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## Neurological complications of rotavirus infection in children: a systematic review and meta-analysis

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## Abstract

**Aim.** To systematically review the clinical features and outcomes of pediatric patients developing neurological complications associated with a rotavirus infection.

**Methods.** A systematic literature review and meta-analysis was performed, including articles published from 1984 to 2020. Neurological complications were classified into four groups: encephalitis, cerebellitis, encephalo-cerebellitis and benign convulsions with mild gastroenteritis (CwG).

**Results.** Out of 68 reports that fulfilled the research criteria, 99 cases of CwG, 39 cases of encephalitis, 18 cases of encephalo-cerebellitis and **five** cases of cerebellitis were collected. Ninety-five patients were from Asia. Median age was 22 (IQR 14-29) months, and the children who developed CwG were significantly younger (19, IQR 12-24 months,  $p < 0.0001$ ) than the others. Status epilepticus was observed in 23% and 5% of the encephalitis and CwG groups, respectively. The most frequently described neuroimaging finding were lesions of the splenium of corpus callosum. Four deaths were reported in the encephalitis group, whereas no fatal events were described in the other groups. Among the surviving children, the encephalo-cerebellitis group showed the most severe long-term outcome. All cases of CwG recovered completely.

**Conclusion.** Older age at diagnosis and the development of encephalo-cerebellitis are associated with a higher risk of long-term complications.

**Keywords:** cerebellitis, convulsions, CwG, encephalitis, gastroenteritis, rotavirus.

**Key Notes:**

- Neurological complications of rotavirus infection include benign convulsions, encephalitis, cerebellitis and encephalo-cerebellitis
- Patients developing benign convulsions are significantly younger (median age 19 months) compared to the children developing encephalitis, cerebellitis or encephalo-cerebellitis
- Older age at diagnosis and the development of encephalo-cerebellitis are associated with a higher risk of long-term complications

**List of abbreviation**

CNS Central nervous system

CwG Benign convulsions with mild gastroenteritis

IQR Interquartile range

## Introduction

Rotavirus is a common cause of benign, self-limiting gastroenteritis in childhood.<sup>1,2</sup> Aside from dehydration and electrolyte-imbalance, several neurological complications have been described in rotavirus infections in recent years, such as encephalitis, cerebellitis and a condition described as benign convulsions with mild gastroenteritis (CwG).<sup>3-6</sup> A direct viral pathomechanism has been postulated since the virus was first detected in the cerebrospinal fluid of a patient suffering from encephalitis in 1995<sup>4</sup> and in subsequent reports.<sup>6,7</sup>

CwG was first described in 1982 by Morooka et al. in patients who presented with convulsions associated with mild gastroenteritis without fever or laboratory abnormalities.<sup>3</sup>

The definition of CwG was further elaborated in 1992 by Komori et al. as convulsions in children with no history of epilepsy, typically occurring between the first and fifth day of gastroenteritis and showing no abnormalities in interictal electroencephalograms.

Typically, the prognosis is good, with complete recovery without long-term sequelae.<sup>8-12</sup>

Although the phenomenon initially seemed to be predominantly Asian, a worldwide occurrence was eventually described.<sup>10-13</sup>

In contrast to this mild and typically transient phenomenon, rotavirus-related encephalitis and cerebellitis are often severe and can be life-threatening. Moreover, an encephalitis with concurrent cerebellitis, defined in this analysis as encephalo-cerebellitis, has also been described in patients with rotavirus gastroenteritis.

Indeed, up to one third of children with encephalitis had a poor prognosis, defined as severe neurological sequelae or death,<sup>14,15</sup> and children between six and 24 months of age are considered a high-risk group for rotavirus-associated neurological complications.<sup>7</sup> Up to now, despite several case reports and case series, no systematic analysis has been performed. This study aims to systematically describe the clinical, laboratory, radiological features and outcomes of patients with neurological complications associated with a rotavirus infection.

