Long-term cognitive and behavioural follow-up in three patients with eye closure-triggered paroxysmal activity

Cristiano Termine1, Federica Teutonico2, Umberto Balottin1, Marco Fasce2, Matteo Ferri1, Silvia Perna1, Paolo Piccinelli1, Guido Rubboli3, Pierangelo Veggiotti2

1 Child Neuropsychiatry Unit, Department of Clinical and Biological Sciences, University of Insubria, Varese
2 Department of Child Neurology and Psychiatry, IRCCS “C. Mondino Institute of Neurology” Foundation, University of Pavia
3 Department of Neurology, Bellaria Hospital, Bologna, Italy

ABSTRACT – Purpose. To study clinical, EEG, neuropsychological and behavioural evolution of three patients presenting with epileptic activity triggered by eye closure (EC) over a mean 10-year follow-up period. Methods. All patients were studied at the time of the first observation (T0) and after a long follow-up period (T1). At both T0 and T1, each patient underwent: 1) traditional and specific activation techniques during prolonged video-EEG monitoring to detect possible inducing factors; 2) neuropsychological evaluations during video-EEG monitoring either with eyes closed or eyes open to detect any transient cognitive impairment (TCI); 3) detailed neuropsychological assessment without EEG recordings, to detect any stable cognitive impairment (SCI). Results. EEG recordings showed transient, generalized paroxysms in one case and a continuous epileptic activity triggered by eye closure in the other two cases, at both T0 and T1. In all patients, no particular epileptiform discharge-induced factors were identified except for eye blinking (spontaneous, voluntary or induced by corneal reflex). The results of neuropsychological assessment while eyes were closed as compared to performances with eyes open, showed no significant differences at T0 or at T1 in two cases, thus possibly indicating the absence of TCI. Wechsler Intelligence Scales showed a decrease in performance at T1 in the two patients with eye closure-induced, continuous epileptiform activity. Detailed neuropsychological assessment without EEG recordings demonstrated an impairment of facial recognition ability in all three patients at T1. Conclusions. The lack of any differences between the results of neuropsychological tests performed with eyes open and eyes closed in two patients might suggest that not all eye-closure-triggered paroxysms are associated with TCI. On the other hand, our data highlight that EC-triggered, EEG epileptic discharges can produce long-lasting neuropsychological and behavioural effects, and also indicate that EEG discharges recurring over time might exert a disruptive effect on cognitive functions. Our three
patients showed extreme variability across the neuropsychological tasks except for a facial recognition deficit that was evident in all cases, thus suggesting a possible dysfunction of tempo-occipital brain structures and/or of the fusiform face area as recently demonstrated by combined fMRI/EEG studies in patients with fixation-off sensitivity.

Key words: reflex epilepsy, eye closure sensitivity, transient cognitive impairment, stable cognitive impairment, neuropsychology

The triggering of spike and wave discharges by eye closure (EC) may be observed in some epileptic patients during routine EEG examination. Various authors have described this peculiar EEG phenomenon, referred to as eye closure sensitivity (ECS), and attributed it to different causes: 1) eye closure mechanism (Green, 1968, Lewis, 1972, Gigli et al. 1991, Wakamoto et al. 1999); 2) interruption of light (Panayiotopoulos 1979, Veggiotti et al. 1992, Termine et al. 2006, Kimura 2000); and 3) fixation-off sensitivity (Ming and Kaplan 1998, Agathonikou et al. 1997, Krakow et al. 2000).

Epileptic discharges can impair cognitive functions transiently (i.e. transient cognitive impairment [TCI]), or when persisting for months in an almost continuous fashion (such as in electrical status epilepticus during slow sleep), they can be associated with permanent neuropsychological deficits (Tassinari et al. 2002). Indeed, it has been postulated that many developmental or acquired defects of language (such as acquired epileptic aphasia or Landau-Kleffner syndrome) or behaviour (such as autism) in children, are a consequence of apparently subclinical spikes interfering with specific cerebral processes (Binnie and Marston, 1992).

ECS represents a useful model for studying the possible transitory and long-term effects of epileptiform EEG discharges on cognitive function, in other words, for studying their association with the development, respectively, of transient cognitive impairment (TCI) (Tassinari et al. 2000, Aldenkamp 1997, Aldenkamp and Arends, 2004), and stable cognitive impairment (SCI) (Binnie 2001, Tromp et al. 2003).

