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Ictal semiology of gelastic seizures

Laura Mirandola [a,*], Gaetano Cantalupo [b], Giuseppe d'Orsi [c,d], Stefano Meletti [e], Anna Elisabetta Vaudano [e], Lidia Di Vito [f], Aglaia Vignoli [g,h], Laura Tassi [i], Veronica Pelliccia [i]

[a] Neurology Unit, San Giovanni Bosco Hospital, Turin, Italy
[b] Child Neuropsychiatry Unit, Department of Surgical Sciences, Dentistry, Gynecology and Pediatrics, University of Verona, Verona, Italy; Research Center for Pediatric Epilepsies Verona, Italy
[c] Neurology Unit, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo (Fg), Italy
[d] Epilepsy Center – Clinic of Nervous System Disease, Policlinico Riuniti, Foggia, Italy
[e] Division of Neurology, University Hospital of Modena, Modena, Italy; Department of Biomedical, Metabolic and Neural Science, University of Modena and Reggio Emilia, Modena, Italy
[f] IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy
[g] Childhood and Adolescence Neurology and Psychiatry Unit, Niguarda Hospital Department of Health Sciences, University of Milan, Milan, Italy
[h] Epilepsy Center-Child Neuropsychiatric Unit, ASST Santi Paolo e Carlo, Milan, Italy
[i] "Claudio Munari" Epilepsy Surgery Center, Niguarda Hospital, Milan, Italy

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ABSTRACT

Gelastic seizures are rare epileptic manifestations characterized by laughter or a smile. The main etiology is represented by hypothalamic hamartoma, but also focal localization of the epileptogenic zone is described.

We reviewed a group of patients with gelastic seizures to describe the semiology and to establish any difference related to diverse epilepsy etiologies.

Thirty-five seizures from 16 patients (6 females) were reviewed.

The study confirms that hypothalamic hamartoma is the more frequent etiology associated with gelastic seizures. Laughter represented the majority of gelastic ictal signs, while the ictal smile was less frequent. In 87.5% of patients, the manifestation of laughter or smile was the only ictal phenomenon, or the first and the most important clinical sign.

Interestingly, it has been observed that patients with a lesion localized in the hypothalamic region had more frequently laughter with emotional involvement and that laughter was the only manifestation of the seizure. On the contrary, patients with lesions localized outside the hypothalamic region had more often seizures with laugh without emotional involvement, resembling a more mechanical action, and associated with other semeiological signs.

It, therefore, seems possible to assume that the emotional involvement and the expression of mirth during the seizure, especially in children, are more frequently associated with hypothalamic hamartoma. On the contrary, when the semiology includes less conveyed emotion similar to a mechanical action and other symptoms, an extra hypothalamic localization should be considered.

1. Introduction

Gelastic seizures (GS) are rare epileptic manifestations characterized by a burst of stereotyped laughter (or smile) lasting usually less than 60 seconds, unprovoked by external stimuli, and unmotivated. The laughter represents the predominant ictal semiology, and it could be less or more intense; nevertheless, in addition to the ictal gelastic sign, other clinical features (objective and subjective) can be associated [1]. In children, there is a well-established association between GS and hypothalamic hamartoma, representing the main known underlying etiology. Gelastic seizures in the setting of the hypothalamic hamartoma are associated with childhood-onset, intractable seizures, precocious puberty, and common cognitive impairment [2–5]. Gelastic seizures can occur with very high frequency but are often misinterpreted: in the majority of patients only when more devastating and recognizable seizures (with richer and more complex semiology) occur, a correct diagnosis is eventually posed [6]. Nevertheless,

* Corresponding author at: Neurology Unit, San Giovanni Bosco Hospital, Turin, Italy.
E-mail address: laura.mirandola@aslcittaditorino.it (L. Mirandola).

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recent reports indicated that GS are associated with focal cortical discharges and are described in structural and unknown epilepsies with the epileptogenic zone (EZ) over the temporal, frontal, opercular-insular, and parietal cortices [7–13], suggesting a larger widespread symptomatogenic network. Accordingly, intracortical electrical stimulation studies indicate the role of these regions in mirth and laughter [14,15].

