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Short communication

Clinical and electroencephalographic features of epilepsy in patients with triple X syndrome: A case series

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ABSTRACT

Purpose: Triple X syndrome, is an often undiagnosed chromosomal abnormality with an incidence of 1/1000 females. Main associated disorders are urogenital malformations, premature ovarian failure or primary amenorrhea, gastrointestinal problems, psychiatric disorders and epilepsy. To date, triple X is not related to a specific epileptic syndrome. Therefore, the purpose of this clinical series is to analyze seizure semiology, electroencephalogram features and the long-term outcome of 13 patients with epilepsy and triple X syndrome.
Methods: We retrospectively evaluated the long-term seizure outcome in patients with triple X syndrome who had been referred to 11 Epilepsy Centers in Italy. A close electroclinical follow-up was made for at least 2 years and outcomes were reported.
Results: Our case series confirms that epilepsy is not an occasional finding but part of the phenotypic spectrum of this syndrome. The seizure semiology shows an higher prevalence of focal seizures in 62% of patients. EEG findings of focal epileptic activity were reported in 85% of patients. Anti-seizure medications were successful in all our patients whom in most cases were responsive to monotherapy.
Conclusion: According to our case series most successful drugs were VPA and LEV. Long term prognosis of epilepsy in our case series was good. Our experience suggests that all triple X patients achieve good seizure control and in 69% of cases normalization of the EEG.

1. Introduction

Chromosomal abnormalities can frequently be associated with afebrile seizures: e.g. trisomy 18 has an high frequency of epilepsy [1]. Among chromosomal abnormalities, triple X syndrome was first described by Jacobs in 1959 [2]. This syndrome is an often undiagnosed chromosomal abnormality with an incidence of 1/1000 females [3]. Physical and behavioral features are extremely variable. There are no

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specific physical features to characterize the syndrome, however facial dysmorphism, hand and feet abnormalities are commonly reported [3]. Main associated disorders are urogenital malformations, premature ovarian failure or primary amenorrhea, gastrointestinal problems, psychiatric disorders and epilepsy. Intellectual disability, speech delay and motor disorders are more common than in the general population. Attention deficits, psychotic and mood disorders can also adversely affect the lifestyle and socialization of these patients [3]. There are no recent data reporting specific neuroimaging features of these patients, however triple X seems to be associated with reduced brain volume and white matter high intensity foci [3]. Sills et al., first reported a patient with 47-XXX karyotype and epilepsy [4]. Further studies have confirmed this association [5,6], however seizure semiology, electroencephalogram (EEG) features and the natural course of epilepsy in these patients have not yet been fully described. Therefore, we decided to carry out a multicenter study with two main aims: to describe and characterize clinical and EEG abnormalities of patients with epilepsy and triple X syndrome and to analyze their long-term outcome.

2. Materials and methods

We retrospectively evaluated the long-term seizure outcome in patients with triple X syndrome who had been referred to 11 Epilepsy Centers in Italy selected in systematic way. Patients were referred by their attending physicians to the observation of the epilepsy center at the appearance of the first seizure. In some cases the onset of seizures has been carried out after the diagnosis of chromosomopathy, while in most cases the investigations carried out by the specialized center led to the diagnosis of trisomy. Patients with personal history of previous brain damage or other known causes of epilepsy were excluded from the study. In all cases the diagnosis of triple X was confirmed by cytogenetic analysis of peripheral blood lymphocytes. Age at seizures onset, seizure semiology, EEG features, brain magnetic resonance imaging (MRI) findings and antiseizure medications (ASM) were analyzed for each case. A close electroclinical follow-up was made for at least 2 years and outcomes were reported. The relevant patient data are summarized in Table 1. Written informed consent was obtained from parents or guardians of all recruited subjects. All data were collected from November 2021 to May 2022.

3. Results

Our series consisted of 13 patients with a median age at the time of enrollment of 13.3 years (range 6 to 51 years). The median age at seizure onset was 4.5 years ranging from 5 months to 8.6 years. In particular, in only 3 cases seizure onset was before the first year of life while the 77% of patient presented the first episode of seizure during childhood.

Eight patients (62%) presented focal seizures, and 5 patients (38%) had generalized epilepsy with 2 of them presenting infantile spasms in cluster. In all patients who showed focal seizures, consciousness impairment was absent except for patients n.7 and 9. No patient had status epilepticus.