We describe three patients with ECS, comparing their clinical, EEG, cognitive and behavioural characteristics at the time of the first observation (T0) and after a long follow-up period (T1), in order to investigate: 1) the relationship between epileptiform EEG discharges and cognitive performances evaluated by means of neuropsychological testing during EEG recordings (i.e. the possible presence of TCI); 2) the possible long-term cognitive and behavioural effects of chronic epileptiform EEG discharges (i.e. the possible presence of SCI).

Methods

We studied three patients, whose main demographic, clinical, EEG, cognitive, and behavioural characteristics are set out in table 1.

At both T0 and T1, each patient underwent the following evaluations:
1) prolonged video-EEG recordings with activation techniques to detect possible inducing factors (eye blinking, fixation-off sensitivity, voluntary ocular movements, intermittent light stimulation, hyperpnoea and sleep) (table 2);
2) neuropsychological evaluation during video-EEG monitoring (digits and words span, graphoesthesis, reaction times to auditory stimuli, sentence repetition, word repetition, digital gnosia, backward counting), either with eyes closed or with eyes open, to evaluate possible transient cognitive effects of epileptic discharges (table 3);
3) extensive neuropsychological assessment to detect any stable cognitive impairment (figure 1).

Results

EEG findings

At T0, EC-induced epileptiform EEG discharges were evident in all three patients: Patient 1 showed transient, brief generalized paroxysms (diffuse polyspike discharges), on rare occasions associated with brief eyelid myoclonia; Patients 2 and 3 showed continuous generalized paroxysms (diffuse polyspikes in Patient 3, and diffuse polyspikes prevalently over frontal regions in patient 2), resembling electrical status epilepticus, that continued, even with prolonged EC, until eye opening. In Patients 2 and 3, EC, after a few seconds, induced eyelid myoclonia associated with upward rotation of the eyeballs, and, in patient 3, this was accompanied by upper limb myoclonia and secondary generalization with clouding of consciousness. These clinical episodes were never consciously self-induced.

At T1, Patients 1 and 3 showed an unchanged EEG pattern on EC (figures 2, 3), while in Patient 2 a reduction and modification of some aspects of the EEG activity (continuous generalized fast activity over frontal regions that maintained the same characteristics on prolonged EC but was not associated with any clinical phenomena) were evident (figure 4).

The unchanged EEG activity observed in Patient 3 on EC, was nevertheless associated with eyelid and upper limb myoclonia followed by clouding of consciousness (figure 3).

In all the patients, blinking (spontaneous, voluntary, or induced by corneal reflex) always resulted in the appearance of the above-mentioned EEG abnormalities, both at T0 and at T1. In Patient 2, at T0, total darkness also induced EEG discharges. As regards the other discharge-
Table 1. Main clinical, EEG, cognitive and behavioural aspects at first observation and at follow up.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Handedness</strong></td>
<td>Right</td>
<td>Right</td>
<td>Right</td>
</tr>
<tr>
<td><strong>Age at seizure on</strong></td>
<td>7 y</td>
<td>12 y</td>
<td>7 y</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td><strong>1st observation</strong></td>
<td>12 y</td>
<td>20 y</td>
<td>12 y</td>
</tr>
<tr>
<td><strong>Follow up</strong></td>
<td>26 y</td>
<td>10 y</td>
<td>19 y</td>
</tr>
<tr>
<td><strong>Major seizure type</strong></td>
<td>Absences with eyelid myoclonias</td>
<td>Absences with eyelid myoclonias</td>
<td>TCS</td>
</tr>
<tr>
<td><strong>EEG on eye closure</strong></td>
<td>Transient brief generalized paroxysms</td>
<td>Transient brief generalized paroxysms</td>
<td>Electrical status epilepticus</td>
</tr>
<tr>
<td><strong>Clinical phenomena on eye closure</strong></td>
<td>-</td>
<td>-</td>
<td>Eyelid myoclonias</td>
</tr>
<tr>
<td><strong>I.Q. (Wechsler scale)</strong></td>
<td>Tot 86</td>
<td>86</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>V 88</td>
<td>80</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>P 86</td>
<td>97</td>
<td>80</td>
</tr>
<tr>
<td><strong>Behavioral problems</strong></td>
<td>Mild obstructionism</td>
<td>Mild obstructionism</td>
<td>Impulsivity</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>-</td>
<td>-</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>VEPs</strong></td>
<td>-</td>
<td>-</td>
<td>Normal</td>
</tr>
<tr>
<td><strong>AEDs</strong></td>
<td>VPA</td>
<td>VPA</td>
<td>VPA</td>
</tr>
</tbody>
</table>

