Epilepsy in Rett syndrome: Clinical and genetic features

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ABSTRACT

Epilepsy often occurs in Rett syndrome and is considered a major problem. The aim of this study was to define the clinical features of epilepsy and the correlation between seizures and both genotype and clinical phenotype in the Rett population. One hundred sixty-five patients with Rett syndrome referred to four Italian centers were recruited. All patients underwent video/EEG monitoring and molecular analysis of the MECP2 gene or, in negative cases, of the CDKL5 and FOXG1 genes. The frequency of epilepsy was 79%. Drug-resistant epilepsy occurred in 30% of all our patients with Rett syndrome and in 38% of those with epilepsy. Our findings demonstrate that epilepsy differs among the various phenotypes and genotypes with respect to age at onset, drug responsiveness, and seizure semiology. The Hanefeld and preserved speech variants represent the extremes of the range of severity of epilepsy: the preserved speech variant is characterized by the mildest epileptic phenotype as epilepsy is much less frequent, starts later, and is less drug resistant than what is observed in the other phenotypes. Another important finding is that seizure onset before 1 year of age and daily frequency are risk factors for drug resistance. Thus, this study should help clinicians provide better clinical counseling to the families of patients with Rett syndrome.

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1. Introduction

Rett syndrome (RS) is a rare neurodevelopmental disorder affecting 1/10,000 to 1/15,000 females [1]. The diagnosis of RS is based on clinical characteristics, including an initial period of apparently normal development (ages 6–12 months), followed by a period of rapid decline with loss of hand use and spoken language and the onset of stereotypic hand movements, abnormal gait, and growth failure. The clinical spectrum varies from classic to variant forms, including formes frustes, which are characterized by preserved ambulation or speech and early onset or congenital presentation, with severe epilepsy [2]. In 1999, MECP2 gene mutations on the X chromosome were found to be associated with RS, and account for approximately 80% of cases [3, 4]. Recently, CDKL5 gene mutations have been identified in girls affected by atypical RS with early-onset seizures [5]. A third gene, FOXg1, is reported to be responsible for some congenital variant forms [6].

Although epilepsy occurs in about 80% of patients with RS [7], and despite being viewed both by families and by clinicians as a major problem in RS [8], there has been little research into the features of seizures and the correlation between genotype and epileptic phenotype [7, 9–11]. Both the presence and the severity of epilepsy have been correlated with low body mass index, early developmental problems, poorer mobility, and greater clinical severity [9, 11]. The effects of X-chromosome inactivation status and other epigenetic influences on gene expression are now being investigated, and the results suggest that one MECP2 target, that is, brain-derived neurotrophic factor (BDNF), plays a significant role in determining seizure severity in RS [12, 13].

The aim of this study was to define the clinical features of epilepsy in RS: age at seizure onset, semiology of seizures, and correlation between seizures and both genotype and clinical phenotype in the Rett population.

2. Methods

This multicenter, retrospective study was carried out between January 2008 and November 2009 at the Giannina Gaslini Children's

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Hospital, Genoa, Italy. To be eligible for this study, patients had to have been clinically diagnosed with Rett syndrome according to European Society of Paediatric Neurology criteria defined in 2001; had to have undergone molecular analysis of the MECP2 gene or, in negative cases, of the CDKL5 gene; and had to have undergone video/EEG monitoring. On the basis of these criteria, data for 165 subjects were collected from a cohort of patients referred to four Italian child neuropsychiatry departments: G. Gaslini Institute, University of Genoa; St. Paolo Hospital, Milan; University Hospital, Siena; Spedali Civili, Brescia.

A questionnaire was made up in order to obtain longitudinal data including clinical information on seizures, EEG findings, and treatment. It was completed by one researcher, collecting data from patients'files, hospital charts and from the physician in charge of the patients. Phenotypes were categorized as follows: classic, congenital, preserved speech variant (PSV), formes frustees (FF), and early-onset seizure type (Hanefeld variant). The genotypes of cases with a previously identified MECP2 mutation were categorized as late truncating C-terminal deletions, large gene deletions, and T158M, R255X, R270X, R306C, R168X, R294X, R133C, R106W, and P152R mutations, and were then grouped into two categories: missense mutations and truncating mutations. As the importance of the MeCP2 protein in terms of functionality is well known, we divided the mutations into those involving (NLS+) and those not involving (NLS–) the nuclear localization signal (NLS) (Table 1).