Despite the singularity of the clinical manifestations, in literature, there are only a few descriptions of the detailed semiology of GS.

Laughter and smile themselves are typical expressions of mirth and encompass both emotional and motor components [14,16]. Compared to a smile, laughter is a much more complex behavior, which involves not only a facial display but also rhythmic and coordinated body movements, involving also diaphragm and inspiratory activity [17]. On the other hand, the different underlying etiologies could explain the different clinical manifestations and also the core phenomenology of gelastic seizures.

In this study we aim to analyze the ictal semiology of GS, looking for eventual clinical differences, and comparing two groups with diverse underlying etiologies and localizations of EZ.

2. Materials and methods

Video-EEG monitoring reports from all patients admitted to five different Italian Epilepsy Centers (Epilepsy Surgery Center "Claudio Munari", Niguarda Hospital, Milano- Neurology Unit, Ospedale Civile Baggiovara Hospital, University Hospital, Modena- IRCCS Neurological Sciences Institute, Bologna- Epilepsy Center, San Paolo Hospital, Milano- Epilepsy Center – Clinic of Nervous System Disease Policlinico Riuniti, Foggia) from 2000 to 2018 were retrospectively reviewed to identify patients with GS. When the ictal semiology description included laughter or smile, the patients were selected and their ictal video-EEG was independently reviewed by all components of the "LICE Videoteca" Study Group Commission to confirm the presence of GS and to characterize the complete semiology of the seizures.

Inclusion criteria were the presence of GS; at least one video-EEG-documented seizure and complete brain MRI with dedicated epilepsy protocol.

Classification of the epilepsy type and EZ was based on the multidisciplinary team discussion.

2.1. Descriptive analysis of semeiological features

By means of the inspective analysis of videos acquired during video-EEG monitoring, we investigated the patient's behavior, during the GS. We decomposed semiological features in different categorical variables, as follows:

– motor involvement of different parts of the face in the expression was dichotomized in "mouth region only" or "Duchenne display" (with eye wrinkles and activation of mouth region jointly) [16];

– presence of suggestive sound of laughter ("smile" vs "laugh");

– presence of rhythmic and coordinated body movements related to "laugh-pulse";

– presence of other gestures;

– presence of conveyed emotion, defined by the expression of spontaneous mirth through both mouth and eye regions activation, and intonation in the laughter.

– absence of conveyed emotion, when a mechanical behavior was observed in the mouth region (see Fig. 1);

– time course of laughter intensity (steady, intermittent, or increasing);

– presence of other signs (and their chronological relationship with smile/laugh);

– awareness;

– presence of postictal deficits;

– evolution to bilateral tonic-clonic seizure;

– occurrence during wakefulness or sleep (see Table 1).

For patients with multiple seizures, we also investigated the intra-individual variability of each semiological feature.

Furthermore, for each patient, we considered the relationship of semiology with the underlying epilepsy etiology and localization of the EZ.

2.2. Cluster analysis

We used a Two-Step Cluster analysis to identify a distinct subgroup of patients based only on the ictal semiological features, in order to understand if the semiology can guide the etiological diagnosis. To this aim, only features that were consistent across different seizures of the same patient were considered. Thus, each patient accounted only for one entry per variable, to avoid biases due to redundancy in patients with multiple seizures.

3. Results

Thirty-five seizures from 16 patients (6 females) with GS were reviewed and included in the study. The mean age at Video-EEG recording was of 26.6 years (range: 3–61 years; 4 children and 12 adults).

3.1. Descriptive analysis of semeiological features

The ictal clinical semiology was represented by laughter with a typical recognizable sound, such as a laugh, in the majority of cases (69% of seizures); in the remaining cases, a clear and prolonged smile was observed.

In 21/35 seizures (60%) the laughter or smile was the only clinical feature of the seizure; in the other seizures, the gelastic component was the presenting symptom in the majority of cases (10 seizures) followed by other clinical signs (such as behavioral arrest, staring, oral/gestural automatisms, or bilateral tonic-clonic movements). In the remaining 4 seizures recorded from 2 patients, the laughter appeared later on during the seizures: in one patient a burst of laughter occurred after body and leg rocking in the contest of sleep-related hyper motor seizure, while in the other one the smile followed the behavioral arrest and staring.