TCS: tonic-clonic seizures; VPA: valproic acid; LTG: lamotrigine; PB: primidone; CBZ: clobazam; FBM: felbamate; CZP: clonazepam; I.Q.: intelligence quotient; I.Q.V: verbal intelligence quotient; I.Q.P: performance intelligence quotient; MRI: magnetic resonance; VEPs: visual evoked potentials; AEDs: anti-epileptic drugs.

Table 2. EEG characteristics and effect of different activation techniques in triggering paroxysmal activities at first observation and at follow up.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EEG on eye closure</strong></td>
<td>Transient brief generalized paroxysms</td>
<td>Transient brief generalized paroxysms</td>
<td>Electrical status epilepticus</td>
</tr>
<tr>
<td><strong>Eye blink</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Fixation off-sensitivity</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Scotosensitivity</strong></td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Voluntary ocular movements</strong></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Intermittent light stimulation</strong></td>
<td>++</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td><strong>Hyperpnoea</strong></td>
<td>++</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td>Normal pattern</td>
<td>Normal pattern</td>
<td>Normal pattern</td>
</tr>
</tbody>
</table>

+: positive; -: negative.
inducing factors, only in patient 1, at T0, were hyperpnoea and intermittent light stimulation (ILS) found to evoke higher amplitude and longer-lasting EEG discharges, even though at T1 hyperpnoea no longer induced EEG discharges and ILS was less effective in inducing them.

TCI: neuropsychological evaluation during EEG with eyes open and with eyes closed at T0 and at T1 (table 3)

Possible transitory effects of epileptic discharges (i.e. TCI) were investigated, both at T0 and T1, with eyes open (i.e. no EEG discharges) or closed (i.e. EEG discharges), during video-EEG monitoring specific neuropsychological evaluations (table 3).

Each test performed revealed performances within the average ability level in all the tests, except in short-term memory (i.e. digits and words span).

In Patients 1 and 2 – the latter has already been described in previous papers at diagnosis (Veggiotti et al. 1992) and at follow-up (Termine et al. 2006) – no significant differences in neuropsychological tasks with eyes closed compared to eyes open condition were found; hence, no detectable TCI was evident at either time point (table 3). On the other hand, in Patient 3, neuropsychological performances with eyes closed were more impaired, both at T0 and at T1. This patient was not able to perform all the tests as serious discomfort, upper limb myoclonia, and clouding of consciousness following prolonged EC occurred; nevertheless the results of the few tests that could be administered suggested the presence of significant TCI in the eyes-closed condition.

SCI: neuropsychological assessment without EEG recording at T0 and at T1

IQ rating (T0 versus T1)

Possible cognitive effects related to the prolonged persistence of epileptic activity on eye closure were evaluated by submitting patients to the Wechsler Intelligence Scales and comparing the results at T0 and T1. Wechsler scale scores obtained at the two time points (T0 versus T1, table 1) revealed a significant decrease in IQ in patients 2 and 3 (both showing continuous EEG discharges on EC). Notably, even though the IQ of patient 2 at the end of the follow-up was lower than 14 years earlier (FIQ 83 versus 71), it was still borderline level, thus revealing only subtle cognitive worsening. However, patient 3 showed a significant IQ decline during the 9-year follow-up (FIQ 74 versus 52).

Detailed neuropsychological outcome

All the evaluations performed at T1 are summarized in figure 1.

In Patient 1, neuropsychological evaluation revealed performances corresponding to average ability on all the tests administered except verbal fluency (z score = -4) and facial recognition (z score = -3.5), in both of which her performances were significantly impaired. In Patient 2, the performances ranged from low-average to borderline level in the majority of the tests administered, although attention and short-term memory deficits, as well as a significant impairment in facial recognition (z score = -2.5) and block design (WAIS-R) (z score = -2.66) were

Table 3. Neuropsychological evaluation during EEG recording in eyes-open and in eyes-closed conditions.

