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Review

Epilepsy and chromosome 18 abnormalities: A review

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ABSTRACT

Purpose: To analyze the various types of epilepsy in subjects with chromosome 18 aberrations in order to define epilepsy and its main clinical, electroclinical and prognostic aspects in chromosome 18 anomalies.
Methods: A careful overview of recent works concerning chromosome 18 aberrations and epilepsy has been carried out considering the major groups of chromosomal 18 aberrations, identified using MEDLINE and EMBASE database from 1980 to 2015.
Results: Epilepsy seems to be particularly frequent in patients with trisomy or duplication of chromosome 18 with a prevalence of up to 65%. Approximately, over half of the patients develop epilepsy during the first year of life. Epilepsy can be focal or generalized; infantile spasms have also been reported. Brain imagines showed anatomical abnormalities in 38% of patients. Some antiepileptic drugs as valproic acid and carbamazepine were useful for treating seizures although a large majority of patients need polytherapy.
Conclusion: Children with chromosomal 18 abnormalities can present different types of epilepsy, more frequently focal seizures in individuals with 18q- deletion syndrome, while both complex partial seizures and generalized tonic–clonic seizures have been described in patients who suffer for trisomy 18. Outcome in term of seizures frequency and duration seems to be variable and epilepsy is drug resistant in half of the children, especially in children with trisomy 18 and generalized epilepsy.

1. Introduction

Epilepsy is among the most common neurological conditions with a prevalence of 0.5–1% in the general population and affecting approximately 50 million people worldwide [1,2]. Studies of epilepsy associated with chromosomal abnormalities may provide information about epilepsy phenotypes, such as in fragile-X, trisomy 12p, Wolf-Hirschhorn, ring 20, and 1p36 deletion syndromes. The mechanisms of chromosomal imbalances associated with epilepsy are of considerable neurobiological interest as dosage imbalances might, for some neuronal genes, lay the basis for the observed epilepsy phenotypes [3]. Trisomy 18 (Edwards syndrome) phenotype results from full, mosaic or partial trisomy 18q [4,5]; complete or full trisomy 18 is the most common variant and is the second most common autosomal trisomy syndrome after trisomy 21. The most frequent chromosome 18 aberrations described in literature associated with seizures are: deletion syndromes of the short (18p- deletion syndrome) and the long (18q- deletion syndrome) arms, duplications of different tracts of the long arm, ring chromosome 18, translocations involving chromosome 18 and trisomy 18. However, although trisomy 18p is much rarer and less characterized than tetrasomy 18p, in which epilepsy affects 23% of patients [6], epilepsy has also been described in patients with trisomy 18p. Epilepsy is infrequent in individuals with 18p- deletion syndrome, while may be part of the clinical picture of patients with 18q- deletion syndrome [7]. Individuals with partial duplication of the long arm of chromosome 18 and ring chromosome 18 display an incomplete trisomy 18 phenotype [8,9]. The aim of the study is to describe the different types of epilepsy and its main electroclinical and prognostic aspects in the various chromosome 18 anomalies (Table 1).

2. Material and methods

This article provides an overview on works concerning chromosome 18 aberrations and epilepsy, starting from 1980. A

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Table 1
Clinical and electroencephalographic characteristics of epilepsy in patients with chromosome 18 aberrations.