## Methods

This systematic review was conducted according to the PRISMA recommendations.<sup>16</sup> The review has not been financially supported and not registered and a review protocol was not prepared. The Medline database was searched using the terms *rotavirus encephalitis*, *rotavirus cerebellitis*, *rotavirus central nervous system (CNS)*, *rotavirus encephalopathy*, *rotavirus meningitis*, *rotavirus infection fatal outcome*, *rotavirus convulsions*, *gastroenteritis convulsions*, *CwG*, *rotavirus*, *CwG and mild encephalitis/encephalopathy with a reversible splenic lesion*, limiting the search to publications in English, French, German, Spanish and Italian dating from 1984 until December 2020. Publications were included if they were available as a full-length article or letter, the included patients were individually described revealing at least age and sex, a description of neurological findings was given and a positive stool rotavirus was detected. Cases with hyponatremia, hypoglycemia, pre-existing neurological disease and coinfections were excluded. The patient's clinical characteristics (including the time from onset of the gastrointestinal symptoms to the first neurological symptoms), laboratory findings (including glycemia, natremia, glucose in the cerebro-spinal fluid, cerebro-spinal fluid/serum glucose ratio, research of rotavirus in stool, liquor and/or serum), and radiological characteristics [cerebral computed tomography (CT) or magnetic resonance imaging (MRI)] were extracted by two independent reviewers (AM, CM). Electroencephalogram findings, follow-up period and long-term consequences were also collected. Encephalitis was defined as an altered level of consciousness with or without other neurological signs and symptoms. Cerebellitis was defined as a cerebellar syndrome without an altered level of consciousness. A combination of a cerebellar syndrome with an altered level of consciousness was described as encefalo-cerebellitis. CwG was defined as focal or generalized seizures without signs of encephalitis or cerebellitis and without fever. Status epilepticus was defined as an uninterrupted seizure or repetitive seizures with a persistent interictal alteration of consciousness lasting longer than 30 minutes. The clinical findings of the last follow-up control were included to describe long-term

consequences. A positive outcome was defined as complete recovery, without residual neurological signs.

### *Statistical analysis*

Continuous data are presented as median and interquartile range (IQR) and categorical data as frequencies and percentages. Group comparison was performed using the Fisher's exact test, or the Kruskal-Wallis test with Dunn's post-hoc procedure, as appropriate. These statistical analyses were performed using GraphPad Prism® software, version 8.0.0 (GraphPad Software, San Diego California).

A proportion meta-analysis was performed to calculate the prevalence of rotavirus-positive subjects among patients with CwG and the prevalence of CwG in subjects with rotavirus-positive gastroenteritis, respectively. These pooled analyses were performed using data retrieved from the selected studies.

A random-effects model was used for statistical pooling of the data, taking into account the heterogeneity between studies. The different weight of each study in the pooled analysis was mainly related to the different sample size. Pooled data were presented with their respective 95% confidence interval (95% CI) values, and data were displayed using forest plots. Heterogeneity was estimated using the I-square index (I<sup>2</sup>), which describes the percentage of variation across studies that was due to the heterogeneity rather than chance. A I<sup>2</sup> value greater than 50% indicated substantial heterogeneity across studies. The proportion meta-analysis was performed using OpenMeta[Analyst]® (Rockville, MD, USA). P-values less than 0.05 were considered statistically significant.

## Results

The analysis of the literature revealed 794 publications, 83 of which were included in this systematic review (Figure 1). Out of these, 68 permitted a detailed analysis of cases<sup>4-8,11,17-78</sup> while 15 publications, dealing with CwG and rotavirus infection, only reported prevalence and therefore did not allow a detailed analysis.<sup>48,79-92</sup> Although these latter 15 publications were not included in the systematic analysis, they were used to calculate the prevalence of CwG in rotavirus infection or the prevalence of rotavirus infection in patients with CwG (Figure 1).

The 68 included reports (58 in English, eight in Spanish, one in French and one in Italian) documented 161 cases.

### *Analysis of all cases*

Of the 161 patients reported in the literature, 85 (53%) were females. Median age was 22 (IQR 14-29) months. Ninety-five children were described in Asian publications (82 from Japan), 39 from Europe, 25 from America, one from Africa and one from Oceania.