<table>
<thead>
<tr>
<th>Test administered</th>
<th>Eyes open (O), closed (C)</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1st obs.</td>
<td>Follow up</td>
<td>1st obs.</td>
<td>Follow up</td>
</tr>
<tr>
<td>Digit span (Orsini et al. 1987)</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Word span (Orsini et al. 1987)</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Graphesthesia (Lezak 1995)</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Reaction times to auditory stimuli (msec)</td>
<td>O</td>
<td>/</td>
<td>316.00 ± 32.04**</td>
<td>/</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>/</td>
<td>289.00 ± 80.75**</td>
<td>/</td>
</tr>
<tr>
<td>Sentence repetition (Vender et al. 1981)</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Word repetition (Fabbro and Galli 2001)</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Digital gnosis (Spinnler and Rognoni 1987)</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Backward counting (100-0) (Reynolds and Bigler 1995)</td>
<td>O</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>C</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

+: normal performance; -: deficient performance; /: performance not evaluated; ** not significant means difference (t-test); * significant means difference (p < 0.01) (t-test).
We hypothesized that these impaired performances could not be attributed to deficits in perceptual organization or in visuoconstructional abilities, given that normal performances were recorded in other tests investigating these abilities, but were due, instead, to impulsivity and carelessness. In fact, this patient showed significant “cognitive” impulsivity, possibly linked to a mild, frontal-prefrontal dysfunction detected in two specific tests (continuous performance test (CPT) and the Wisconsin card sorting test (WCST)). The performance in the CPT was characterized by atypically fast responses (97th percentile) and high number of commission errors (99th percentile).

Figure 1. Follow-up (T1) neuropsychological assessment. All three patients show a facial recognition deficit (arrow).

(3) Spinnler H, Tognoni G. Test di fluenza verbale. In: Standardizzazione e taratura italiana di test neuropsicologici. The Italian Journal of Neurological Sciences 1987a; (Suppl. 8).
(8) Spinelli H, Tognoni G. Test delle matrici-visua search. In: Standardizzazione e taratura italiana di test neuropsicologici. The Italian Journal of Neurological Sciences 1987a; (Suppl. 8).
suggesting impulsivity. The patient’s performances in the WCST were within the low average ability level (between 13th and 23rd percentile, as reported in figure 1). Nevertheless, the “Learning to learn” performance was classed as defective (<1 percentile; z score = -2.33), thus indicating reduced conceptual efficiency across consecutive categories, presumably due to defective learning and/or impulsivity.

Figure 2. Transient brief generalized paroxysms (diffuse polyspike discharges) very occasionally associated with brief eyelid myoclonias in patient 1 at T1. EMG1: right deltoid; EMG2: left deltoid. High frequency filter: 70 Hz; Low frequency filter: 0.8 Hz; speed 15 mm/sec; amplitude: 100 μV/cm.

Figure 3. EEG activity on eye closure, associated with eyelid and upper limb myoclonias followed by clouding of consciousness in patient 3 at T1. EMG1-Ref: left palpebral orbicularis; EMG2-Ref: left wrist flexor; EMG3-Ref: left wrist extensor. Speed 15 mm/sec; amplitude: 100 μV/cm; low frequency filter: 0.5 Hz; high frequency filter: 100 Hz; notch: 50 Hz.
Indeed, a subtle “frontal”-“prefrontal” cognitive pattern (i.e. impaired executive functioning) was a behavioural trait that was also apparent in his daily life (e.g. he destroyed a newly purchased hi-fi system) and possibly linked to the prevalently frontal EEG activity recorded during EC at T1.

In Patient 3, the neuropsychological evaluation revealed impaired executive functioning, associated with attention (z score = -2) and short-term memory (word span, z score = -2.03; digit span, z score = -2) deficits, and significantly impaired performances on two tests of highly automated abilities (i.e. reading [z score = -4.5] and backward counting [z score = -5.8]), the latter suggestive of the slower processing speed often found in subjects with reduced brain efficiency.

In this patient, presenting with the most significant reduction in cognitive ability at the end of the 9-year follow-up, the neuropsychological profile showed an impairment in several fields, with only few preserved abilities (phonological processing, sentence comprehension, receptive vocabulary, ideomotor praxis and some visuo-motor construction aspects). Nevertheless, this patient, like the other two, showed significantly impaired facial recognition ability (z score = -3), without evident deficits in visuo-perceptual organization, visuospatial processing, or visuo-constructual abilities. Finally, in this patient, the sustained and significant reduction in cognitive ability was associated with interfering behaviours (e.g. sexual compulsivity) and impaired adaptive abilities, which necessitated her institutionalisation.

