

# Comorbidities in patients with epilepsy: frequency, mechanisms and effects on long-term outcome

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## Introduction

•Comorbidities are conditions that coexist and include distinct clinical diseases and syndromes along with signs or symptoms of the index disease.

•About 50% of adults with epilepsy have one or more comorbidities. Some diseases are more prevalent in people with epilepsy compared with the general population, like migraine and psychiatric disorders.

•Focusing on pre-existing classification schemes, Keezer<sup>1</sup> divided the mechanisms of association with epilepsy into five categories: chance and artifactual comorbidities, causative mechanisms, resultant mechanisms, shared risk factors and bidirectional effects.

•To our knowledge, there are no published studies investigating the mechanisms of comorbidities and their prognostic significance in a large sample of patients with epilepsy in clinical practice.

## Objectives

The aim of this study was to apply the above mechanisms to a large cohort of newly diagnosed patients with epilepsy to assess prevalence and types of comorbidities and verify the association of comorbidities (in total and by type) with the long-term outcome of epilepsy (remission periods and prognostic patterns).

## Materials & Methods

Nationwide multicenter retrospective cohort study done in 13 Italian epilepsy centers and providing long-lasting excellent care to patients with epilepsy.

### Population and definitions

- All ages (excluding neonates) residing in the center's catchment area, with epilepsy diagnosis<sup>2</sup> before December 31, 2005, followed for at least 10 years.

- **Seizure freedom** during follow-up was classified in two main categories: less than 2-year remission and 2+ years of remission.

- **Prognostic patterns** were defined as follows:

1. **Sustained remission:** 1+ years seizure freedom persisting for the entire follow-up;
2. **Relapsing-remitting course:** at least one 1+ years seizure freedom followed by a relapse
3. **No remission:** No periods of seizure freedom lasting 1+ years during the entire follow-up.

### Comorbidities

Comorbidity was defined as any clinical condition occurring before, during or after epilepsy.

-Each comorbidity was classified **by type and organ/system categories**.

-Comorbidities were also classified **by mechanism**:

**Causal mechanism:** a comorbid condition preceding the onset of seizures and having a causal role in the development of seizures.

**Shared risk factors:** a common cause of epilepsy and the comorbid condition is diagnosed.

**Bidirectional effects:** epilepsy and the comorbid condition can cause each other.

**Consequence:** the comorbid condition follows the onset of seizures and can be interpreted as the consequence of epilepsy or its treatment.

**Chance association:** None of the above definitions is satisfied.

### Data review

Patients with comorbidities were identified and their records were examined by two pairs of raters.

Each pair assessed half of the total number of patients' records and classified each comorbidity according to type (organ/system category) and underlying mechanism.

The observed agreement for organ/system was 82% and the K value was 0.82 (95% CI 0.78-0.86), indicating an almost perfect agreement. For the underlying mechanism, the observed agreement was 70%, while the K value was 0.56 (95% CI 0.49-0.62), indicating a moderate agreement.

Disagreements were solved by a third reviewer.

**Table 1. Total number of comorbidities by type and relationship with epilepsy**

	n	%
Total number of comorbidities	408	100
Comorbidity type		
Cancer	10	2.5
Cardiovascular	64	15.7
Cerebrovascular	31	7.6
Developmental/Perinatal	87	21.3
Endocrine/Metabolic	42	10.3
Gastrointestinal	10	2.5
Hematological	6	1.5
Immune	8	2.0
Infectious	14	3.4
Neurological	20	4.9
Psychiatric	68	16.7
Respiratory	6	1.5
Sense organs	8	2.0
Toxic	10	2.5
Traumatic	11	2.7
Urogenital	13	3.2
Underlying mechanism		
Bidirectional effects	14	3.4
Causal mechanism	107	26.2
Chance association	160	39.2
Consequence	1	0.3
Shared risk factors	126	30.9