Seizures were classified according to criteria of the International League Against Epilepsy [14]. We took into consideration seizure semiology at onset and at last follow-up. Each subject was scored with respect to frequency of seizures: 1 = daily seizures, 2 = weekly seizures, 3 = monthly or sporadic seizures, 4 = absence of seizures. An epileptic score was assigned to each patient: 1 = no epileptic seizures, 2 = drug-responsive epileptic seizures, 3 = drug-resistant epileptic seizures. Microcephaly was also taken into consideration as a parameter in our investigation to identify the presence of a correlation with epilepsy. Drug-resistant epilepsy was defined as the failure of two appropriate AEDs, the occurrence of an average of one or more seizures per month for ≥18 months, and no longer than a 3-month seizure-free hiatus during those 18 months [15].

The reasons for and methods of the study protocol were carefully explained to the families of the patients, and informed consent was obtained.

2.1. Statistical analysis

Data are described as means and SD or median and range for continuous variables, and as absolute and relative frequencies for categorical variables. Nonparametric analysis (Mann–Whitney U test) for continuous variables and the Chi square or Fisher's exact test for categorical variables were used to measure differences between

Table 1
Characteristics of patients with Rett syndrome.

Characteristic	All	No epilepsy	Drug-responsive epilepsy	Drug-resistant epilepsy
N	165	35 (21.2)	81 (49.1)	49 (29.7)
Phenotype				
Classic forms	140 (84.8)[a]	25 (18)	73 (52)	42 (30)
Preserved speech variant	15 (9.1)	8 (53.3)	5 (33.3)	2 (13.3)
Formes frustes	3 (1.8)	2 (67)	1 (33)	–
Hanefeld variant	6 (3.6)	–	1 (17)	5 (83)
Congenital variant	1 (0.6)	–	1 (100)	–
Genotype				
MECP2+	147 (89.1)	30 (20.4)	75 (51)	42 (28.6)
CDKL5+	5 (3)	–	1 (20)	4 (80)
FOXG1+	1 (0.6)	–	1 (100)	–
Negative on genetic investigation	12 (7.3)	5 (41.7)	4 (33.3)	3 (25)
Mecp2 mutations				
Late truncating C-terminal deletions	29 (19.7)	10 (34.5)	17 (58.6)	2 (6.9)
Large deletions	10 (6.8)	1 (10)	7 (70)	2 (20)
T158M	17 (11.6)	3 (17.6)	6 (35.3)	8 (47.1)
R255X	16 (10.9)	2 (12.5)	7 (43.8)	7 (43.8)
R270X	14 (9.5)	3 (21.4)	8 (57.1)	3 (21.4)
R306C	14 (9.5)	2 (14.3)	8 (57.1)	4 (28.6)
R168X	10 (6.8)	2 (20)	4 (40)	4 (40)
R294X	9 (6.1)	1 (11)	4 (44.5)	4 (44.5)
R133C	6 (4.1)	2 (33.3)	3 (50)	1 (16.7)
R106W	6 (4.1)	–	3 (50)	3 (50)
P152R	5 (3.4)	1 (20)	3 (60)	1 (20)
Others[b]	11 (7.5)	3 (27)	5 (46)	3 (27)
Type of MECP2 mutation				
Group 1[c]				
Missense	54	10 (18.5)	25 (46.3)	19 (35.1)
Truncating	54	9 (16.6)	26 (48.2)	19 (35.1)
Group 2				
NLS–	84	20 (23.8)	42 (50)	22 (26.2)
NLS+	63	10 (15.9)	33 (52.3)	20 (31.7)
Microcephaly	96 (60.4)	17 (51.5)	51 (65.4)	28 (58.3)
Age at epilepsy onset				
Mean ± SD	4.7 ± 3.7	–	5.3 ± 4.2	3.6 ± 2.5[d]
Median (range)	4 (0.1–21)		4 (0.1–21)	3.2 (0.1–12)
Age at last follow-up				
Mean ± SD	14.9 ± 8.5	13.7 ± 10.4	15 ± 7.9	16 ± 8.2
Median (range)	14 (2–40)	14 (3–37)	14 (2–37)	15 (3–40)

[a] N (%).
[b] Includes one patient for each of the following mutations: E14fs, P251fs, P302L, Q297X R111G, R306H, R453X, T322A, L124F, Y141X, D156E.
[c] Group 1 does not include late truncating C-terminal deletions and large deletions.
[d] Drug-resistant epilepsy versus drug-responsive epilepsy, P = 0.02.

groups. P values ≤0.05 were considered statistically significant, and all P values were based on two-tailed tests. Statistical analysis was performed using SPSS for Windows (SPSS Inc., Chicago, IL, USA).