The first recognizable behavioral change suggesting mirth has been observed either in the mouth (40% of seizures) or simultaneously in the eyes and the mouth, such as "Duchenne display" (60% of seizures). A motor component of the laughter involving muscles outside the face was observed in 31% of seizures, such as rhythmic and coordinated movements of the shoulders and the trunk.

A clear emotion-conveying behavior was observed in 51% of seizures. In all these seizures a spontaneous and growing intonation in the laughter was noticed.

Five patients (23% of seizures) repeatedly brought one hand (either left or right in an indifferent way) to the face: in 4 of them in an attempt to cover the eyes and in the other patient covered the nose and mouth (Fig. 2).

The average laughter length based on the inspective clinical analysis was of 19.9 seconds (4–45 s). The time course of the laughter or smile appeared intermittent in 34% of seizures, constant in 43% of seizures, and increasing throughout the development of the seizure in 23% of seizures.

In the majority of patients (and in 71% of the seizures) awareness was not impaired during the seizure.

Fig. 1. Emotional and non-emotional laugh or smile. -On the left two patients express an emotional laugh. The presence of conveyed emotion is associated with the expression of spontaneous mirth through both mouth and eye region activation. The patients at the center of the figure express a smile without conveying emotion, similar to the patient on the right side, showing a non-emotional laugh. Mechanical behavior is observed in the mouth region.

Table 1
Ictal semiology of gelastic seizures in patients with hypothalamic hamartoma (Group 1) and other etiologies (Group 2).

Ictal semiological features	Group 1 (n° of seizures – n° of patients)	Group 2 (n° of seizures – n° of patients)	Total (n° of seizures – n° of patients)
Auditory component	Laugh (15 – 5) Smile (8 – 5)	Laugh (9 – 5) Smile (3 – 1)	Laugh (24–10) Smile (11 – 6)
Laugh/Smile only	Yes (17 – 8) No (6 – 2)	Yes (4 – 2) No (8 – 4)	Yes (21 – 10) No (14 – 6)
Face	Mouth (10 – 6) Mouth and eyes (13 – 4)	Mouth (4 – 2) Mouth and eyes (8 – 4)	Mouth (14 – 8) Mouth and eyes (21 – 8)
Body (shoulders/ trunk)	Yes (10 – 3) No (13 – 7)	Yes (1 – 1) No (11 – 5)	Yes (11 – 4) No (24 – 12)
Emotional involvement	Yes (16 – 7) No (7 – 3)	Yes (2 – 2) No (10 – 4)	Yes (18 – 9) No (17 – 7)
Hand to face	Yes (8 – 5) No (15 – 5)	Yes (0 – 0) No (12 – 6)	Yes (8 – 5) No (27 – 11)
Awareness impairment	Yes (6 – 3) No (17 – 7)	Yes (1 – 1) No (8 – 4) n.a. (3 – 1)	Yes (7 – 4) No (25 – 11) n.a. (3 – 11)
Post ictal impairment	Yes (6 – 3) No (17 – 7)	Yes (1 – 1) No (8 – 4) n.a. (3 – 1)	Yes (7 – 4) No (25 – 11) n.a. (3 – 1)
Vigilance state	Wake (20 – 9) Sleep (3 – 1)	Wake (6 – 4) Sleep (6 – 2)	Wake (26 – 13) Sleep (9 – 3)

GS: gelastic seizures; n.a.: not applicable.

In only 26% of cases, the GS arose from sleep: one patient was suffering from "Sleep-Related Epilepsy" (SHE) [18] with laughter associated with a hyper motor seizure. Only one patient had a GS evolving into a bilateral tonic-clonic seizure (BTCS).