Ninety-nine cases of CwG, 39 cases of encephalitis, 18 cases of encephalo-cerebellitis and five cases of cerebellitis were reported (Table 1).

The median time from onset of gastrointestinal symptoms to the beginning of neurological symptoms was 3.0 (IQR 2.0-3.0) days.

The youngest children were those with CwG, followed by the children with encephalitis, while the children with encephalo-cerebellitis or cerebellitis were older compared to the other groups ( $p < 0.01$  in the Kruskal-Wallis test, Table 1).

Convulsions were reported not only in the CwG group, but were the most common presenting symptom in children with encephalitis (27/39, 70%), and also occurred in 20% of the cerebellitis group (1/5, 20%). Further presenting symptoms and signs are shown in figure 2. Of the 27 children presenting with convulsions in the encephalitis group, 17 had generalized convulsions and two had focal convulsions, while in eight cases the seizure semiology was not specified. In the encephalo-cerebellitis group, three cases had

generalized convulsions and in four patients the type of convulsion was not specified. The convulsion of the cerebellitis group was not further described.

Status epilepticus occurred in 6/26 (23%) children with convulsions associated with encephalitis, while it was not described in children with cerebellitis or encephalo-cerebellitis. Most of the convulsions in the CwG group were generalized, lasting <30 minutes. However, 5% of patients suffered from status epilepticus (Figure 3).

Rotavirus-analysis by polymerase chain reaction (PCR) in the cerebro-spinal fluid was positive in ten out of 21 (47%) patients in the encephalitis group, in three out of six (50%) in the encephalo-cerebellitis group, in one out of three (33%) in the cerebellitis group and in 13 out of 14 (93%) in the CwG group. Only limited data regarding liquor composition was available, and hematological or chemical blood analysis were not contributive.

An electroencephalogram was performed in 22 out of 39 (56%) patients in the encephalitis group, in eight out of 18 (44%) in the encephalo-cerebellitis group, in three out of five (60%) in the cerebellitis group and in 64 out of 99 (65%) in the CwG group, showing alterations without any further details in 17 out of 22 (77%), in seven out of eight (87.5%), in zero out of three (0%) and in seven out of 64 (11%) of these groups, respectively.

Seventeen out of 25 (68%) in the encephalitis group, 18 out of 18 (100%) in the encephalo-cerebellitis group, four out of five (80%) in the cerebellitis group and four out of 30 (13%) in the CwG group showed pathological findings at cerebral CT scan or MRI. The most frequent lesion observed was hyperintensity in the splenium of corpus callosum described in nine patients in the encephalitis group, in eight patients in the encephalo-cerebellitis group, and in four patients in the CwG group. In the latter cases the lesion disappeared completely within one to eight weeks.

Other reported lesions were cerebral edema, hyperintensity in the cerebellar hemispheres and vermis, cerebellar atrophy and hyperintensity of the basal ganglia.

Follow-up was described in 35 out of 39 (90%) cases in the encephalitis group, in all cases in the encephalo-cerebellitis group, in four out of five (80%) cases in the cerebellitis group and in 92 out of 99 (93%) cases in the CwG group. The median follow-up period



was 180 days (IQR 40-427.5 days). Out of the 35 reported follow-up children in the encephalitis group, ten patients (29%) had a particularly severe outcome: four children died, and the surviving six patients presented with severe neurological sequelae. Fourteen patients (77%) in the encephalo-cerebellitis group had a severe outcome, mainly with chronic ataxia and dysarthria, while one patient presented residual cognitive impairment. Two patients (50%) in the cerebellitis group had a poor prognosis, one with persistent speech problems and dysarthria, the other with persistent wide-based gait as a sign of persistent ataxia and a moderate expressive aphasia. All 92 cases of CwG had a good outcome with complete recovery. The encephalo-cerebellitis group showed the most severe outcome compared to the other groups ( $p=0.001$ , Table 1).

#### *Prevalence of convulsions with mild gastroenteritis in children with rotavirus-positive gastroenteritis*

The prevalence of rotavirus-positive subjects among patients with CwG ranged from 26.5% to 70% with a pooled prevalence of 48.1% (95% CI: 40.4-55.9) calculated through a meta-analysis of 12 studies (537 patients) (Figure 4).<sup>48,79-81,84,85,87-92</sup> I<sup>2</sup> index was 66.6% demonstrating a statistical heterogeneity among the included studies.

