Respiratory Syncytial Virus–Associated Neurologic Complications in Children: A Systematic Review and Aggregated Case Series

Gemma L. Saravanos, BN, BSc(Hons)[1,2], Catherine L. King, MAppSci, PhD[2], Lucy Deng, FRACP[2], Nicole Dinsmore, BN, GCertNur(Paed)[2], Isabelle Ramos, MD[3], Mari Takashima, BN, MEpi[4], Nigel Crawford, PhD, FRACP[5], Julia E. Clark, FRACP, FRCPCH[6], Russell C. Dale, MBChB, FRACP[1,7], Cheryl A. Jones, PhD, FRACP[1,7], Nicholas J. Wood, PhD, FRACP[1,2,7], and Philip N. Britton, PhD, FRACP[1,7]

Objectives To describe the features and frequency of respiratory syncytial virus (RSV)-associated severe acute neurologic disease in children.

Study design We performed a systematic review of the literature to identify reports of severe acute neurologic complications associated with acute RSV infection in children aged <15 years (PROSPERO Registration CRD42019125722). Main outcomes included neurologic, clinical, and demographic features of cases and the frequency of disease. We aggregated available case data from the published literature and from the Australian Acute Childhood Encephalitis (ACE) study.

Results We identified 87 unique studies from 26 countries describing a spectrum of RSV-associated severe acute neurologic syndromes including proven encephalitis, acute encephalopathy, complex seizures, hyponatremic seizures, and immune-mediated disorders. The frequency of RSV infection in acute childhood encephalitis/encephalopathy was 1.2%-6.5%. We aggregated data from 155 individual cases with RSV-associated severe acute neurologic complications; median age was 11.0 months (IQR 2.0-21.5), most were previously healthy (71/104, 68%). Seizure was the most frequently reported neurologic feature (127/150, 85%). RSV was detected in the central nervous system of 12 cases. Most children recovered (81/122, 66%); however, some reports described partial recovery (33/122, 27%) and death (8/122, 7%).

Conclusions RSV-associated neurologic complications have been widely reported, but there is substantial heterogeneity in the design and quality of existing studies. The findings from our study have implications for the investigation, management, and prevention of RSV-associated neurologic complications. Further, this systematic review can inform the design of future studies aiming to quantify the burden of childhood RSV-associated neurologic disease. *(J Pediatr 2021;239:39-49)*.

See editorial, p 14 and related articles, p 24 and p 32

Respiratory syncytial virus (RSV) is a leading cause of acute lower respiratory infection in young children globally, and characterizing the full burden of RSV disease is increasingly important as we approach RSV-specific interventions such as vaccines.[1] Accordingly, there is a need to characterize the burden of less-common complications associated with RSV infection. RSV-associated acute neurologic disease is one such complication that is generally underappreciated despite existing reports of clinically severe disease.

Reports on RSV-associated acute neurologic disease in children describe a spectrum of syndromes including seizures, encephalopathy, and encephalitis.[2-4] A systematic review that synthesizes existing studies and case-level data can support the characterization of atypical conditions[5] and is therefore an appropriate method to examine RSV-associated acute neurologic disease.

The Australian Acute Childhood Encephalitis (ACE) study, a prospective cohort study that commenced in 2013, aimed to determine the causes of encephalitis in Australian children.[6] This study has enhanced understanding of the frequency and features of influenza-associated encephalitis/encephalopathy.[7]

ACE	Acute Childhood Encephalitis
CNS	Central nervous system
CSF	Cerebrospinal fluid
ICU	Intensive care unit
RSV	Respiratory syncytial virus

From the [1]University of Sydney, Sydney; [2]National Centre for Immunisation Research and Surveillance, Sydney; [3]The University of Notre Dame, Fremantle; [4]Griffith University, Brisbane; [5]Royal Children's Hospital, Melbourne; [6]Queensland Children's Hospital, Brisbane; and [7]The Children's Hospital at Westmead, Sydney, Australia

Supported by a University of Sydney Postgraduate Award (to G.S.); NHMRC ECF (GNT1145817 [to P.B.]); and The ACE Study funded by NHMRC CRE for Emerging Infectious Diseases (CREID) (GNT 1102962 [to C.J.]). The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The authors declare no conflicts of interest.

https://doi.org/10.1016/j.jpeds.2021.06.045

The ACE study can similarly contribute to the elucidation of RSV-associated neurologic disease, specifically RSV-associated encephalitis/encephalopathy in children. In this study, we aimed to describe the features and frequency of RSV-associated severe acute neurologic complications in children through a systematic review of the published literature and synthesis of individual case data from the literature and from the ACE study.