In order to investigate the relationship between ictal semiological features and individual patient fixed variables (such as age, gender, etiology, etc), we investigated, only in patients with multiple recorded seizures (n = 8; median number of seizures per patient = 3, range 2–5), which semiological features were consistent across different seizures in the same patient. We found out that all investigated features were consistent across all seizures in 5/8 patients, while inconsistency in two patients was limited only to hand-to-face gestures (in both patients being present only in half the four seizures of each), with all remaining features repeatable. The third patient with inconsistent semiology was the only patient with seizures rapidly evolving to BTCS.

Regarding etiology, in 10 patients (23 GS recorded; mean age: 23.8 years) it was represented by a lesion in the hypothalamic region: 9 patients had hypothalamic hamartoma (HH), and one had a hypothalamic cerebral tuberculoma. In the remaining 6 (12 GS recorded; mean age: 31.3 years) different etiologies were responsible for their focal epilepsy. Three patients had focal cortical dysplasia localized in the frontal lobe (2 on the right side, one on the left), a patient had a single subcortical heterotopic nodule localized in the right fronto-insular white matter, a patient had MRI-negative focal epilepsy with right temporal lobe onset seizures, and the remaining patient had a cavernoma localized in the right frontal lobe (Fig. 3).

The main etiology for children (n = 4) was represented by hypothalamic hamartoma (n = 3), with only one child with a single subcortical heterotopic nodule localized in the right frontal white matter. Eight out of the 9 seizures recorded from children (age 3–7 years) were represented by a laugh and only one by a smile.

A comparison of the main ictal features between the two etiology-based groups (HH vs focal) is summarized in Table 1. Gelastic seizures in patients with hypothalamic hamartoma appeared to be more often represented by laughter alone without associated