The prevalence of CwG in subjects with rotavirus-positive gastroenteritis ranged from 1.8% to 5.2% with a pooled prevalence of 2.7% (95% CI: 1.7-3.8) calculated through a meta-analysis of 4 studies (4'739 patients) (Figure 5).<sup>80,82,83,86</sup> I<sup>2</sup> index was 77.8% demonstrating a statistical heterogeneity among the included studies.

## Discussion

Rotavirus infection is one of the most common causes of acute gastroenteritis worldwide, in particular in children under five years of age.<sup>1,93,94</sup> Rotavirus gastroenteritis may be associated with neurological involvement, manifesting mainly as febrile or afebrile seizures, encephalopathy, encephalitis or cerebellitis.<sup>5,74,91</sup> While encephalitis, cerebellitis, and encephalo-cerebellitis may have chronic sequelae, CwG is a benign condition with a favorable outcome characterized by afebrile convulsions occurring in children with mild acute gastroenteritis.

In this analysis, patients with CwG were younger (median 19 months) compared to subjects diagnosed with rotavirus-related encephalitis, cerebellitis, and encephalo-cerebellitis, and the prevalence of neuroimaging pathological findings in the CwG population was low (12%), with a complete resolution within two months. This implies that, although neurological complications of rotavirus infection appear mostly between the age of one and four years of age, younger patients have the most benign outcome, without middle-term neurological sequelae. This apparent paradox might be explained by the high prevalence of rotavirus disease in this age group.

More than 90% of the subjects developing CwG tested positive for rotavirus in liquor. On the other side, approximately one third of patients with non-CwG manifestations and adverse outcomes showed no viral detection in the liquor. This latter finding may suggest that immune response and inflammation could be the cause of CNS damage, representing a potential target for treatment.

While 48% of patients with CwG tested positive for rotavirus infection, among patients with rotavirus infection the prevalence of CwG is 2.7%. Similarly, the reported prevalence of rotavirus-associated CNS involvement is 2-6%.<sup>49,91,95,96</sup> This figure implies that neurological complications associated with gastroenteritis or rotavirus infection are rare. Nevertheless, considering the high prevalence of children suffering from rotavirus infection, CNS involvement can be observed in a significant number of children and represents a relevant epidemiological burden.

Over a median follow-up of almost eight months, the reported outcome of patients with rotavirus-associated CwG was always benign, without sequelae. The most severe course was reported for subjects developing encephalo-cerebellitis, with almost 3/4 of patients presenting a severe middle-term outcome. In the encephalitis and cerebellitis groups, a severe outcome was observed in 1/3 and 1/2 of patients, respectively. The most common sequelae for the non-CwG cohort were speech problems, ataxia, and cognitive impairment.

The present analysis did not allow to study the preventative effects of rotavirus vaccination regarding neurological complications. Of note, a study conducted in Spain did not reveal any impact of rotavirus vaccine coverage on seizure-related hospitalizations in children <5 years.<sup>97</sup>

The most important limitations of this analysis are the inclusion of relative low-quality retrospective studies without standardized methods and indications for instrumental analyses (electroencephalogram, neuroimaging). Furthermore, the relatively short follow-up does not permit the assessment of long-term outcomes.

The main limitations of our meta-analyses were the statistical heterogeneity among the included studies, likely due to different patients characteristics and the relatively low number of included studies in the pooled analyses.

Nevertheless, this analysis confirms the association between rotavirus infections and neurological complications. Furthermore, the systematic description of cases of rotavirus infection complicated by neurological events presents for the first time an objective demographic analysis of presentation, laboratory and imaging findings and outcomes. Importantly, it discloses that rotavirus children presenting with encephalitis, encephalo-cerebellitis or cerebellitis have a relevant risk of medium-term sequelae, while CwG always presents a benign course.

