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Continuous spikes and waves during sleep in children with shunted hydrocephalus

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Abstract Focal epileptiform abnormalities in awake children submitted to ventricular shunting are well described in the literature, but there are few reports about EEG patterns during sleep. We studied 20 children affected by hydrocephalus of various aetiology and submitted to shunting during the first year of life. We found focal abnormalities in all the children and in 95% of cases they were on the same side as the shunt; in 65% of cases they had an amplitude of 300 mV or more. During sleep there was activation of abnormalities in all subjects, and in 33% we found continuous spikes and waves during slow sleep (CSWS). We discuss the aetiology of CSWS and its possible role in causing the neuropsychological disturbances of our patients.

Key words Hydrocephalus · CSWS · Secondary bilateral synchrony · Ventriculo-peritoneal shunt

Introduction

There are many reports in the literature of the presence of focal epileptiform abnormalities in subjects with shunted hydrocephalus [8]. Focal slow spikes and sharp waves have been described in wakeful subjects, and these are statistically more frequent in those who have undergone such an intervention.

There are, however, few reports concerning the behaviour of these abnormalities during sleep or the concomitant presence of generalised abnormalities [1, 16]. We describe our observations in a group of children with congenital hydrocephalus who had undergone ventriculoperitoneal shunting, concentrating on their neurophysiological and clinical characteristics. In particular, we discuss the relationship between the presence of continuous spikes and waves during slow sleep (CSWS) and the behavioural and neuropsychological problems of these patients.

Patients and methods

This study involved a population of 20 children (13 boys and 7 girls; mean age: 5 years; age range: 1–16 years) who came to our notice in the period 1994–1996. With the exception of one patient , who had been treated later, all had undergone placement of a ventriculoperitoneal shunt during the first year of life. The causes of the patients' hydrocephalus are given in Tables 1 and 2. The children were, at a later stage, divided into two subgroups. The first contained patients showing the presence of continuous spikes and waves during slow sleep (CSWS), and the second was made up of those who did not present this electroencephalographic (EEG) pattern during sleep. It must be underlined that CSWS was taken to mean the presence of continuous spikes and waves during at least 85% of slow sleep. As far as most of the patients were concerned, we did not have access to EEG documentation relating to the first year of life, the earliest available to us referring to the second or third year of life, the period in which these subjects were first seen in our department. All the subjects were submitted to periodic EEG polygraphic recordings (every 4–6 months) while awake and during afternoon sleep. Those in whom CSWS was present during afternoon sleep were submitted to nocturnal EEG recording or to 24-h EEG recording using Brain spy (Micromed) to confirm the diagnosis. Afterwards these patients were submitted to two additional EEGs (during afternoon sleep) during the first month after diagnosis and to regular examinations every 2 months at the time of day or night at which CSWS were present. During consultations, or during the control period, all the patients underwent a further neuroradiological examination using magnetic resonance imaging (MRI). Particular attention was paid to the following features: (1) cortical atrophy; (2) ventriculomegaly; (3) alterations of the white matter (parasagittal damage and periventricular leucomalacia). The patients were also evaluated, when possible at the start of their assessment and then periodically, using Griffiths' scale or the Revised Wechsler Intelligence Scale for Children (WISC-R). Some patients of this study had previously performed an

Table 1 General characteristics of patients with CSWS (*DQ* development quotient obtained with Griffiths mental development scales, *IQ* intelligence quotient obtained with the Revised Wechsler Intelligence Scale for Children; *Not testable* means severe mental retardation or serious behavioural disturbances made testing impossible)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Clinical aspects						
Sex	M	M	M	F	M	F
Age at 6/30/96	7 years 6 months	10 years	4 years 3 months	6 years 6 months	7 years 6 months	2 years 6 months
Type of hydrocephalus	Post-haemorrhagic	Post-haemorrhagic	Arachnoid cyst	Infectious	Infectious	Sylvian aqueduct stenosis
Age at shunt	<1 year	<1 year	<1 year	<1 year	<1 year	<1 year
Age at seizure onset	3 years 9 months	9 years	3 years 6 months	1 year 6 months	1 year 6 months	10 months
Seizure type	Partial motor, absence	Partial motor	Partial motor	Partial motor spasms	Partial/ generalized	Partial motor
Drugs used at CSWS onset	PB	PB	PB	PB	PB	CBZ
Neuroradiological findings						
Cortical atrophy	+	+	+	+	+	+
Ventriculomegaly	+	+	+	+	+	+
White matter alterations				+	+	+
EEG aspects						
Awake						
Shunt-side focal abnormalities	+	+	+	+	+	+
Abnormalities amplitude >300 μV	+	+	+	+	+	
Secondary bilateral synchrony	+	+	+	+	+	+
Sleep						
CSWS	+	+	+	+	+	+
Spike wave index (%)	90	90	85	85	85	90
Duration of CSWS	2 years	1 year	2 years	2 years	1 years	1 year
Developmental evaluation						
Before CSWS	DQ100	IQ105	Not testable	Not testable	DQ95	DQ30
During CSWS	DQ80	IQ90	Not testable	Not testable	IQ80	DQ15
After CSWS	DQ95	IQ105	Not testable	Not testable	IQ95	DQ35