Authors	Chromosomal aberrations	N° of patients/ gender	Type of seizures	Onset age of seizures	EEG findings	Brain MRI findings
Novotny et al. (1987) [33]	Trisomy 18q	1 M	CPS, Myo	1 y	NA	Microcephaly
Johansson et al. (1988) [35]	Trisomy 18p	1 F	SPS	11 y	Bilateral SLWS	NA
Kanazawa et al. (1989) [13]	18qDS	1 M	GTC, SE	14 y	Ictal EEGs: continuous 2 Hz high voltage slow waves superimposed by S and poly-spikes + irregular S discharges in the L O regions	Immaturity of the brain
Shinzel et al. (1991) [14]	18qDS	1 F	Tonic–clonic seizures	2 y	NA	NA
Vaquerizo et al. (1995) [11]	18pDS	1 F	West syndrome	NA	Hyp	NA
Gustavsson et al. (1999) [15]	18qDS	1 F	Unspecified type of epilepsy	NA	NA	NA
Bal et al. (2000) [24]	De novo t(2;18) (q21;q22)	1 M	Mixed type of epilepsy	NA	S, poly-spikes and SPW complexes	Loss of volume of the white matter and delayed myelination
Sturm et al. (2000) [16]	18qDS	1 M	Autonomic seizures	NA	NA	Multifocal demyelination
Rao et al. (2001) [25]	t(14;18) (p11;q11.2), -18	1 M	GTC	First mo of life	NA	Hydrocephalus
Kumada et al. (2003) [19]	18qDS	1 F	CPS + autonomic seizures	3 mo	S in R P-T region	Diffuse cerebral atrophy, severe white matter demyelination
Verrotti et al. (2003) [17]	18qDS	1 F	CPS	6 mo	Low-voltage S in F-C region	Normal
Adab et al. (2005) [20]	18qDS	1 F	CPS	28 y	Low amplitude with diffuse fast activity	NA
Grosso et al. (2005) [7]	18qDS	1 F 3 M	CPS	20 mo	Low-medium voltage S with slow waves, or low voltage SLWS in the R C region in two children, in the F-C-T region in one patient and in the L C-T region in one child	NA
Grosso et al. (2005) [7]	t(17;18)	1 M	FS, Generalized epilepsy	2.6 y	Symmetric or asymmetric S or SPW complexes of medium-high voltage in the O-C-T regions	NA
Grosso et al. (2005) [7]	Trisomy 18p	2 M	CPS	Mean 4.5 y	Symmetric or asymmetric S and SPW of medium-high voltage in the O region + generalized S and poly-spike and wave-activity	NA
Stephenson et al. (2005) [18]	18qDS	1 M	Autonomic seizures (epileptic apnoea)	13 mo	Discharges with a wave-form with slow theta frequency in R T region	NA
Yamanouchi et al. (2005) [27]	Trisomy 18	1 M	Generalized epilepsy	4 y	Multifocal S in the R P and L T regions	Cerebellar hypogenesis + thin corpus callosum + dysplastic hippocampus
Ceccarini et al. (2007) [8]	18q21.31-q22.2 duplication	1 M	GTC, FS induced by reading	19 y	Isolated short saw-tooth theta waves sequences in F-C-T region	Enlarged cisterna magna and cerebellar hypoplasia (vermis and right hemisphere)
Cerminara et al. (2008) [12]	18pDS	1 M	TS + automatisms	6 y	S and SLWS in F regions often synchronously	NA
Kumada et al. (2010) [34]	Trisomy 18	1 F	CPS + autonomic seizures	10 mo	Alfa-waves (10–12 Hz) originating in L hemisphere for 2 seconds, followed by high-voltage Theta-waves and Delta-waves	Slight enlargement of the lateral ventricles
Celep et al. (2011) [23]	Ring chromosome 18	1 M	Febrile seizures	NA	Generalized epileptiform abnormality from bilateral C P region	MRI spectroscopy: decreased NAA/Cr ratio on the white matter (F region)
Lo Castro et al. (2011) [9]	Ring chromosome 18	1 F	FS	3 y	Focal anomalies in central R region	Hyperintensities in semioval centres, subcortical gliotic lesions
Poulton et al. (2011) [21]	18qDS	1 M	FS, GTC, Myo	2 mo	4 mo: High voltage asymmetric multifocal activity with progressing into burst; 7 mo: Hyp	Simplified gyral pattern of the cerebral cortex and delayed myelination, no overt cerebellar abnormality + microcephaly

Table 1 (*Continued*)