Further studies are warranted in order to define additional risk factors for developing long-term complications in subjects with a rotavirus infection and neurological symptoms, to further explore the role of immune response in encephalitis and cerebellitis by analysis of

multiple cytokines together with immune cell subsets in the cerebrospinal fluid, and to identify potential treatments during the acute phase.

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**Conflict of interest statement:** All authors declare that they have no conflicts of interest.

**Data availability statement:** The data that support the findings of this study are available from the corresponding author, SGD, upon reasonable request.

**Ethical statement:** Not applicable for reviews and meta-analyses.

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## Figure legends

**Figure 1.** Article selection process according to PRISMA flow diagram

**Figure 2.** Distribution of clinical manifestations in patients with encephalitis, cerebellitis or encephalo-cerebellitis

**Figure 3.** Distribution of type and duration of convulsions in patients with mild CwG caused by rotavirus infection

**Figure 4.** Prevalence of rotavirus-positive subjects among patients with CwG

**Figure 5.** Prevalence of CwG in subjects with rotavirus-positive gastroenteritis

**Table 1: Baseline characteristics and outcome of subjects with neurological involvement during rotavirus infection.**

	<b>Encephalitis</b>	<b>Encephalo-cerebellitis</b>	<b>Cerebellitis</b>	<b>CwG</b>
<b>n. (%)</b>	39 (24)	18 (11)	5 (3)	99 (62)
<b>Age (months) - Median (IQR)</b>	24 (13-35)	36 (30-48) <sup>+</sup>	38 (36-46) <sup>%</sup>	19 (12-24)
<b>Sex, M - n. (%)</b>	24 (61.5)	3 (17)	3 (60)	46 (46)
<b>Latency (days) - Median (IQR)</b>	2 (2-3) <sup>°</sup>	3 (3-4)	6 (3-7)	3 (2-4)
<b>Positive liquor - n. (%)</b>	10/21 (47) <sup>*</sup>	3/6 (50)	1/3 (33)	13/14 (93)
<b>Positive serum - n. (%)</b>	6/9 (67)	1/3 (33)	0/0 (0)	4/10 (40)
<b>Pathological cerebral CT or MRI – positive / total reported (%)</b>	17/25 (68)	18/18 (100)	4/5 (80)	4/30 (13) <sup>&amp;</sup>
<b>Pathological EEG – positive / total reported (%)</b>	17/22 (77)	7/8 (87.5)	0/3 (0) <sup>&amp;</sup>	7/64 (11) <sup>&amp;</sup>
<b>Follow-up (yes) – n. (%)</b>	35 (90)	18 (100)	4 (80)	92 (93)
<b>Benign outcome- n. (%)</b>	25/35 (64) <sup>*</sup>	4/18 (23) <sup>**</sup>	2/4 (50)	92/92 (100)