intelligence test since they were included in a clinical follow-up that comprised a periodical psychometric evaluation.

Observations and results

The general characteristics of the patients are summarised in Tables 1 and 2. Sixty-five per cent (65%) of the patients had partial seizures, 80% of which were partial motor seizures. The average age at which seizures first appeared was 2 years and 9 months. EEG recordings made when the patients were awake revealed that all of them had focal EEG abnormalities, which were on the same side as the shunt in 95% of cases. These abnormalities consisted of spikes followed by slow waves and, in 13 subjects (65%), they had an amplitude of 300 μV or more (Fig. 1). As mentioned in the Methods section, the patients were divided into two subgroups according to the presence or absence of CSWS. The first group contained 6 subjects (33%) with CSWS lasting, on average, 18 months. All the subjects (100%) in the CSWS group had presented abnormalities, which consisted of spikes followed by slow waves with an amplitude greater than 300 μV (see Fig. 1) and secondary bilateral synchrony (see Fig. 2). In contrast, in the group of patients without CSWS, wide-amplitude abnormalities were found in only 50% of the subjects, while secondary bilateral synchrony was not found in any of them. All the subjects (100%) in the CSWS group had epileptic seizures: in 83% these were partial motor seizures, while in the other 17%

Table 2 General characteristics of patients without CSWS. *IQ* intelligence quotient (using Revised Wechsler Intelligence Scale for Children)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	Case 11	Case 12	Case 13	Case 14
Clinical aspects														
Sex	M	F	M	F	F	F	M	M	M	M	M	F	M	M
Age at 6/30/96	5 years 6 months	16 years	6 years	2 years 4 months	2 years 3 months	5 years	7 years	1 year 10 months	3 years	9 years	5 years 6 months	1 year	5 years 9 months	1 year
Type of hydrocephalus	Post-haemor-rhagic	Post-haemor-rhagic	Arnold-Chiari	Infectious	Post-haemor-rhagic	Arnold-Chiari	Arnold-Chiari	Arnold-Chiari	Dandy–Walker	Arnold-Chiari	Sylvian aqueduct stenosis	Post-haemor-rhagic	Post-haemor-rhagic	Arnold-Chiari
Age at shunt	<1 year	>1 year	<1 year	<1 year	<1 year	<1 year	<1 year	<1 year	<1 year	<1 year	< 1 year	< 1 year	< 1 year	< 1 year
Age at seizure onset	–	2 years 6 months	5 years	–	–	–	3 years 3 months	7 months	4 months	6 years	–	–	3 year	–
Seizures type	–	Partial complex	Simple partial	–	–	–	Partial motor	Partial motor	Partial motor	Partial motor	–	–	Simple partial	–
Neuroradiological findings														
Cortical atrophy			+		+				+		+			+
Ventriculomegaly	+	+		+	+		+		+	+				
White matter alterations		+						+			+			
EEG aspects														
Awake														
Shunt-side focal abnormalities	+	+	+	+	+	+	+	+	+	+		+	+	+
Abnormalities with amplitude >300 μV	+		+	+				+	+	+			+	
Secondary bilateral synchrony	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Sleep														
Activation of abnormalities	+		+	+	+	+	+	+	+				+	
Spike wave index (%)	45		50	35	40	55	45	60	45				40	
Development evaluation														
IQ	60	Not testable	55	55	Not testable	80	87	63	Not testable	103	82	86	Not testable	60