Authors	Chromosomal aberrations	N° of patients/ gender	Type of seizures	Onset age of seizures	EEG findings	Brain MRI findings
D'Orsi et al. (2012) [28]	Trisomy 18q	1 M	GTC, epileptic spasms induced by eating	25 y	Ictal EEGs: diffuse slow wave complex in anterior regions	Bilateral opercular dysplasia and corpus callosum hypoplasia
Vecchio et al. (2012) [26]	t(1;18) (q44;p11.3)	1 M	Generalized epilepsy	13 mo	Bilateral F SPW	Normal
Kosho et al. (2013) [29]	Trisomy 18	13 children	GTC	Mean 2 mo	NA	NA
Orendi et al. (2013) [36]	Trisomy 18p	1 M	Absence	4 y	Focal monomorphic delta-theta waves intermingled with high potentials and SPW complexes in O regions	NA
Wang et al. (2013) [22]	18q12.1 duplication	1 F	FS	5 y	Normal	Spinal segmentation anomaly (C2- C3) + focal protrusion of the C3-C4 intervertebral disc + mild spinal stenosis
Kumada et al. (2013) [32]	Trisomy 18	7 children	2 children: CPS 4 children: GTC 1 child: unclassified epilepsy	Mean 11 mo	NA	NA
Del Gaudio et al. (2014) [30]	Trisomy 18q	1 M	Mixed type of seizures	6 y	Multiple focal discharges in posterior regions	Mild cerebral atrophy
Kobayashi et al. (2014) [31]	Trisomy 18	1 F	Generalized epilepsy	1.5 y	Background slowing and repetitive generalized S–poly-spike and wave discharges in bilateral F regions	Mild brain atrophy

M, male; F, female; y, years; mo, months; Hyp, hypsarrythmia; CPS, complex partial seizures; GTC, generalized tonic–clonic seizures; SE, status epilepticus; FS, focal seizures; TLE, temporal-lobe epilepsy; SPS, simple partial seizures; Myo, myoclonic seizures; TS, tonic seizures; SPW, spike and waves; S, spike; SLWS, sharp and slow wave; R, right; L, left; C, centro; T, temporal; O, occipital; F, frontal; P, parietal; FT, frontotemporal; NA, not available.

PubMed search indexed for MEDLINE and EMBASE was undertaken to identify studies in children and adults using terms "chromosome 18", "chromosome 18 aberrations", "18p- deletion syndrome", "18q- deletion syndrome", "chromosome 18q duplications", ring chromosome 18″, "translocations 18p", "trisomy 18", "epilepsy" and "seizures" as key words. Only English language articles were reviewed. References of the selected article were consulted for possible additional relevant articles. The date of our last search was April 2015. In this work, we listed the major groups of chromosomal 18 aberrations and the main types of epileptic manifestations. The following data were recorded: age, gender, chromosomal mutation, epileptic features, MRI brain lesions and response to therapy. The classification of seizures was based on the clinical and EEG findings according to criteria of International League Against Epilepsy [10].

3. Results

3.1. 18p- deletion syndrome

There are only two case reports: a Spanish child with 18p monosomy presenting with West syndrome [11] and one patient with a normal karyotype (46,XY) and a del(18)(p11.1pter).ish(18q-terfi18p11;tel 18p-) de novo who developed intractable epilepsy [12]. Both of them showed a multidrug-resistant epilepsy: Vaquerizo et al. described a classical West syndrome phenotype characterized by infantile spasms in the first year of life and the typical EEG pattern of hypsarrhytmia, while Cerminara et al. reported a novel finding in a young male patient. At age 6, the boy developed nocturnal seizures with prominent tonic and postural manifestations, automatisms and occasional secondary generalization. Sleep EEG showed spikes and sharp waves localized on frontal leads often synchronously. Carbamazepine, oxcarbazepine, lamotrigine, topiramate, valproic acid and clobazam were used with poor seizure control.

3.2. 18q- deletion syndrome

There are fourteen individuals with 18q- deletion syndrome and epilepsy. Two papers described tonic–clonic seizure as the most common type of epilepsy in patients carrying 18q- deletion syndrome: in 1989, Kanazawa et al. reported a 15-year-old boy with grand mal seizures that developed status epilepticus; ictal EEGs showed a prominent left occipital paroxysmal activity [13]. Some years later, Shinzel et al. observed in a 4-year-old male generalized tonic–clonic seizures [14]. An unspecified type of epilepsy was described in a 4.11-year-old female with an atypical Rett syndrome carrying an interstitial deletion of chromosome 18q [15]. By contrast, Sturm et al. reported an adult patient with autonomic seizures related to the insular/temporal lobe and its multifocal demyelination, confirmed by brain MRI investigations; the patient was treated with carbamazepine and remained seizure free [16]. Complex partial seizures were also observed in a 3-year-old female with benign focal epilepsy from the age of six months; valproic acid was prescribed with complete disappearance of the seizures after one month of therapy [17]. Therefore, in most patients seizures appeared to be focal, occurring during the first years of life and well controllable. In particular, Grosso et al. reported four patients: three boys and one girl who suffered from complex partial seizures, with motor arrest, loss of contact, staring gaze or ocular revulsion and autonomic symptoms. The age at seizure onset was mean 20 months. Awake and sleep EEGs recorded low-medium voltage spikes with or without slow waves,