+ p<0.01 with encephalitis and CwG groups

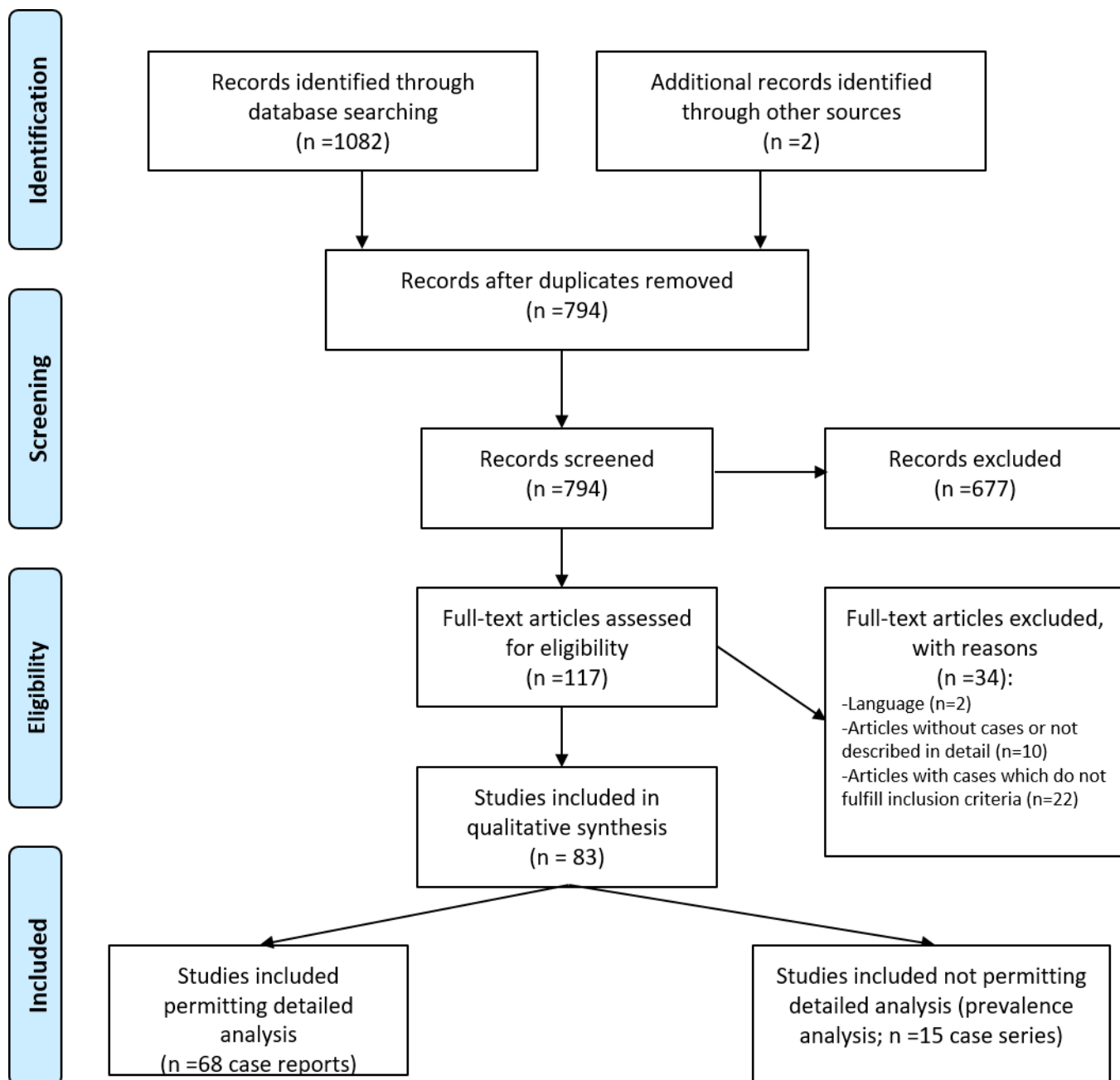
% p<0.01 with CwG group