Interictal-EEG showed focal and multifocal epileptic activity in 11 patients (85%), mainly involving the posterior regions. Diffuse slow activity and generalized spike and wave discharges were reported in 2 patients. Only 1 patient presented absence with typical EEG pattern. We must underline that often patients who showed generalized seizure had a focal interictal EEG suggesting that in these patients the tonic clonic seizure were apparently generalized. Among patients presenting infantile spasms, EEG findings did not show hypsarrhythmia.

Neuroimaging studies demonstrated the absence of anatomical alterations justifying epilepsy.

All patients but 2 received ASM: the most used ASMs were sodium valproate (VPA) and levetiracetam (LEV). Carbamazepine (CBZ), topiramate (TPM) and felbamate (FBM) were also used. A patient received adrenocorticotropic hormone (ACTH) and vigabatrin (VGB) for infantile

Table 1
Demographic and electroclinical data of patients.

Patient	Age at seizure onset	Seizure semiology	Interictal EEG	Therapy	Age at follow-ups	EEG outcome	Seizure outcome
1	2.5 y	generalized tonic seizures, GTCS	right occipital epileptiform discharges	CBZ, LEV	6.1 y	normal	SF
2	10 m	epileptic spasms	left temporo-occipital abnormalities	LEV, VPA, FBM	8.6 y	dysregulated brain electrical activity, without epileptic abnormalities	SF
3	8.6 y	FBTCS	right fronto-temporal spike	VPA, TPM	16.5 y	normal	SF
4	6.5 y	focal tonic seizures	diffuse slow activity	VPA	16.2 y	unchanged	SF
5	5.3 y	gaze deviation, vomiting, hypotonia, focal clonic seizures	left parieto-occipital spikes and waves	VPA	8.4 y	normal	SF
6	7.8 y	CAE	3 Hz spike and wave discharges	LEV	10.4 y	normal	SF
7	5.5 y	vomiting, aresponsiveness, focal clonic seizures	temporo-occipital epileptiform discharges with alternating side prevalence	LEV	10.7 y	normal	SF
8	4 y	GTCS	centro-temporal spikes	VPA	6.8 y	normal	SF
9	3.7 y	focal motor seizures, gaze deviation, loss of consciousness	focal repetitive spikes or sharp in temporal-posterior regions	no therapy	6 y	normal	SF
10	5 m	focal motor seizures	occipital spikes and waves	no therapy	13.2 y	dysregulated brain electrical activity, without epileptic abnormalities	SF
11	8 m	epileptic spasms	epileptiform discharges in the posterior regions	ACTH, VGB	12.5 y	centro-parietal abnormalities	SF
12	8.1 y	focal motor seizures, FBTCS	centro-temporal spikes	LEV	51 y	normal	SF
13	4 y	focal motor seizures	epileptiform discharges in the posterior regions	VPA	7.1 y	normal	SF

ACTH: adrenocorticotropic hormone; CAE: childhood absence epilepsy; FBM: felbamate; FBTCS: focal to bilateral tonic-clonic seizur; GTCS: generalized tonic-clonic seizure; LEV: levetiracetam; SF: seizure free; TPM: topiramate, VGB: vigabatrin; VPA: valproic acid,.

spasms. Most patients were treated with monotherapy, however 4 cases required polytherapy. Among patients in polytherapy 2 presented infantile spasms, 1 generalized seizures and 1 focal to bilateral tonic-clonic seizures (FBTCS). All patients with focal seizures responded to monotherapy and in 2 cases did not require any ASM. No adverse side effects of ASM were reported. All patients showed a good response to antiepileptic therapy, in some cases up to the interruption of ASM with maintenance of seizure control. Clinical improvement was associated with an improvement of the EEG that was normalized in 9 patients.

4. Discussion and conclusion

X chromosome abnormalities are known to be associated with epilepsy and variable involvement of the central nervous system. X-fragile syndrome, Klinefelter syndrome and Turner syndrome are some examples of this association [5]. Previous studies have analyzed the correlation between epilepsy and triple X [3]. However, few reported clinical and EEG features and described the long-term follow-up of these patients with a small population sample [5,6]. In addition, few data in the literature discuss the response of these patients to ASM.

We analyzed a group of 13 patients with triple X syndrome associated with epilepsy with a long-term follow-up in order to clarify seizure semiology, EEG features and the natural course of epilepsy in this syndrome.