Methods

Eligibility Criteria

We included any published article that was the primary source of data for children aged <15 years with RSV-associated severe acute neurologic complications. We included articles of any type reporting at least 1 case of acute neurologic disease associated with acute RSV infection, which we defined as laboratory detection of RSV from any biological specimen within 72 hours of the acute neurologic presentation. Neurologic features sought included (but were not limited to) encephalopathy, paralysis, visual disturbance, seizures, meningitis, and RSV detection in the central nervous system (CNS).

We sought cases of "severe" acute neurologic disease; hence, we excluded reports describing simple febrile seizure or apnea in isolation. We defined a simple febrile seizure as a generalized tonic–clonic seizure lasting less than 15 minutes with no recurrence or postictal pathology associated with a febrile illness in a child aged older than 1 month,[8] or when described as a simple febrile seizure by study authors. We excluded reports in which neurologic features or seizures were not further described, as we were unable to adequately determine whether these met the eligibility criteria. We did not apply any exclusion criteria related to publication year, language, or publication type. The study protocol was registered on PROSPERO: CRD42019125722.

Search Strategy and Information Sources

Bibliographic databases were searched by an information specialist and included OVID Medline All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions (1946-September 10, 2019) (**Figure 1**; available at www.jpeds.com), OVID Embase (1974-October 3, 2019), Cochrane Library Database of Systematic Reviews (Issue 10 of 12, October 2019), Cochrane Library Central Register of Controlled Trials (Issue 10 of 12, October 2019), and Web of Science Core Collection including Science Citation Index Expanded (1900-October 2019), Social Sciences Citation Index (1956-October 2019), Arts & Humanities Citation Index (1975-October 2019), Emerging Sources Citation Index (2015-October 2019), Conference Proceedings Citation Index-Science (1990-October 2019), and Conference Proceedings Citation Index-Social Science & Humanities (1990-October 2019).

Key online sources of gray literature were searched by 2 reviewers between November 2019 to January 2020 and included internationally recognized centers of infectious disease surveillance (US Centers for Disease Control and Prevention, World Health Organization, European Centre for Disease Control, US National Institutes of Health), and, internationally recognized centers of expertise on RSV, neurology, and neuroinfectious disease (RSV Consortium Europe, Mayo Clinic, University of Liverpool, University of California San Francisco, American Academy of Neurology, American Neurological Association, and European Academy of Neurology).

Reference lists of included articles were searched by hand for additional eligible articles. For articles published from 2005 onwards not reporting individual case data, we attempted to retrieve this data via contact with authors. In addition, we included unpublished case data from the Australian ACE study (May 2013 to July 2020).

Study Selection

Screening of titles and abstracts was performed by the primary reviewer and a second independent reviewer. Full-text review was performed by the primary reviewer and eligibility was confirmed by a second independent reviewer. Where eligibility was unclear and/or consensus was not achieved, arbitration was sought from the senior author. We attempted to retrieve the full text of all articles meeting criteria for full text review via institutional and interlibrary loan; however, a small number of articles were not able to be obtained and these were excluded.

Data Collection

Data items were predefined and were collected into piloted forms. For included articles, data related to the article (publication details and language) and the study (ethics, funding, study design features, neurologic features, number of eligible cases) were extracted by 2 independent reviewers. For articles reporting case data (age, sex, clinical presentation), these and additional reported data (demographics, clinical history, investigations, treatments, outcomes, and causality) were extracted by the primary reviewer. Extracted case data were reviewed by senior authors, an infectious diseases pediatrician, and general pediatrician, respectively. Cases were included only once; duplicates were identified through screening for multiple reports of data from the same study groups, and, for cases reporting identical demographic and clinical features.

Data Synthesis and Analyses

We first described article characteristics and identified articles representing duplicate reports of studies or cases. Study design was categorized as case report, case series, cross-

sectional study, and cohort study according to published definitions.[5,9] We performed a narrative synthesis of studies with a focus on those that reported on specific neurologic syndromes and those that reported the frequency of RSV-associated neurologic disease amongst defined cohorts.

We then carried out a quantitative synthesis of individual case data. This included case data derived from the literature (n = 150) and case data derived from the ACE study (n = 5). We categorized cases as confirmed or possible according to a published encephalitis causality framework.[10] We performed a post hoc analysis of a subgroup of cases reporting moderate to severe hyponatremia (serum sodium <130 mmol/L), given the frequency of reports relating to this subgroup.[11] For the quantitative case synthesis, we excluded cases reporting an alternative non-RSV cause of neurologic symptoms, such as detection of a non-RSV pathogen, trauma, toxicity, or an underlying disorder considered contributory to the acute neurologic presentation.

