.

The most similar condition clinically and electroencephalographically, is the classical spike wave stupor. It was suggested by Gloor [10] that bilateral synchronous spike and wave discharges may reflect a state of diffuse cortical hyperexcitability, particularly prominent under conditions in which the ascending reticular formation is relatively inactive. Accordingly, absences rarely occur during periods of enhanced attention. On the other hand, Wikler et al. [33] postulated a difference in recovery rate from barbiturate depression at cortical and diencephalic levels during withdrawal whereby cortical refractory periods are though to return to a normal value after withdrawal of barbiturates faster than the diencephalic structures. Considering Gloor's hypothesis this should facilitate a hyperexcitability of cortical neurons. Indeed, petit-mal-like behavior and bilateral synchronous high voltage, partly spike wave configurated EEG discharges have been observed experimentally following barbiturate withdrawal in cats [5].

Alternatively one may consider a complex partial status epilepticus in which focally beginning seizure activity within the fronto-basal-medial structures may give rise to a second-

ary generalization with bilateral synchronous activity through the well-known dense connections of these structures to the remainder of the temporal and frontal cortex [12, 17, 32], described as borderline cases of petit-mal-status by Hess et al. [12]. Karbowsky reported continous spike wave discharges in patients with a clinical psychomotor status epilepticus [17]. It was indeed shown experimentally in rats with focal cortical lesions that withdrawal of sodium-barbital led to continous focal convulsions [5]. Finally, focal elementary status epilepticus following alcohol withdrawal were described by Victor and Brausch [35].

It has previously been claimed that there might be a dual mechanism operating in the withdrawal periods: in the early phase of withdrawal a general hyperexcitability with seizures and increased sensitivity to photic stimulation, while in the later phase delirium tremens and insensitivity to seizures and photic stimulation occur [4, 5]. On the basis of this assumption one could argue that in those two patients with secondary delirium the convulsive phase was shortened by the administration of benzodiazepines. The slow wave of the spike and wave pattern has long been considered as the expression of inhibitory mechanisms [21]. If this is so, taking into account the slow wave EEG pattern and the cloudiness of petit-mal, our patients could be partially understood as being the expression of a diffuse inhibitory phenomenon in the cortex.

In conclusion, we assume that some of the clouded confusional states following the withdrawal of sedative-hypnotic drugs and presenting without agitation, vegetative and productive psychotic signs may be of epileptic origin. Hence the recording of an EEG is indicated. Provided a bilateral, synchronous slow wave activity is encountered, administration of a small dose of benzodiazepines which may immediately interrupt the confusional state is justified. Further, the abrupt onset of seizures or an acute confusional state in adult life should always raise the suspicion of addiction to sedative-hypnotic drugs.

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