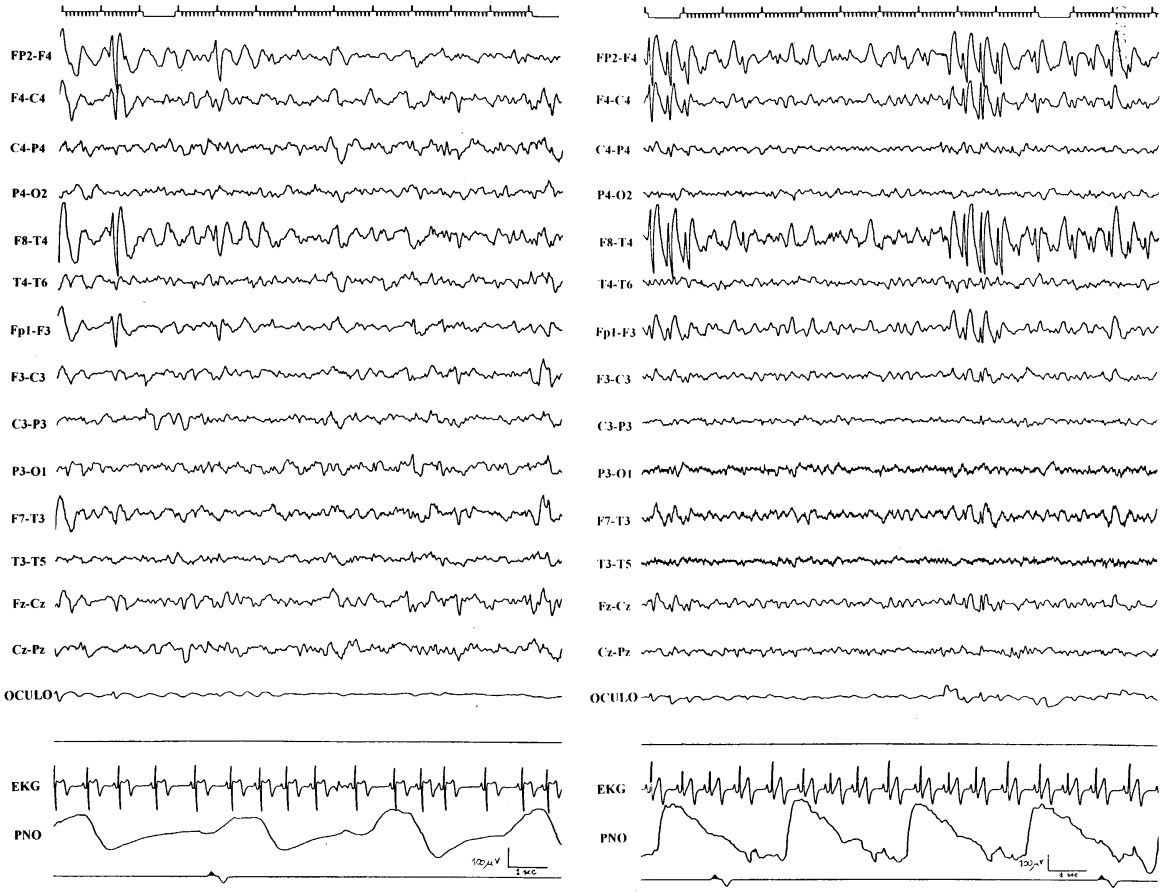

Fig. 1 Focal abnormalities with an amplitude of 300 μV

they were partial secondary generalised seizures. Subject 1 also experienced absences and subject 4, infantile spasms. In the group of patients without CSWS, only 50% of the subjects were found to have seizures: in 4 out of 7 patients (57%) these were partial motor seizures, in 2 out of 7 (29%) they were simple partial seizures, and in 1 out of 7 (14%) they were complex partial seizures.

Examination of the three main neuroradiological features mentioned in the Methods section revealed that all three were present in 3 out of the 6 patients (50%) in the CSWS group, while cortical atrophy and ventriculomegaly were present in all of them (100%). Meanwhile, 79% of the patients in the non-CSWS group showed alterations that could be detected neuroradiologically, but none of them presented all three of these alterations simultaneously. Cortical atrophy together with ventriculomegaly was present in only 14% of the subjects, while ventriculomegaly together with alterations of the white matter occurred in only 1 subject (7%). Six patients were not testable with standardised tests because of severe mental retardation or serious behavioural disturbances. Eight patients showed mental retardation, which could be classed as severe in 3 of them and as moderate to slight in the others. In 4 patients in the CSWS group it proved possible to perform intelligence assessments in series (i.e., before the appearance of CSWS, during CSWS and after its disappearance). In this way, we were able to demonstrate that the intellectual capacity of all the subjects deteriorated in the presence of the abnormalities, returning to previous levels when the CSWS disappeared (Table 1).