or low-voltage sharp waves in the right central region in two patients, in the fronto-centro-temporal area in one patient and in the left centro-temporal area in the last one. In three patients, seizures were quickly controlled by carbamazepine, while in one child epilepsy control was achieved after 9 months by combination therapy with carbamazepine and topiramate [7]. In the same year, Stephenson et al. reported a male infant, aged 14 months, with autonomic epilepsy (epileptic apnea), documented by appropriate polygraphic recording (cardiac dysrhythmia simulating syncope and blood pressure changes) and by EEG recording that showed focal discharges with a smooth wave-form with slow theta frequency more often from right temporal region [18]. Kumada et al. also reported an infant having complex partial seizures with apnoeic attacks. Ictal EEGs and 18F-fluorodeoxy glucose-positron emission tomography showed epileptic focus in the right parietal-temporal region, while MRI revealed diffuse cerebral atrophy and severe white matter demyelination [19]. Adab et al. reported a 29-year-old woman with chromosome 18q- deletion syndrome who also suffered for complex partial seizures. EEG generally showed low amplitude with excessive diffuse fast activity but no focal epileptic discharges. Treatment with carbamazepine was ineffective, while lamotrigine reduced the frequency of seizures [20]. Finally, another male infant presented epilepsy at 2 months of age: seizures were a combination of focal seizures with secondary generalization and generalized seizures. EEG showed high voltage asymmetric multifocal activity with abnormal background progressing into burst-suppression on sleep EEG at 4 months and hypsarrythmia at 7 months. Brain MRI showed a simplified gyral pattern of the cerebral cortex and delayed myelination. Epilepsy was drug-resistant despite the treatment with clonazepam, vigabatrin and valproic acid [21].

3.3. Chromosome 18q duplications

There are two cases reported with this chromosome abnormality: Ceccarini et al. reported three siblings carrying an interstitial duplication of the long arm of chromosome 18 inherited from a healthy mosaic carrier mother. The duplicated region spanned between 18q21.31 and 18q22.2 for about 12 Mb. The first sibling was a 22-year-old man with "reading epilepsy" syndrome type from the age of 19 years. EEG showed isolated, intercritical short saw-tooth theta waves sequences in the fronto-centro-temporal area bilaterally, triggered by hyperpnoea and photic stimulation with good response to anticonvulsant therapy [8]. Some years later a 8-year-old female was described with recurrent focal seizures, characterized by leftward deviation of the eyes and head, blinking and transient unresponsiveness to external stimuli, were effectively treated by lamotrigine. Awake EEG was normal [22].

3.4. Ring chromosome 18

Epileptic seizures are rarely reported in patients with ring chromosome 18: a child with febrile seizures [23] and one girl with focal epilepsy have been described: at the age of 3 years she presented an episode of febrile seizure and, after a few months, partial seizures characterized by motion arrest, decreased responsiveness and staring of eyes. EEG showed focal paroxysmal anomalies in the central right regions. Valproic acid was effective with a complete disappearance of seizures [9].

3.5. Translocations chromosome 18

There are four cases reported with this chromosome abnormality: three children with translocation 18q[7,24,25] and a 7-year-old male with t(1;18)(q44;p11.3) [26]. In particular, patients carrying translocation 18q presented both partial and generalized epilepsies with various EEG discharges (spikes, polyspikes and spike-waves) in the posterior regions. Among these children, only one was effectively treated by valproic acid and topiramate [7]. Finally, the patient with translocation 18p presented generalized epilepsy; EEG showed spike-wave discharges and multiple spike discharges in both frontal derivations. Polytherapy (phenobarbital, valproic acid and lamotrigine) was required to reduce seizure frequency with poor results [26].