\* p= <0.01 with the CwG group

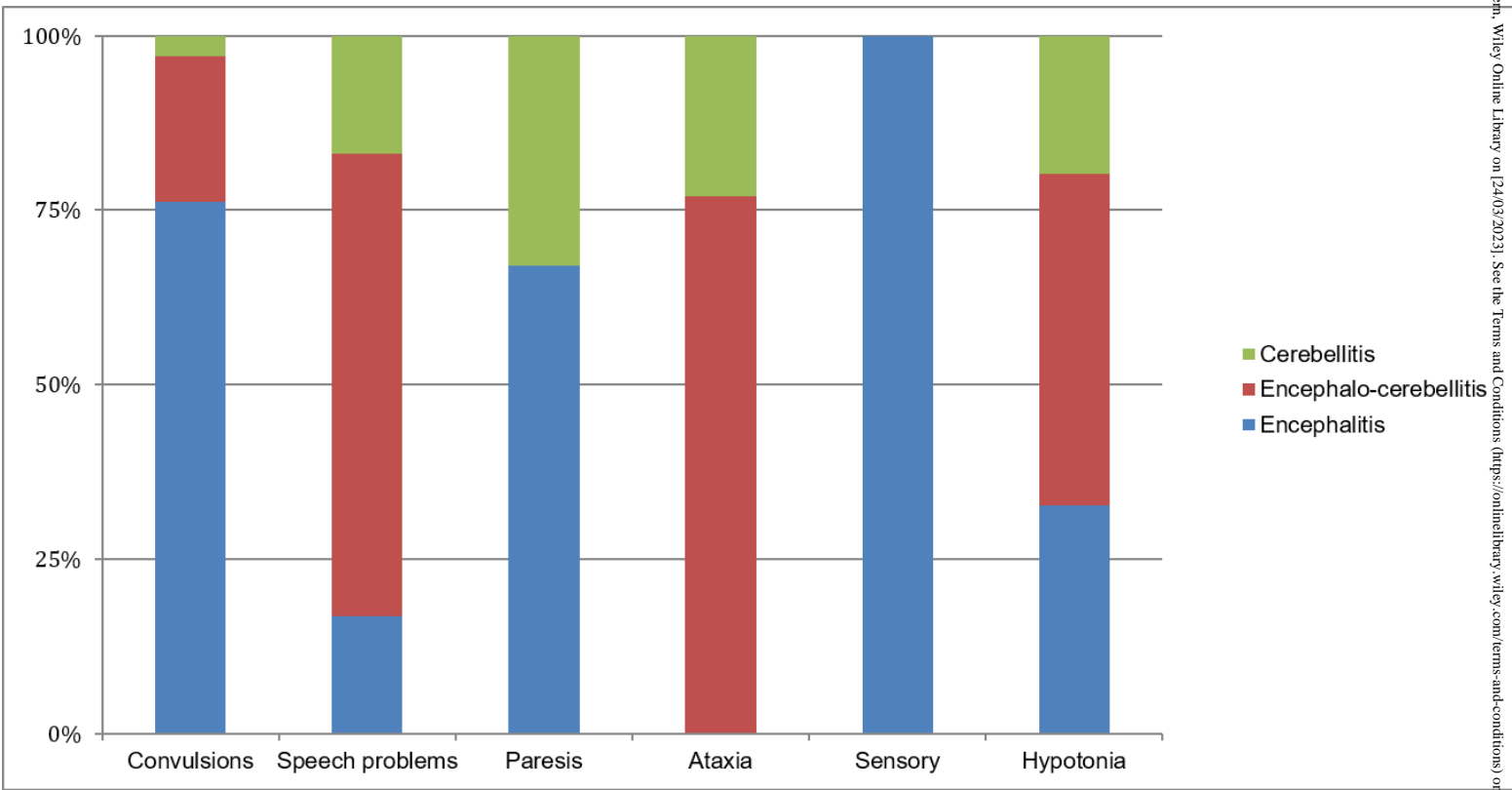
& p<0.05 with encephalitis and encephalo-cerebellitis groups