Quality and Risk of Bias Assessment

A quality and risk of bias assessment of included articles was performed by 2 independent reviewers with arbitration sought from a third independent reviewer when consensus was not achieved. We adapted a published framework developed for the specific purpose of assessing the methodological quality of case series and case reports[5] and applied this to all included study types. Four domains were assessed: (1) Selection, (2) Ascertainment, (3) Causality, and (4) Reporting (**Figure 2**; available at www.jpeds.com). We did not exclude articles from synthesis based on the quality assessment.

Tools and Resources

EndNote X9.3.1; Clarivate Analytics was used to manage retrieved articles and support the screening process. Data were collected and managed using REDCap (Research Electronic Data Capture) 9.3.3 hosted at the University of Sydney.[12] Open-source software (Google Translate; Google) was used alongside the support of native language speakers to determine eligibility, perform quality assessment, and extract data from the published literature.

Ethics

Ethics approval was not required for the systematic review component of this study. Independent Human Research Ethics Committee approvals were previously obtained for the ACE study (HREC/18/SCHN/402).

Results

Study Selection

We identified 3614 articles through database searching and via other sources (**Figure 3**). We screened 2609 articles and excluded 2368 at screening. The remaining 241 articles were assessed for eligibility following full text review; 141 were excluded with reasons and 100 met the eligibility criteria (**Table I**; available at www.jpeds.com). Once duplicate studies were removed and overlapping studies were collapsed, 87 unique studies from 26 countries remained.

Synthesis of Study Data

The 87 unique studies described cases with a broad spectrum of RSV-associated severe acute neurologic complications. Across all studies, the most reported syndromes included seizure or convulsion (44 studies), encephalopathy (30 studies), encephalitis (11 studies), and status epilepticus (8 studies). Some studies reported specific, acute-onset encephalopathy syndromes including hemorrhagic shock and encephalopathy syndrome,[13-16] acute necrotizing encephalopathy,[17-19] mild encephalopathy with a reversible splenial lesion,[13,20] acute encephalopathy with biphasic seizures and late reduced diffusion,[13,14] and acute disseminated encephalomyelitis.[21] RSV detection in the CNS was reported by 9 studies describing 12 individual cases, of which 11 reported extractable case data.[21-29] Most cases (6/12, 50%) were reported from 1 study group across several articles.[27-32]

A minority of studies reported on the frequency of RSV-associated acute neurologic complications among specific cohorts of children. Some reported on broadly defined acute neurologic disease, a heterogeneous mix of neurologic syndromes, among all RSV-infected hospitalized children. In this group, 1.1%-7.1%[4,33-37] of children experienced acute neurologic complications with greater frequencies generally reported for children admitted to the intensive care unit (ICU) (6.6%-36.4%).[4,38,39] Conversely, one study sought cases of magnetic resonance imaging confirmed encephalitis among RSV-infected hospitalized children, a highly specific case definition, and found less than 0.1% (3/3856) of cases occurred among this group.[21]

Several studies examined defined cohorts of children with all-cause acute childhood encephalitis/encephalopathy and found that RSV infection was associated with 1.2%-6.5% of all cases.[13,40-45] The largest study, a pediatric hospital-based survey in Japan spanning 3 years, found that RSV was associated with 1.7% (17/983) of cases and was the fourth most common pathogen identified.[13] The greatest frequency was reported from a single-center cross-sectional study in Sweden, which found that RSV infection was associated with 6.5% (6/93) of all cases over 5 years.[41]

Other studies reported on the frequency of RSV-associated seizures including specific seizure syndromes (simple and complex febrile seizures, afebrile seizures, status epilepticus, and hyponatremic seizures).[14,23,35,36,38,46-49] Of these, 5 studies examined RSV-infected hospitalized children and found that 1.9%-6.6% experienced seizures of any type.[35,36,38,46,47] Two studies examined children hospitalized with febrile seizures (simple and complex) and found that RSV infection was associated with 2.7%-6.3% of all cases.[23,46] One study examined children hospitalized with febrile status epilepticus and found that RSV infection was associated with 19.2% (19/99) of all cases.[14] A further study examined all