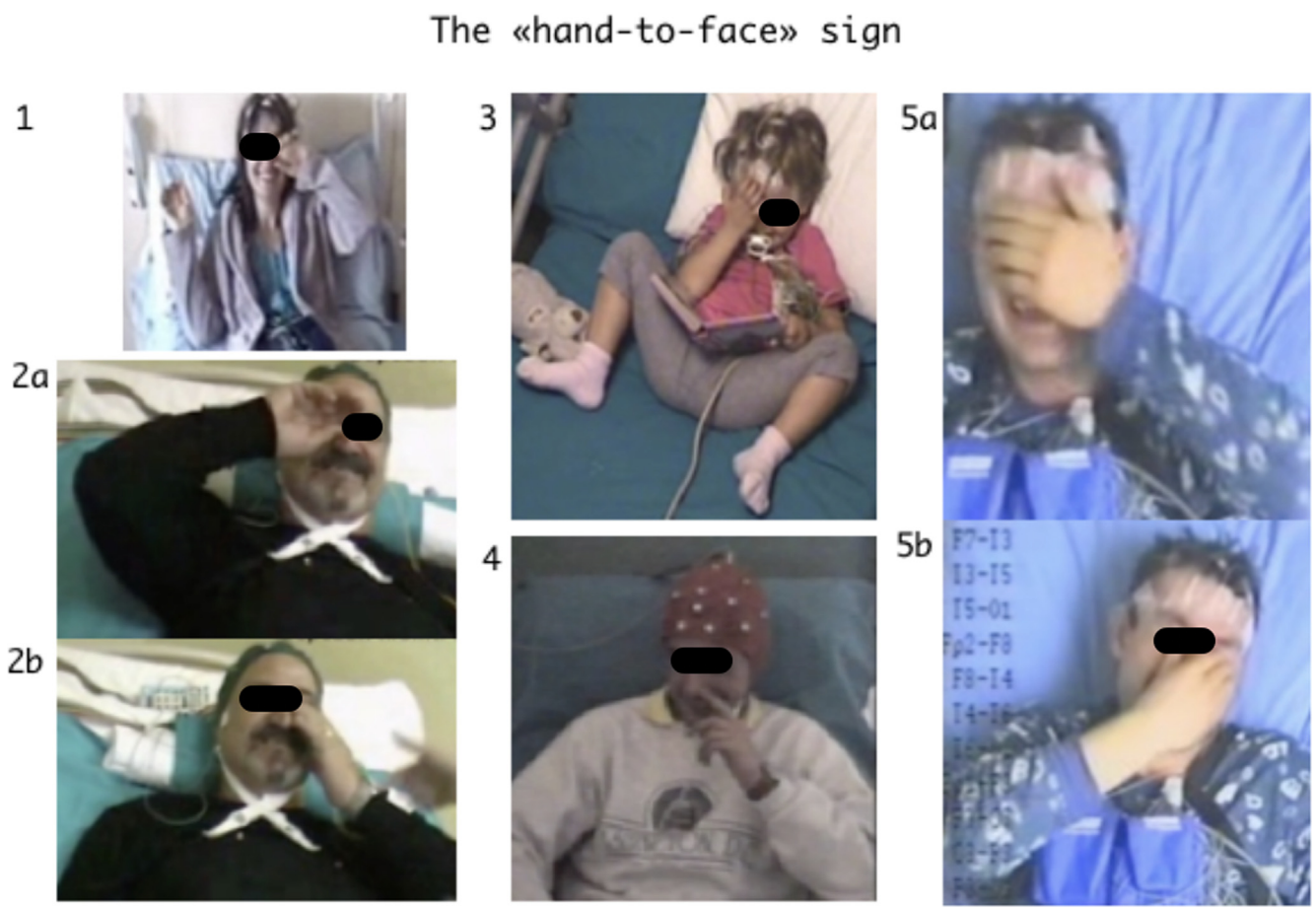


Fig. 2. Hand-to-face sign. The hand-to-face sign of five patients with hypothalamic hamartoma is shown. In all patients except one, the hand is directed to cover the eye region, while in the patient of box 4 the hand is directed to the mouth region. In two patients (box 2 and box 5) both hands are used alternatively to cover the face throughout the seizure.

objective or subjective symptoms, and with more emotional involvement, compared to the seizures of patients with other etiologies. Moreover, the ictal sign of "hand-to-face" was observed only in patients with hypothalamic hamartoma. Gelastic seizures arising from sleep were more frequent in the second group.

3.2. Cluster analysis

Cluster analysis identified three clusters with good quality. The first cluster included patients (n = 6, 37.5%) with gelastic seizures manifesting as laughing conveying emotion or "emotional laugh cluster", a second cluster included patients (n = 6, 37.5%) with seizures manifesting as a smile without clear emotional content, "non-emotional smile cluster", and the third one included patients (n = 4, 25%) with laugh without emotional conveyance, or "non-emotional laugh cluster".

Investigating the role of the two groups (hypothalamic hamartoma vs focal) with respect to the clusters, it was observed that the "non-emotional laugh cluster" was represented only by patients with GS of focal origin (100%, n = 4/4), while the other two clusters, "emotional laugh" and "non-emotional smile", were mainly represented by patients with hypothalamic hamartoma (83.3%, n = 10/12). Chi-square T-test resulted in significant (p = 0.012).