# p= 0.001 with encephalitis group

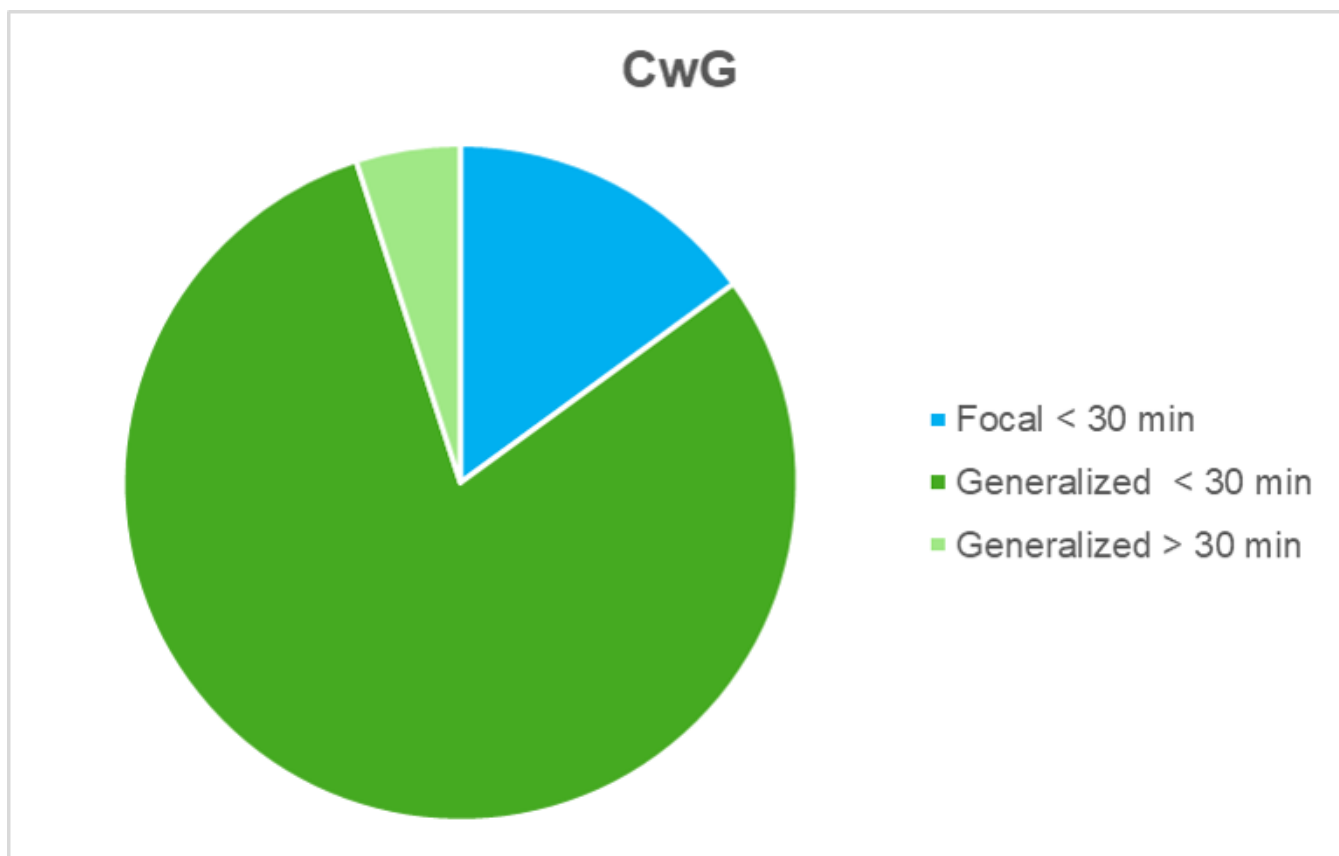
°p = 0.03 with cerebellitis group



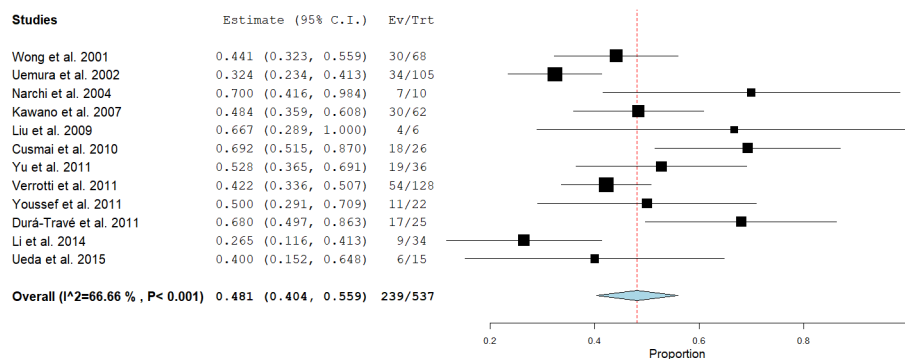
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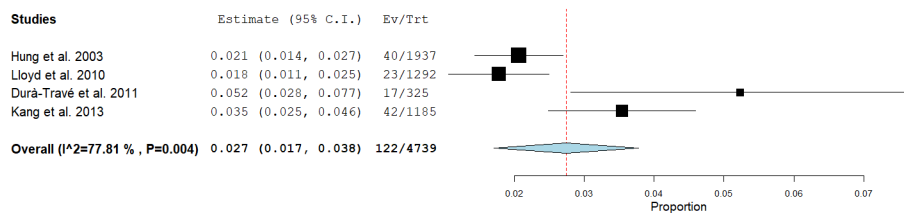
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