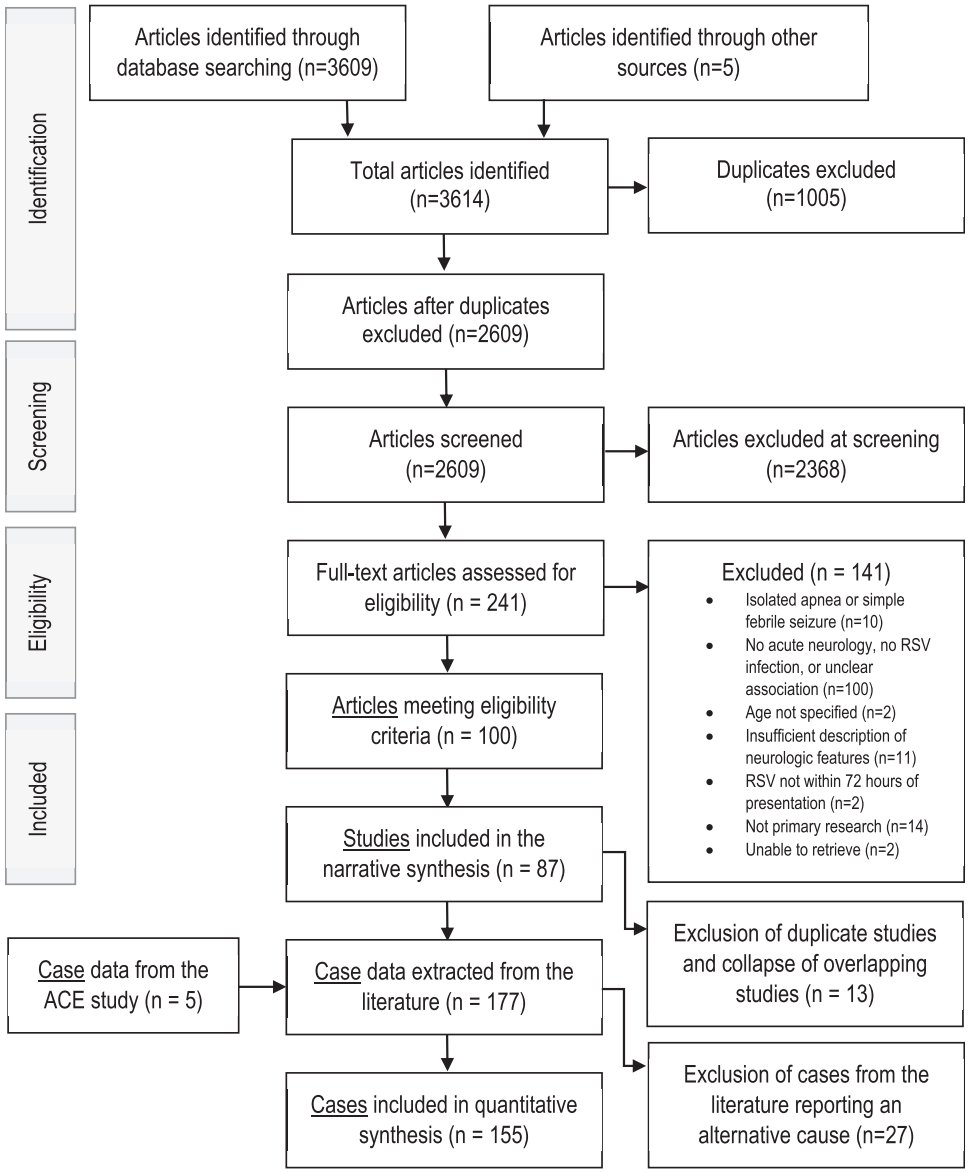

Figure 3. PRISMA systematic review flow chart.

RSV-infected children in the ICU during a single season and found that 4.4% (4/91) had hyponatremic seizures.[49]

Synthesis of Case Data

Following the identification and removal of duplicate case reports we extracted case data for 177 individual cases. We excluded 27 cases reporting an alternative non-RSV cause of neurologic symptoms. The majority were excluded due to the reported detection of another pathogen (*Clostridium botulinum*, *Mycoplasma pneumoniae*, *Streptococcus pneumoniae*, adenovirus, coronavirus, enterovirus, influenza, parainfluenza, rhinovirus), or the presence of an underlying disorder considered contributory to the neurologic presentation, a heterogeneous mix of neurologic and metabolic conditions including inborn errors.