4. Discussion

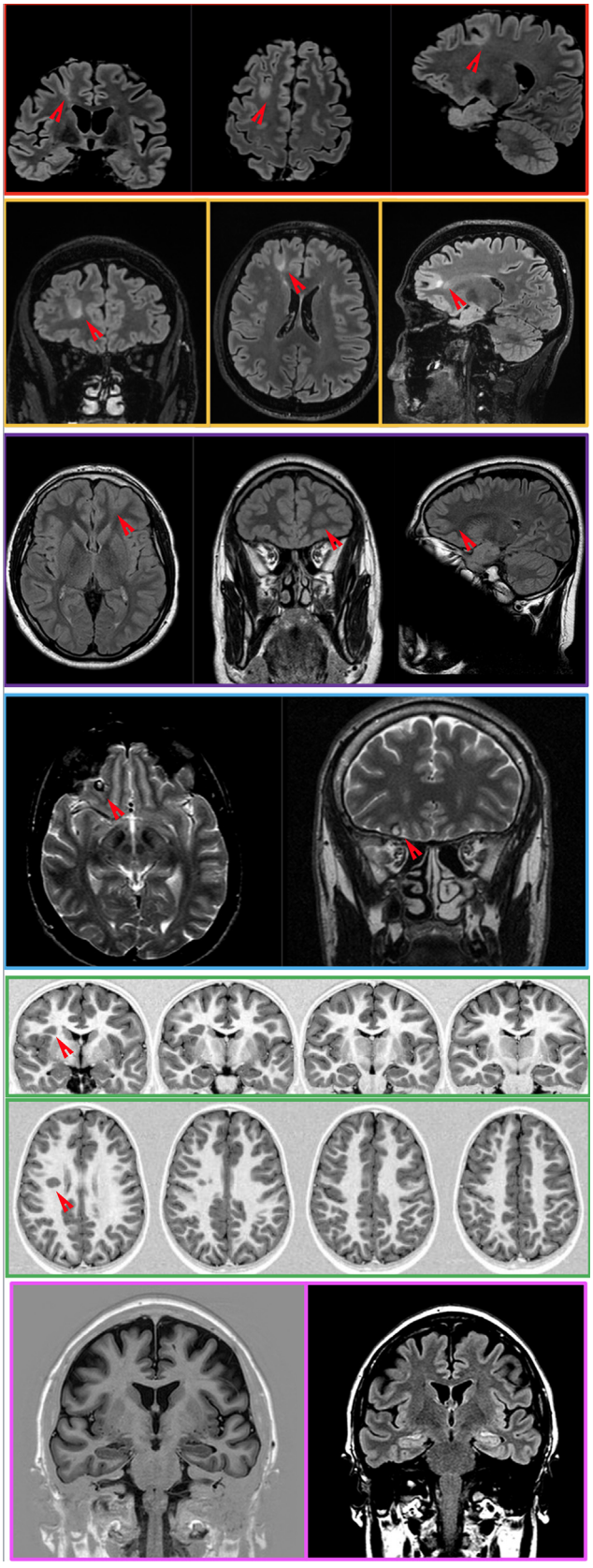
In the present study, the semiology of 35 GS has been analyzed in order to define the main clinical features of these rare epileptic manifestations. The main ictal sign, by definition, is represented by the act of laughing, with a range of expressions that goes from sonorous laughter to a smile without sound. Compared to a smile, laughter is a much more complex behavior, even if many reports suggest that, from a functional point of view, a smile is a weaker form of laughter, or probably its precursor, devoid of vocalizations but sharing with it several social and affective functions [17,19–20]. For this reason, the core of the gelastic ictal sign is the same and it represents the characteristic and distinctive element of GS.

First of all, in line with previous studies [21] laughter represented overall the majority of gelastic ictal signs, while the ictal smile was less frequent. The muscles of the face, in particular bilateral orbicularis oris and oculi, were the most involved during GS, and their simultaneous activation was the most frequent first ictal sign. Only in 30% of cases, rhythmic movements involved arms and trunk muscles during laughter.

In 87.5% of patients, the manifestation of laughter or smile was the only ictal phenomenon (10 patients) or the first one at the beginning of the seizure (4 patients), being the most important clinical sign.

Other semiological signs coming after the laughter/smile, included behavioral arrest, staring, oral and gestural automatisms, suggesting a seizure spreading to the temporal lobe [22], or hyperkinetic movements which could depend on the seizure spreading to the frontal lobe [23].

In 5 patients a new ictal gestural sign was noticed: these patients brought one hand to the face in an attempt to cover the eyes or the nose/mouth region (Fig. 2). This sign appeared different



from gestural automatisms, typically described in temporal lobe seizures [22], as it was not rhythmic nor stereotyped, showing a clear intention in covering a part of the face. Moreover, in two patients, the gesture was performed firstly with one hand, and then, when the neurophysiologist technician tried to remove the hand from the face in order to better visualize the clinical semiology, using the other hand to cover the eyes (Fig. 2). This behavior suggests it was not a forced movement or a lateralizing automatism, rather we hypothesize it could represent the expression of embarrassment during the sudden onset of involuntary laughter [24].

Overall, the main clinical features of GS appeared consistent across different seizures in the same patient, suggesting a good intra-subject stereotypy.