3. Results

The clinical features of our series of 165 patients are detailed in Table 1. The median age at last follow up was 14 years (range: 2–40).

There were 140 (84.8%) patients with classic forms, 15 (9.1%) with the PSV, 6 (3.6%) with the Hanefeld variant, 3 (1.8%) with formes frustes, and 1 (0.6) with the congenital form. Eight patients with classic forms were negative on genetic investigation and 132 were found to carry an MECP2 mutation. Fourteen patients with the PSV had a mutation in the MECP2 gene. All patients with forma frusta were negative on genetic investigation. Patients with the Hanefeld variant included all five subjects with CDKL5 mutations and one subject with a MECP2 mutation (R106W). The patient with the congenital form had a mutation in the FOXG1 gene.

There were 130 (79%) patients with epilepsy in our cohort, and their median age at last follow-up was 14.5 years (range: 2–40); 37 (28.5%) were ≥20 years of age. The median age at epilepsy onset was 4 years (range: 1.5 months to 21 years). Seizures started after 10 years of age in 10 (7.7%) patients. Epileptic seizures always occurred in those with the Hanefeld variant, whereas they occurred in 82% of patients with classic forms but in only 46.7% of those with the PSV (P = 0.004). Patients with the PSV started having seizures later in life than those with classic forms (6.1 ± 4.3 years vs 4.8 ± 3.6 years, P = 0.01).

With respect to genotype, all patients with CDKL5 mutations started having seizures within the first 12 months of life (0.45 ± 0.49 years), whereas the mean age at seizure onset was 4.7 years for patients with an MECP2 mutation and 6.6 years for patients without any identified mutation. Among our patients with MECP2 mutations, we observed that subjects with large gene deletions started having seizures later (6.72 ± 7.14 years) than those with the other types of mutations, particularly those with R168X and R255X mutations (3.12 ± 1.86 and 3.9 ± 2.0 years, respectively).

There were no differences in age at seizure onset between those with NLS+ mutations and those with NLS– mutations (4.5 ± 3.8 years vs 4.9 ± 3.5 years, P = 0.46).

Patients were subdivided into three groups on the basis of epileptic score: patients without epileptic seizures (n = 35, 21.2%), patients with drug-responsive epileptic seizures (n = 81, 49.1%), and patients with drug-resistant epileptic seizures (n = 49, 29.7%) (Table 1). There were no significant differences among the groups with respect to age at last follow-up.

We observed that of the 37 patients who were ≥20 years of age, 25 (67.5%) were drug responsive and 12 (32.5%) were drug resistant, whereas in the group <20 years of age, 56 (60%) subjects were drug responsive. Eighty percent of patients with late-onset seizures (after 10 years of age) were drug responsive and had monthly or sporadic seizures.

With respect to the correlation between epileptic score and clinical phenotype, we found that drug-resistant epilepsy occurred significantly more often in those with the Hanefeld variant than in those with classic forms (83% vs 30%, P = 0.03). This difference was also observed between patients with the Hanefeld variant and those with the PSV (13%), but it did not reach statistical significance, most likely because of the small number of patients (Fig. 1). The mean age at seizure onset differed significantly between patients with drug-responsive seizures (5.3 ± 4.2 years) and those with drug-resistant seizures (3.6 ± 2.5 years, P = 0.02).