Discussion and conclusions

As seen in the Results, focal EEG abnormalities were detected in all our subjects, presenting on the same side as the shunt in 95% of cases, a finding which is in accordance with accounts that have been appearing in the literature for some time now. Indeed, many authors have drawn attention to the particular localisation of the focal abnormalities in subjects with shunted hydrocephalus, all reporting their tendency to be present, almost constantly, on the same side as the shunt. Laws and Niedermeyer [11] studied 18 patients with hydrocephalus treated with shunt procedures

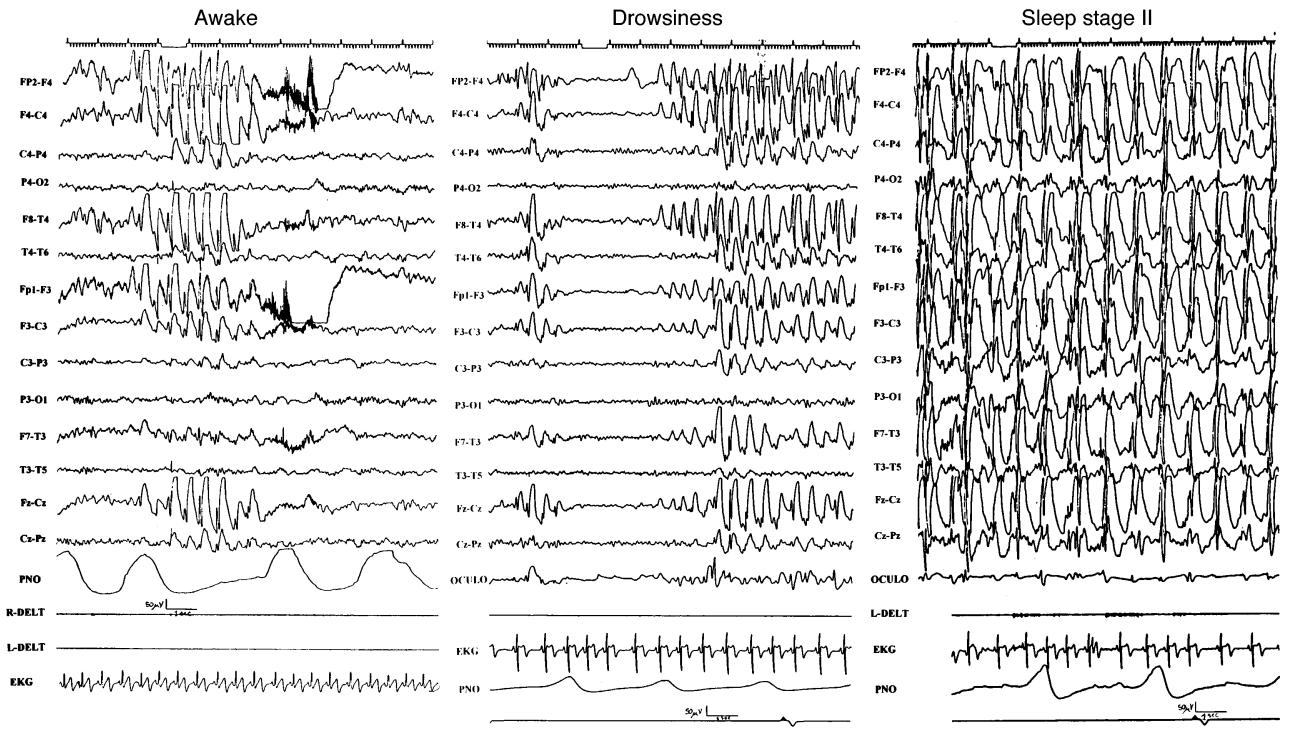

Fig. 2 *Left* focal abnormalities; *centre* secondary bilateral synchrony; *right* continuous spikes and waves during sleep (CSWS)