Figure 4. Diffuse polyspikes prevalent over the frontal region in patient 2 at T1. EMG1-Ref: left palpebral orbicularis; EMG-Ref: right palpebral orbicularis. Speed 15 mm/sec; amplitude: 70 μV/cm; low frequency filter: 0.5 Hz; high frequency filter: 100 Hz; notch: 50 Hz.

Discussion

In this report, we described the neuropsychological features of three patients with epileptic activity triggered by EC, examined at onset and after a long follow-up period (mean: 10 years; range: 8-14 yrs).

The results of neuropsychological assessment during tasks with eyes closed compared to with eyes open, showed no significant differences at T0 or at T1 in patients 1 and 2, thus possibly indicating the absence of a TCI.

For Patient 3, in whom remarkable worsening of cognitive tasks was demonstrated during video-EEG monitoring, it is very difficult to determine whether the differences between the two conditions (eyes open and closed) were really due to epileptic activity versus other EC-induced phenomena.

Consequently, on the basis of these considerations, our findings demonstrate that not all eye-closure-triggered paroxysms are associated with TCI, in accordance with other studies supporting the hypothesis that subclinical EEG discharges are not necessarily associated with TCI (Binnie and Marston, 1992).

Nevertheless, our results could have been influenced by certain methodological shortcomings, e.g. non-computerized administration of cognitive tasks during EEG recording and not having used an ocular Barraquer blepharostat to impede the involuntary blinking reflex in the administration of neuropsychological evaluations during video-EEG (Aldenkamp and Arends, 2004).

On the other hand, our data highlight that EC-triggered EEG epileptic discharges can produce long-lasting neu-
ropsychological and behavioural effects, as demonstrated in the two patients with EC-induced, continuous electrical activity (i.e., patients 2 and 3). In these patients, significant intellectual developmental slowing, in terms of lack of acquisition of new skills at the expected rate, was demonstrated by a decrease in IQ at follow-up. In agreement with other reports (Binnie 2001, Brinciotti et al. 1989), we hypothesize that EEG discharges recurring over time, might exert a disruptive effect on cognitive functions. Moreover, in the evaluation of cognitive disorders in epilepsy, their possible multifactorial origin, related to etiology, epilepsy syndrome, seizure effects, antiepileptic drug regimen, possible psychological aspects, must be taken into account (Aldenkamp, 1997, Aldenkamp and Arends, 2004, Binnie, 2001, Brinciotti et al. 1989, Veggio et al. 2002, Tromp et al. 2003, Tuchman and Rapin 1997, Jokeit et al. 2004).

With reference to the different cognitive outcomes of Patients 2 and 3, the following factors might be involved: – EEG pattern: the most significant decrease in IQ (i.e. Patient 3) was associated with EEG activity characterized by polyspikes or generalized fast activity similar to that observed in some epilepticencephalopathies. Moreover, this electrical pattern, was unchanged from baseline to follow-up, retained the same characteristics on prolonged; – EC, and was associated with clinical phenomena (table 1, figure 3); – seizure frequency: in Patient 3, there was no drug withdrawal and seizures were frequent. Conversely, in Patient 2 the seizures were rare and induced only by drug withdrawal (table 1); – age-at-onset of continuous generalized EEG discharges: the more severe outcome (in Patient 3) was related to the earlier EC-status-onset (i.e. 7 years versus 11 years), supporting the hypothesis advanced in a previous paper (Binnie, 2001); – possible, different “cognitive” side effects of the different AED regimens could not be excluded (table 1).

Finally, we underscore that neuropsychological evaluation in patients with reflex epilepsy is mandatory and could provide important pathogenetic clues.

In fact, our three patients showed an extreme variability across tasks except for a facial recognition deficit that was evident in all cases (figure 1), suggesting a possible dysfunction of temporo-occipital brain structures and/or the fusiform face area. Abnormal functioning of these cortical areas, involved in the processing of visual stimuli, might play a role in the ECS displayed by our patients, as recently demonstrated by combined IMRI/EEG studies in patients with fixation-off sensitivity (Lanni et al. 2002, Di Bonaventura et al. 2005).

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