Moreover, monthly or sporadic seizures started at an older age as compared with daily seizures (5.8 ± 5.3 years vs 3.1 ± 2.2 years, P = 0.02). Thus, we observed that an age at epilepsy onset ≤1 year and daily frequency at onset represent risk factors for drug resistance in
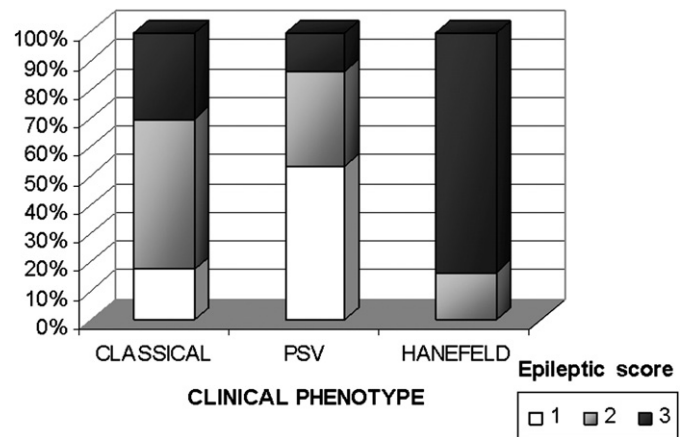

Fig. 1. Epileptic score versus phenotype. Epileptic score: 1 = no epileptic seizures, 2 = drug-responsive epileptic seizures, 3 = drug-resistant epileptic seizures.

patients with Rett syndrome with epilepsy (OR = 4.27, 95% CI = 1.23–14, P = 0.02; OR = 6.24, 95% CI = 1.90–20, P = 0.009) (Table 2).

To statistically evaluate the correlation between epilepsy and genotype, we could include only patients with no mutations and those with the most frequently found mutations, that is, late truncating C-terminal deletions, large gene deletions, and T158M, R255X, R270X, R306C, R168X, and R294X mutations. Epilepsy occurred more frequently in patients with large gene deletions (N = 9/10, 90%) and the R294X mutation (N = 8/9, 89%), and less frequently in subjects with no identified mutations (N = 7/12, 58%) and C-terminal deletions (N = 19/29, 66%). Moreover, C-terminal deletions seem to be a protective factor compared with the other mutations with respect to both the occurrence of epilepsy and drug resistance (OR = 0.43, 95% CI = 0.16–1.13, P = 0.054, and OR = 0.16, 95% CI = 0.02–0.78, P = 0.02, respectively). In particular, C-terminal deletions are a protective factor for drug-resistant epilepsy as compared with the most frequent mutations: R255X (OR = 0.12, 95% CI = 0.01–0.89, P = 0.02); T158M (OR = 0.09, 95% CI = 0.01–0.67, P = 0.007), R294X (OR = 0.12, 95% CI = 0.01–1.19, P = 0.04).

Of the 52 patients known to have X inactivation, 33 had balanced X inactivation. No significant correlations were found with either the presence or severity of epilepsy.

We observed that microcephaly was more frequent in patients with classic forms (65%) than in those with the PSV and Hanefeld variant (21.4 a d 33.3%, P = 0.01). Microcephaly occurred more frequently in patients carrying NLS+ mutations (80%) than in those carrying NLS– mutations (51%) (P = 0.001). No significant correlation

Table 2
Clinical risk factors for drug-resistant epilepsy: Univariate analysis.

Characteristic	Drug-responsive epilepsy	Drug-resistant epilepsy	OR	95% CI	P value
Age at epilepsy onset					
>1 year	76 (95)	39 (81.3)	Ref.		
≤1 year	4 (5)	9 (18.8)	4.27	1.23–14	0.02
Microcephaly					
No	27 (34.6)	20 (41.7)			
Yes	51 (65.4)	28 (58.3)	0.74	0.35–1.55	0.43
Seizure semiology					
Complex partial seizures	36 (46.2)	20 (44.4)	Ref.		
Generalized seizures	37 (47.4)	41 (51.1)	1.12	0.53–2.38	
Both	5 (6.4)	2 (4.4)	0.72	0.13–4.06	0.87
Seizure frequency at onset					
Monthly	23 (47.9)	5 (16.7)	Ref.		
Weekly	11 (22.9)	6 (20)	2.51	0.63–10	
Daily	14 (29.2)	19 (63.3)	6.24	1.90–20	0.009

was found with either the presence or the severity of epilepsy. ($P = 0.33$ and $P = 0.37$, respectively).