Although this is not an epidemiological study, our case series confirms that epilepsy is not an occasional finding but part of the phenotypic spectrum of this syndrome. In agreement with this hypothesis, neither anatomical alteration nor other epilepsy cause emerged from our research. Notably, polyploidies are per se related to epilepsy. In addition, it is well known the contribution of X-linked genes in the development of central nervous system [7], and that at least 100 genes in the X chromosome are associated with epilepsy [8].

The seizure semiology of our sample shows a higher prevalence of focal seizures in 62% of patients. To date, triple X is not related to a specific epileptic syndrome. Our study allows to better characterize the seizure types associated with this chromosomopathy and to speculate that focal motor seizure may be the most frequent form in agreement with previous reports [5,6]. In a recent case report of a triple X patient multifocal epilepsy was found and should be considered as a possible manifestation of the syndrome [9]. According to the authors, the patient responded to a politherapy with brivaracetam, higher-dose lamotrigine and low-dose valproic acid [9].

Among patients with generalized epilepsy, we observed two patients with epileptic spasms without hypsarrhythmia (ESWoH). Previous studies reported ESWoH sometimes in patients with a well-defined electroclinical syndrome, sometimes associated with an epileptic encephalopathy and other types of seizures, as in our case [10]. In addition, cases of ESWoH with a focal onset of seizure due to focal brain lesion may benefit from surgical treatment [11].

Although triple X syndrome is not associated to a characteristic EEG feature, our EEG findings confirmed a higher prevalence of focal epileptic activity in 85% of patients. Although clinical data showed a majority of motor seizure, EEG findings revealed a prevalence of epileptic activity in the posterior areas.

ASMs were successful in all our patients whom in most cases were responsive to monotherapy (54%). Interestingly, among patients with focal epilepsy the ones treated with ASMs responded to monotherapy with the exception of 1 case with FBTCS that required polytherapy, while the two remaining cases with focal epilepsy did not require any ASM. On the other hand, all cases with generalized epilepsy required ASMs and the 60% of them required polytherapy. According to our case series most successful drugs were VPA and LEV. Both drugs may be first choice in these patients, but we advise the use of LEV considering that triple X can present premature ovarian failure and reproductive endocrine dysfunctions. Indeed, VPA can have important adverse effect on ovarian function [12], hence LEV may be more suitable.

Literature data provided inconsistent information concerning the long-term prognosis of epilepsy in patients with triple X. Our experience suggests that all triple X patients achieve good seizure control and in 69% of cases normalization of the EEG with a good long-term prognosis of epilepsy.

In conclusion, although our study has limitations related to its retrospective nature and possible bias related to the multicenter data collection, it highlights the association of triple X syndrome and epilepsy. The cause of epilepsy in these patients remains unknown. However, we report focal epilepsy as the most frequent form followed by generalized tonic-clonic seizure, with a good long-term prognosis. Prospective studies are necessary to better analyze this association and categorize these epileptic seizures.

CRediT authorship contribution statement

Giovanni Battista Dell'Isola: Formal analysis, Writing – original draft, Funding acquisition, Data curation, Writing – review & editing. **Elisabetta Mencaroni:** Conceptualization, Funding acquisition, Writing – review & editing. **Paolo Prontera:** Conceptualization, Funding acquisition, Writing – review & editing. **Giuseppe Di Cara:** Conceptualization, Funding acquisition, Writing – review & editing. **Luigi Ferraro:** Conceptualization, Funding acquisition, Writing – review & editing. **Paolo Bonanni:** Conceptualization, Funding acquisition, Writing – review & editing. **Marco Carotenuto:** Conceptualization, Funding acquisition, Writing – review & editing. **Giulia Iapadre:** Conceptualization, Funding acquisition, Writing – review & editing. **Sara Matricardi:** Conceptualization, Funding acquisition, Writing – review & editing. **Francesca Operto:** Conceptualization, Funding acquisition, Writing – review & editing. **Alessandro Orsini:** Conceptualization, Funding acquisition, Writing – review & editing. **Pasquale Parisi:** Conceptualization, Funding acquisition, Writing – review & editing. **Piero Pavone:** Conceptualization, Funding acquisition, Writing – review & editing. **Vincenzo Salpietro:** Conceptualization, Funding acquisition, Writing – review & editing. **Salvatore Savasta:** Conceptualization, Funding acquisition, Writing – review & editing. **Pasquale Striano:** Conceptualization, Funding acquisition, Writing – review & editing. **Alberto Verrotti:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent for publication

The study was conducted in accordance with Declaration of Helsinki. Written informed consent for publication of identifying images or other personal or clinical details was obtained from both of the parents of the patient.

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