and found that, among the subjects showing EEG abnormalities (73% of the sample), such abnormalities were on the same side as the shunt. Meanwhile in a comparison group of 25 patients with hydrocephalus and no surgical treatment none showed significant lateralisation of the abnormalities. The same authors hypothesised that the abnormalities detected in the patients who had undergone shunting could be due to an infection of the valve implantation area. As infectious complications occurred in only 4 out of 20 of our patients (20%), we were not able to add weight to the hypothesis that this factor (infection of the valve implantation area) plays a part in the pathogenesis. Ines Desiderio et al. [8], in an attempt to clarify the genesis of focal abnormalities, likened the effect of the valve to that of a foreign body; they also asserted that the development of epileptic seizures, commonly within 4 years after the operation in their patients, has the same temporal relationship as seen in epilepsy following other types of cerebral trauma. With the exception of 1 subject, all the children in our sample had undergone placement of a ventriculoperitoneal shunt during the first year of life, but the time of seizure onset in these subjects is not always compatible with Ines' hypothesis. Nevertheless, in view of the fact that, in our sample, the side of the EEG abnormalities almost always coincided with that of the shunt, we too support the view that this intervention can be considered extremely important factor in the genesis of EEG abnormalities. As also demonstrated in the literature, where comparisons with a "non-shunt" population are possible, the quantity of EEG abnormalities detected and the percentage of patients with seizures are much lower in non-shunt than in shunt populations [3, 8]. We must also consider the morphological characteristics of the epileptiform abnormalities detected in our sample and particularly the fact that, in a significant number of patients, these showed a wide amplitude. We underline that the latter is a feature never before reported in the literature. Wright et al. [17] reported wide amplitude abnormalities in experiments performed on cats with hydrocephalus; in man, this is a finding typical of cases of lissencephaly. In his classic work on lissencephaly, Gastaut et al. [5], in an attempt to explain the amplitude of the electrical signal detected in patients suffering from the aforementioned pathology, correlated the wide amplitude of the electrical signals with the defect in cortical gyration and organisation. According to this hypothesis, the origin of potential of higher amplitude would lie in a cortical rearrangement in which the dipoles are positioned parallel to one another, and no longer in a radial pattern. To demonstrate this, Gastaut refers to an experimental study carried out by Régis: in this study, alpha or beta frequencies with amplitudes greater than 300 μV were recorded in children affected by severe hydrocephalus and whose cortical mantle was thinner and smoother than normal. Alongside these observations, wide amplitude abnormalities were, as mentioned earlier, found in an experimental model of hydrocephalus in the cat. Furthermore, cytological alterations and alterations of the cortical architecture, with structural disruption of both the top and deeper layers, were also ob-

served. All this was attributed to increased pressure of the cerebrospinal fluid which, owing to the effect of compression, upsets both the normal horizontal pattern of the cortical cells and the normal orientation of the dipoles. Consequently, the experimental data referring to the cat appear to confirm that, in hydrocephalus, it is possible to observe cytological alterations and alterations and structural disruption of the cortical architecture that are comparable to the changes in cases of lissencephaly. In our sample, ventriculomegaly was present in 10 (77%) and cortical atrophy was found in 8 (61%) of the 13 subjects in whom a wide-amplitude electrical signal was found. This allows us to advance the hypothesis that it is the hydrocephalus itself that may have affected the structural organisation of the cortex, causing cortical atrophy and thinning and, possibly, provoking disruption of the organisation of the pyramidal cells sufficient to interfere with the genesis of the electrical signal. Thus, on the basis of our data, we can confirm that the origin of the EEG abnormalities may lie in the mechanical insult (the implantation of the valve), but state our belief that the high amplitude of these abnormalities cannot be attributed solely to the action of the shunt system; rather, they must be attributed to the cytoarchitectural disruption of the cortex, which may interfere with the genesis of the electrical signal. Another aspect that must be considered is the high percentage (33%) of subjects showing the presence of CSWS. The syndrome represented by the presence of continuous spike-and-wave patterns during slow sleep has been classified by the International League against Epilepsy in the group of "Epilepsies and syndromes undetermined whether focal or generalized". Owing to methodological difficulties, the effective incidence of the syndrome is hard to calculate, but it is, in any case, rare [14]. Cases have been described in association with perinatal asphyxia, meningitis, congenital cytomegalovirus infection, and encephalopathy of unknown origin; so-called cryptogenetic cases appear to be more frequent, even though the role of genetic factors remains to be established. Although, to our knowledge, no other author has ever reported the existence of a possible relationship between CSWS and hydrocephalus, CSWS is seen to occur with significant frequency among our population of hydrocephalic subjects. In view of the absence of any previous report to this effect, the relationship between these two pathologic conditions appears difficult to explain even though, taking some of the characteristics of the sample studied, certain considerations are possible. In particular, all the subjects presenting CSWS showed a tendency towards secondary bilateral synchrony when awake, which supports the findings of Dalla Bernardina et al. [2, 12, 13], according to whom the presence of CSWS in patients with partial epilepsies and partial seizures should be considered the effect of a secondary bilateral synchrony of the focal abnormalities occurring during wakefulness. This has been confirmed by many studies, including experimental ones, such as that conducted in 1994 by Kobayashi et al. [9, 10], which also underlined the role possibly played by the corpus callosum in the generation of secondary bilateral synchrony in subjects with a strong genetic predisposition to epilepsy. The nosological classification of our patients with cerebral lesions remains unclear, as these subjects certainly cannot be grouped with patients affected by genetic epilepsy. We thus believe it is very important to consider the concept of "hereditary cerebral maturation disorder" [4], according to which the association between organic lesions and genetic profile may provide an explanation of the wide variety of conditions, including shunted hydrocephalus, that are associated with CSWS.