Data concerning the semiology of seizures at onset were available for 123 patients (Table 3). Complex partial seizures (CPS) occurred in 56 patients (45.5%), and generalized seizures (GS) in 60 subjects (48.8%). Seven patients (5.7%) had both kinds of seizures: three patients had CPS and generalized tonic–clonic seizures [GTCS], two patients had CPS and atypical absences, one patient had CPS and myoclonic seizures, and 1 patient had CPS and spasms). Among 56 patients with partial seizures, 30 (53%) had a secondary generalization. Five patients had two kinds of generalized seizures: one had atypical absences and spasms; one had GTCS and atypical absences; one had atonic and tonic seizures; one had GTCS, atonic, and tonic seizures; and one had atypical absences and tonic seizures. Generalized seizure semiology is illustrated in Fig. 2.

Because of the peculiarity of the CDKL5 epileptic phenotype [5, 16–20] we also studied it as a distinct category: seizures at onset were generalized in two patients (one with GTCS and one with spasms) and partial in two other cases (both with generalization), whereas one patient had partial seizures and spasms. There were no significant differences in seizure semiology at onset between patients with and those without the MECP2 mutation or among the patients with different kinds of mutations.

As for drug responsiveness, there were no differences between patients with partial and those with generalized seizures (64.3% vs 61.7%, respectively) at onset. At follow-up, seizure semiology was known for 92 subjects (Table 3). Generalized seizure semiology was similar to what it was at seizure onset. Among the patients with CDKL5 mutations, two still had generalized seizures (one with myoclonic seizures and the other with myoclonic seizures, spasms, and GTCS), whereas spasms and partial seizures occurred in two cases, and GTCS in another case.

Patients with the Hanefeld variant more frequently presented with spasms (50%) and myoclonic seizures (25%) than those with the other phenotypes (7% and 6%, respectively).

Partial seizures responded to drugs more frequently than generalized seizures (65.2% vs 48.7%, respectively), but this difference was not statistically significant ($P = 0.22$).

Physicians reported epileptic status in only 11 of our cases; however, no additional data are available.

4. Discussion

In this study we analyzed the clinical features of epilepsy in RS, particularly with respect to age at seizure onset, semiology of seizures, and correlation with genotype and clinical phenotype. The frequency of epilepsy among our cases was about 80%. This is in agreement with data from the largest reports, such as the Australian study [7, 9].
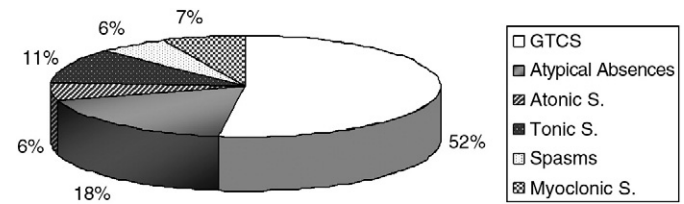

Fig. 2. Generalized seizure semiology at onset.

Most seizures among our patients started between 2 and 5 years of age. Only a very small percentage of our patients had seizure onset after 10 years of age, and epilepsy was mild in most of these patients, with sporadic frequency and drug-responsive seizures. We observed similar percentages of partial and generalized seizures at onset, and GTCS were the most frequent. At their last follow-up, most patients were still having one kind of seizure, and GTCS were again the most frequent, followed by atypical absences.

Our data show that semiology of seizures is not significantly correlated with severity of epilepsy, even if generalized seizures would appear to be more often associated with drug-resistant epilepsy, as reported by Steffenburg et al. [21].

As the role of head circumference growth in association with epilepsy is not clear [9], we investigated the correlation between epilepsy and microcephaly and found that microcephaly is more frequent in patients with classic forms than in those with the PSV or Hanefeld variant. We also found that it is more frequent in patients carrying NLS+ mutations than in those with NLS– mutations, but, unlike Steffenburg et al. [21] and Moser et al. [22], we found no correlation with either the presence or the severity of epilepsy. This finding is similar to that reported by Glaze et al. in the American cohort [11].

With respect to clinical phenotype, we found that the PSV is significantly correlated with a lower incidence of epilepsy than classic forms. In people with the PSV, seizures start later and are drug responsive in most cases. Thus, epileptic features of the PSV are milder than classic phenotypes, as has been observed for various clinical parameters reported by other authors [23, 24]. No differences were found in seizure semiology among the clinical phenotypes at seizure onset or at last follow-up, except for patients with the Hanefeld variant, who more frequently had spasms and myoclonic seizures as compared with patients with the other phenotypes.