**Table 2. Frequencies and percentages of comorbidities by type and causal relationship with epilepsy in the entire study sample**

	Total (n=1006)	
	n	%
1+ comorbidities	266	26.4
Total number of comorbidities		
0	740	73.6
1	172	17.1
2	61	6.1
3+	33	3.3
Comorbidity type		
Cancer	10	1.0
Cardiovascular	53	5.3
Cerebrovascular	28	2.8
Developmental/Perinatal	75	7.5
Endocrine/Metabolic	38	3.8
Gastrointestinal	10	1.0
Hematological	6	0.6
Immune	8	0.8
Infectious	14	1.4
Neurological	18	1.8
Psychiatric	62	6.2
Respiratory	6	0.6
Sense organs	8	0.8
Toxic	9	0.9
Traumatic	11	1.1
Urogenital	12	1.2
Underlying mechanism		
Bidirectional effects	13	1.3
Causal mechanism	95	9.4
Chance association	112	11.1
Consequence	1	0.1
Shared risk factors	102	10.1

## Results & Discussion

•The sample included 486 females and 520 males aged 1 month to 72 years.

•266 (26.4%) had one or more comorbidities.

•Patients with comorbidities were older and had higher seizure frequencies. Focal epilepsy, structural etiology, and abnormal neuroimaging predominated in patients with comorbidities. In contrast, EEG epileptiform abnormalities were most prevalent in patients without comorbidities. Follow-up was shorter in patients with comorbidities.

•The total number of comorbidities per patient ranged from 1 to 7, with 172 patients (17.1%) having 1 comorbidity, 61 patients (6.1%) having 2 comorbidities, and 23 (2.3%), and 33 (3.3%) had 3 or more comorbidities.

•A total of 408 diseases were diagnosed in the entire sample (Table 1).

•The percentages of patients presenting at least 1 comorbidity by organ/system and mechanism are shown in Table 2.

•Endocrine/metabolic, psychiatric and respiratory diseases were more common in patients with less than 2-year remissions than in those who achieved 2-year remission or longer (9.4% vs. 3.1%, 12.3% vs. 5.4%, 2.8% vs. 0.3%, respectively).

•Shared risk factors were observed more frequently in patients without than in those with 2-year remission or longer (17.9% vs. 9.2%).

•Endocrine/metabolic (9.6%), psychiatric (13.3%) and respiratory (3.6%) comorbidities were the most frequent organ/systems in patients with no remission, compared to relapsing-remitting (respectively 3.4%, 5.9%, 0.3%) and sustained remission (2.9%, 4.8%, 0.3%).

•Chance association (18.1%) and shared risk factors (18.1%) were most represented in the no remission group compared to relapsing-remitting (respectively 11.5% and 9.8%) and sustained remission (8.6% each).

## Conclusions

Comorbidities in epilepsy are not uncommon and reflect differing underlying mechanisms.

Although a strict causal relationship is present in approximately 10% of cases, comorbidities appear to have a larger influence on epilepsy outcome through other - indirect - mechanisms. Among these, bidirectional association and disease (and treatment) complications are fairly rare, suggesting that in clinical practice these mechanisms might be influenced by the importance attributed to them by caring physicians.

This might reflect scarce attention paid to otherwise important pathophysiological events, but on the other side it might tell us that these phenomena have modest clinical implications.

### # PRO-LONG Study Group:

Romeo A (Milano); Viri M (Novara); Specchio L, Trivisano M (Foggia); Mecarelli O, Zarabla A (Roma); Capovilla G, Beccaria F (Mantova); Sasanelli F (Melegnano); Galimberti CA, Tartara E (Pavia); Zamponi N, Cappanera S (Ancona); Aguglia U (Catanzaro); Ferlazzo E (Reggio Calabria); La Neve A, Luisi C, Pontrelli G (Bari); Cantisani AT (Perugia); De Maria G (Brescia); Albanese J (Milano).

### References:

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