Moreover, the study confirms the rarity of GS and that hypothalamic hamartoma is the more frequent etiology associated with gelastic seizures.

Interestingly, a comparison of the clinical semiology of GS was investigated between the two groups of patients with different epilepsy etiologies; although without reaching a statistical significance, due to the low number of patients included, it has been observed that patients with a lesion localized in the hypothalamic region had more frequently gelastic seizures represented by a laugh with emotional involvement and that the laughter was the only manifestation of the seizure, sometimes associated to a new ictal sign that we defined "hand-to face", to describe a spontaneous gesture of embarrassment to the involuntary laughter. On the contrary, patients with lesions localized outside the hypothalamic region had more often seizures with laugh without emotional involvement, resembling a more mechanical action, often with other semiological signs associated. The "hand-to-face" sign has not been observed in this latter group of patients.

These findings were corroborated by the cluster analysis, which reached statistical power and identified three semiological clusters: emotional laugh and non-emotional smile correlated to patients with hypothalamic lesions, and non-emotional laugh correlated to patients with focal cortical lesions.

A possible explanation of these semiological differences could be related to the seizure's involvement of cerebral structures belonging to different anatomo-physiological networks, subserving the spontaneous emotional laughter on one side, and the voluntary laughter on the other side. The cerebral regions belonging to the spontaneous emotional laughter network are hypothesized to be located in the anterior cingulate cortex (ACC), the ventral anterior insula, the amygdala, the hypothalamus, and peri-acqueductal gray [25–26]. The voluntary laughter network has been associated with the supplementary motor area (SMA) and pre-SMA, the frontal motor opercular areas, and motor and parietal cortices [14,25–26]. In particular, Caruana and colleagues [14] (2016) performed a study on patients who underwent Stereo-EEG, investigating laughter elicited by electrical stimulation of the frontal operculum (FO); they speculated on the possible role of the FO in the volun-

Fig. 3. Neuroradiological findings. The figure reports the lesion in the symptomatic focal epilepsies: Red and yellow: right frontal FCD type II (red: anterior part of superior frontal-middle frontal sulcus with transmantal sign to ventricle; yellow: frontal pole with transmantal sign to ventricle) Purple: left frontal FCD type II (frontal pole with transmantal sign to ventricle) Blue: right frontal basal cavernoma (lateral and middle part of the orbitary region) Green: right fronto-insular nodular heterotopia Pink: negative MRI in patient with right temporal origin of the seizure.

tary control of facial expressions, representing a link with the emotional network, gating limbic information to the motor system.

Linking our findings to this neuro-anatomical background, we could hypothesize that patients belonging to the first group, with epileptogenic lesions localized in the hypothalamic area, would be more prone to elicit through the seizure the spontaneous emotional laughter network, while on the contrary, patients of the second group, and in particular those with lesions localized in the frontal operculum, would activate the voluntary laughter network.

Resting-state functional connectivity studies, revealing brain-organized networks through functional MRI, have shown that the human hypothalamus is particularly connected to parts of the cingulate and temporal cortices (beyond other subcortical regions) [27], reinforcing our hypothesis.

5. Conclusion

Gelastic seizures are rare epileptic phenomena, which manifest with laughter or a smile. Inspective analysis of the video-EEG data can help in detecting clinical features typical of these phenomena. The emotional involvement and expression of mirth during the seizure are associated with the simultaneous contraction of the eyes and the mouth; in a minority of cases, neck, trunk, and limb muscles can be involved by a sussultatory movement. Other signs or symptoms can follow the gelastic component. Especially in children, the most frequent aetiology is represented by hypothalamic hamartoma.

When the behavior during the seizure appears with less conveyed emotion similar to a mechanical action (mainly localized to the mouth muscles), and enriched by prominent motor symptoms (unilateral clonic or tonic movements, hyper motor seizures) a localization extra hypothalamus of the EZ needs to be considered.

Data Availability statement

The authors state that the anonymized data on which the article is based will be shared upon request of any qualified investigator.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Ethical approval

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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