In most cases (83%), the Hanefeld variant was associated with a CDKL5 mutation, and it has been confirmed as being the form with the most severe epileptic phenotype [5, 16–20].

We found that mutations of the CDKL5 gene were always correlated with early-onset epilepsy, and that all patients had seizures within 12 months, whereas patients with no identified mutations had

Table 3
Semiology of seizures.

Characteristic	At onset			At follow-up		
	Complex partial seizures	Generalized seizures	Both	Complex partial seizures	Generalized seizures	Both
N	56 (45.5)[a]	60 (48.8)	7 (5.7)	24 (26.1)	39 (42.4)	29 (31.5)
Phenotype						
Classic forms	50 (46.3)	53 (49.1)	5 (4.6)	22 (27.2)	34 (42)	25 (30.9)
Preserved speech variant	2 (28.6)	4 (57.1)	1 (14.3)		3 (75%)	1 (25)
Formes frustes		1 (100)		1 (100)		
Hanefeld variant	3 (50)	2 (33.3)	1 (16.7)	1 (16.7)	2 (33.3)	3 (50)
Congenital variant	1 (100)					
Genotype						
MECP2+	50 (45.5)	55 (50)	5 (4.5)	21 (26)	37 (46)	23 (28)
CDKL5+	2 (40)	2 (40)	1 (20)	–	2 (40)	3 (60)
FOXG1+	1 (100)			–	–	–
Negative on genetic investigations	3 (42.9)	3 (42.9)	1 (14.3)	3 (50)	–	3 (50)

[a] N (%).

a much lower seizure frequency than other groups and their seizures started later. The latter point differs from what was reported by the Australians [7], probably because our group of patients with no mutations did not include any patients with CDKL5 mutations, whereas the Australian study most likely did.

In patients with MECP2 mutations, C-terminal deletions proved to be a protective factor as compared with the remaining Rett population, with respect to both the occurrence of epilepsy and drug resistance. At this point it is important to consider that a specific BDNF polymorphism may influence epileptic phenotype and drug responsiveness [12, 13]. Therefore, further genetic analysis is being carried out in our patients.

Drug-resistant epilepsy occurred in 30% of all our patients with RS and in 38% of those with RS with epilepsy. These data show a higher percentage of drug resistance than what was reported by Buoni et al. [25]. Nonetheless, they confirm that most cases of Rett syndrome with epilepsy are not drug resistant. Patients with drug-resistant epilepsy start having seizures significantly earlier than subjects with drug-responsive epilepsy (3.6 ± 2.5 years vs 5.3 ± 4.2 years, $P = 0.02$), and their seizures are more frequent, often occurring daily.

We observed that both seizure onset before 1 year of age and daily frequency are risk factors for drug resistance. Moreover, unlike Steffenburg et al. [21], we observed no significant differences in drug responsiveness between patients with epilepsy ≥ 20 years of age and younger subjects. This could mean that drug-resistant epilepsy often continues, even at a later age.

In conclusion, epilepsy in Rett syndrome differs among the various phenotypes and genotypes with respect to age at onset, drug responsiveness, and seizure semiology. CDKL5 mutations are always correlated with early-onset epilepsy, which is drug resistant in most cases. About 80% of patients with MECP2 mutations have seizures, with a 28% rate of drug resistance. Patients with no identified mutations have the lowest prevalence of epileptic seizures and the latest onset. Taking into consideration the phenotypes, except for the Hanefeld variant, which is associated with the highest frequency of myoclonic seizures and spasms, we observed similar percentages of cases having partial and generalized seizures in both patients with classic forms and those with the PSV, with GTCS being the most frequent type. Compared with the other phenotypes, the PSV is characterized by mild epilepsy, that is, less frequent seizures, later onset, and less drug resistance.

The most clinically relevant points of this study include the definition of epileptic features for various phenotypes and genotypes of Rett syndrome and the improvement of our prognostic knowledge of epilepsy, thus providing the basis for clinical counseling for the families of patients with Rett syndrome.

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