3.6. Trisomy 18

Seizures and central apnoea are described in 25–50% of the children [5], even if the electroclinical aspects are not well defined; in fact, both complex partial seizures and generalized tonic–clonic seizures have been described. Nine patients presented generalized tonic–clonic seizures [27–32]. In two of them generalized seizures were preceded, respectively, by spasms and tonic asymmetric seizures until the age of 12 years [30] or by reflex periodic spasms triggered by eating until the age of 25 years [28]. In all patients, different antiepileptic drugs (AEDs) were used (phenobarbital, valproic acid and rufinamide) but seizure control was poor. Six patients, instead, presented complex partial seizures characterized by loss of consciousness, eye deviation towards the right or the left side, with or without deviation of the head [7,32–35]. One of them also presented cyanosis and apnoeic episodes (autonomic seizures) [34], while another patient also suffered from myoclonic seizures [33]. EEG showed medium-high voltage waves. All these patients achieved a good control of seizures respectively with valproic acid and clonazepam, and zonisamide. Furthermore, Johansson et al. described a 12-year-old female with simple partial epileptic seizures that started when she was 11 years old and bilateral sharp-waves were found on EEG; seizures disappeared with carbamazepine treatment [35]. Four patients also presented epileptic spasms [31,32]. In particular, Kobayashi et al. reported a female who used valproic acid without obtaining seizure-control: EEG showed generalized bilateral spikes/polyspikes and waves without typical hypsarrhytmia and focal hyperexcitability with monomorphic delta-theta waves intermingled with high potentials and spike-wave complexes in the occipital areas [31]. Moreover, absence epilepsy occurred, between 4 and 8 years of age, in a patient who was successfully treated with lamotrigine [36].

On the whole, the most frequent seizures reported in Trisomy 18 patients are tonic–clonic and partial complex seizures. AEDs did not prove to be effective in most patients with generalized tonic–clonic seizures whereas all patients with partial complex seizures achieved a good seizure control through AEDs therapy (in particular with valproic acid and clonazepam, and with zonisamide).

4. Discussion

A detailed analysis of the electroclinical pattern of epilepsy associated with chromosomal disorders can help to define the phenotype and to detect genes related to seizure susceptibility [1]. Over 500 different chromosomal imbalances have been described with seizures or EEG abnormalities. Some chromosomal disorders had a high association with epilepsy, e.g., Wolf-Hirschhorn (4p-), Miller-Dieker (del 17p13.3), Angelman syndrome (del 15q11-q13), inversion duplication 15, and ring chromosomes 14 and 20. Many other segments had a weaker association with seizures. Less than 50 patients with rearrangements involving chromosome 18 are available in literature but the incomplete description of the epilepsy in many reports makes it often difficult to identify precise genotype–phenotype correlations. However, epilepsy seems to be particularly frequent in patients with trisomy or duplication of