Other authors [6] have also described the presence of electrical abnormalities with benign evolution, during slow sleep in subjects with severe alterations of the cortical structure, such as cortical dysplasia. Our patients can, in fact, be considered similar to those described by Guerrini et al. [6], in terms of their neuropathological characteristics, in terms of the cytological and cytoarchitectural modifications provoked by the condition of hydrocephalus, and in terms of the relatively benign evolution of the condition following the start of appropriate pharmacological treatment.

In conclusion, we must stress the importance of the possible association of genetic with organic factors in the aetiopathogenesis of CSWS in general, and in particular in the subjects examined in our study. In addition to the neurophysiological aspects discussed so far, we feel it is useful to underline a pharmacological problem which may play a part in the genesis of CSWS. We noted that as many as 5 out of the 6 patients with CSWS (83%) were taking phenobarbital at the time of onset of the abnormalities in slow sleep. Hirsch et al. [7] have underlined that use of phenobarbital may be considered one of the factors that favour the onset of CSWS in subjects presenting with partial seizures and focal abnormalities: our data also correspond with this line of thought and will undoubtedly be investigated more thoroughly in further studies. The last aspect to be taken into consideration is the correlation between neurospychological disturbances and CSWS. This correlation was highlighted by Tassinari et al. as far back as 1982 [15], and all subsequent studies have confirmed that the presence of continuous abnormalities during sleep interferes with children's language and learning capacity. It is important to underline that, in some cases [1, 2, 5, 6], a close correlation was found between the presence of CSWS and learning and cognitive disturbances, which were resolved by the introduction of pharmacological treatment leading to the disappearance of the EEG abnormalities. It is often suggested that the appearance of learning difficulties, poor performance and concentration problems in hydrocephalic subjects derives from neurosurgical problems linked to a possible chronic malfunctioning of the ventriculoperitoneal shunt system. By reporting the possible presence of CSWS in subjects with shunted hydrocephalus and the close correlation between this and the presence of neuropsychological disturbances, we have

opened up a possible new line of research concerning these subjects. Indeed, especially in subjects who present abnormalities while awake and show a tendency to develop secondary bilateral synchrony, an EEG recording during sleep can show that CSWS is the real cause of the deterioration. Cognitive evaluations showed that CSWS affected the performances of our subjects only transiently (thanks to the pharmacological intervention) and that there is a return to the previous condition after the regression of the EEG pattern. In conclusion, the findings described in the present paper represent new information relating both to hydrocephalus and to CSWS. Although the association between these two conditions has not previously been described, we found it in a large percentage of our population. We also described EEG abnormalities with unusual amplitude, which we suggest may be correlated with possible neuropathological findings. Although we cannot draw any definitive conclusions about the relationship between CSWS and hydrocephalus, the close correlation between CSWS and attention and behavioural disturbances underlines once again how important EEG monitoring is for accurate clinical and prognostic evaluation of patients of this type.

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