chromosome 18 with a prevalence of up to 65% [32]. Notably, over half of the patients develop epilepsy during infancy or early childhood. Epilepsy can be focal or generalized and some patients with epileptic encephalopathy, namely, infantile spasms, have also been reported. Outcome in terms of seizures frequency and duration is variable and seizures may be drug-resistant in half of the children, especially in those presenting with generalized epilepsy. In this re-evaluation of the literature only two children were described with 18p- deletion syndrome and epilepsy: seizures are infrequent in individuals with this type of anomaly and epilepsy seems to be characterized by poor seizure control. We also found fourteen patients with 18q- deletion syndrome who suffered from epilepsy: in most cases, seizures appear to be focal, mainly occurring during the first years of life and well controllable. In addition, ten individuals were observed with epilepsy and chromosome 18q duplications in four cases, ring chromosome 18 in other two children and translocations 18p in four patients: these chromosome anomalies are associated with both partial and generalized epilepsies and prognosis is variable. In patients with translocation involving the long arm of chromosome 18, it is not possible to establish whether epilepsy depends on chromosome 18 anomalies or on the other chromosomes involved in the rearrangement. The association between epilepsy and Edwards syndrome lacks detailed descriptions and this is probably due to the high mortality of these patients in the first year of life [30]. Even if the descriptions are rare, epilepsy in partial trisomy 18 (18p and 18q) seems to have a common clinical and electroencephalographic pattern being characterized by late onset epilepsy with generalized and focal seizures (18q) or only focal (18p) and an EEG pattern with generalized and focal discharges mainly over the posterior regions. Overall, outcome in terms of seizures frequency and duration can vary with better prognosis in 18p than 18q trisomy [7,28]. More data are available for full trisomy 18: epilepsy appears to be characterized by the occurrence of both focal and generalized seizures and an EEG showing focal and generalized discharges, onset is usually during infancy, commonly in the first year of life; an infant with trisomy 18 developed epileptic apnea similar to central apnea: no epileptic discharges were detected in any interictal EEGs, while ictal EEG and the [18F] fluorodeoxyglucose-positron emission tomography findings confirmed that the apneic episodes were complex partial seizures, probably originating in the left fronto-temporal area. Epileptogenic foci in apneic seizures were most commonly located in the temporal lobe and less commonly in the frontal and parietal lobes. Differentiation of epileptic apnea from central apnea is crucial: a misdiagnosis can be harmful to infants with epileptic apnea. Outcome is very variable: some patients may respond well to one AED, while others can be resistant to all therapies. In particular, patients with focal epilepsy with complex partial seizures showed a good prognosis of the epilepsy, while in generalized epilepsy, characterized by spasms or tonic seizures as common phenotypes, seizures were markedly intractable [34]. The reason why patients with trisomy 18 develop epilepsy at high frequency is still unknown. It is possible that the different phenotype of these conditions (18q, 18p and full trisomy 18) reflects the different gene content of the aberration [30]. However, genotype–phenotype correlations are quite difficult as most rearrangements, although cytogenetically short, encompass dozens if not hundreds of genes. However, the mechanisms of the enlarging number of chromosomal imbalances associated with epilepsy are of considerable neurobiological interest. These dosage imbalances might, for some neuronal genes, lay the basis for the observed epilepsy phenotypes. Among these, some genes are of special interest as they could be implicated in epilepsy pathogenesis: SYP4 that encodes synaptogamin 4, a protein with a crucial role in synaptic transmission [37]; IER3IP1, which codifies immediate early response 3 interacting protein 1 and is mutated in patients with myoclonic epilepsy [21]; MBD1 and MBD2, that codify methyl-CpG binding domain protein 1 and 2, nuclear proteins with a methyl-CpG binding domain [38]; TCF4 which encodes a protein called transcription factor 4 involved in the pathogenesis of Pitt–Hopkins Syndrome, an encephalopathy characterized by severe epilepsy[39]; NEDD4L, that codifies a member of the Nedd4 family of HECT domain E3 ubiquitin ligases implicated in the origin of a epileptic encephalopathy [40]. It is difficult to state which of these genes plays a major role in the pathophysiology of epilepsy associated with chromosome 18 rearrangements. The associated phenotypes, may reflect a "general" effect in which neuronal development, migration, differentiation and functioning have progressed less than optimally, because of haploinsufficiency or excess of a collection of genes, resulting in fairly nonspecific neurologic abnormalities, including a lowered seizure threshold. It is also possible that the overall burden of the rearranged products and their interactions lead to the disease. Although the function of the proteins encoded by these genes make them promising candidate genes for the pathophysiology of epilepsy in this condition, functional studies are needed to clarify their exact role.

5. Conclusions

Among chromosome 18 abnormalities, 18q- deletion syndrome and full trisomy 18 are frequently associated with epilepsy. In most patients with 18q- deletion syndrome, seizures are focal, occurring during the first years of life with fair response to valproic acid or carbamazepine, while trisomy 18 is associated with both partial and generalized epilepsies with onset in the first year of life and a variable prognosis. The treatment of epilepsy in children with 18 chromosome abnormalities should be prompt and aggressive with adequate doses of effective medications in order to reduce the risk of prolonged seizures. The large majority of AEDs is not effective in patients with generalized seizures whereas many patients with partial complex seizure achieve a good seizure control through AEDs therapy; the most used AEDs are valproic acid or lamotrigine monotherapy; when polytherapy is required, the most useful association could be carbamazepine and topiramate, valproic acid and topiramate, or valproic acid and clonazepam.

The identification of additional patients with epilepsy and chromosome 18 rearrangements will better clarify whether this chromosomal abnormality is associated with a specific epileptic syndrome and the eventual role of specific genes in determining the phenotype of these patients.

Conflict of interest

None declared.

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