Data from the remaining 150 cases from the literature and an additional 5 cases from the ACE study were aggregated for quantitative synthesis (**Table II**).[4,14-19,21,22,24-30,33-36,43,48-80] We categorized cases into subgroups according to causality consistent with terminology proposed by Granerod et al.[10] For 12 cases in which RSV was detected in the CNS, these were considered "confirmed RSV neurologic disease" (**Table III**). For cases in which RSV was only detected in a respiratory specimen, or where the specimen type was not reported, these were classified as "possible RSV neurologic disease." Of the "possible" cases, those reporting moderate-

Table II. Reported features among cases of RSV-associated neurologic disease (n = 155)

Reported features	Total (%) (n = 155)	Subgroup analysis		
		Confirmed (%) (n = 12)	Possible (%) (n = 118)	Possible (%) (with hyponatremia*) (n = 25)
Individual features				
Median age, mo (IQR)				
Age category	11.0 (2.0-21.5)	18.8 (9.25-36.0)	12.0 (3.2-23.8)	1.6 (1.4-2.0)
<6 mo	63 (41)	3 (25)	35 (30)	25 (100)
6 mo to <1 y	18 (11)	1 (8)	17 (14)	0 (0)
1-4 y	65 (42)	7 (58)	58 (49)	0 (0)
5-9 y	8 (5)	1 (8)	7 (6)	0 (0)
10-14 y	1 (1)	0 (0)	1 (1)	0 (0)
Sex (male)	84/153 (55)	9/12 (75)	63/118 (53)	12/23 (52)
Comorbidity or prematurity†	33/104 (32)	4/11 (36)	19/70 (27)	10/23 (44)
Presenting features				
Any respiratory symptoms	102/108 (94)	11/11 (100)	66/72 (92)	25/25 (100)
Severe respiratory symptoms‡	74/102 (73)	4/11 (36)	46/66 (70)	24/25 (96)
Any reported fever	79/111 (71)	11/11 (100)	64/86 (74)	4/14 (29)
Seizures	127/150 (85)	8/12 (67)	95/113 (84)	24/25 (96)
Status epilepticus§	34/60 (57)	3/7 (43)	29/42 (69)	2/11 (18)
Other neurologic features	93/155 (60)	11/11 (100)	68/118 (58)	13/25 (52)
Reduced consciousness	64/93 (69)	11/11 (100)	44/68 (65)	9/25 (36)
Encephalopathy	58/93 (62)	9/11 (82)	46/68 (68)	3/25 (12)
Abnormal motor	29/93 (31)	3/11 (27)	22/68 (32)	4/25 (16)
Abnormal tone	20/93 (22)	1/11 (9)	13/68 (19)	6/25 (24)
Abnormal reflexes	11/93 (12)	1/11 (9)	8/68 (12)	2/25 (8)
Abnormal behavior	7/93 (8)	0/11 (0)	5/68 (7)	2/25 (8)
Vision disturbance	6/93 (7)	2/11 (18)	4/68 (6)	0/25 (0)
Urinary retention/anuria	4/93 (4)	1/11 (9)	3/68 (4)	0/25 (0)
Investigations				
CSF pleocytosis¶	21/64 (33)	6/10 (60)	13/49 (27)	2/5 (40)
RSV detected in CNS**	12/23 (52)	12/12 (100)	0/8 (0)	0/3 (0)
Abnormal MRI	37/69 (54)	5/8 (63)	28/56 (50)	4/5 (80)
Abnormal CT	21/53 (40)	5/7 (71)	14/36 (39)	2/10 (20)
Abnormal EEG	49/87 (56)	6/7 (86)	36/66 (55)	7/14 (50)
Outcome				
Complete recovery	81/122 (66)	6/11 (55)	62/94 (66)	13/17 (77)
Partial recovery	33/122 (27)	4/11 (36)	26/94 (28)	3/17 (18)
Death	8/122 (7)	1/11 (9)	6/94 (6)	1/17 (6)

CT, computed tomography; *EEG*, electroencephalogram; *MRI*, magnetic resonance imaging; *WBC*, white blood cells.
*Moderate-to-severe hyponatremia (serum sodium <130 mmol/L). Missing serum sodium value for 1 case, however, included in this group based on clinical diagnosis of hyponatremia and syndrome of inappropriate diuretic hormone. Sex not reported for 2 cases in this subgroup.
†Most commonly a history of prematurity (18) or respiratory disease (10).
‡Cases reporting lower respiratory tract infection (bronchiolitis or pneumonia), respiratory distress, respiratory failure, cardiopulmonary arrest, or any respiratory symptoms plus hypoxia, cyanosis or consolidation on chest radiograph, or apnea requiring ventilation.
§Defined as seizure duration >30 minutes, or, where described as "status epilepticus" by study authors.
¶Defined as >5 WBC/mm^3; or >15 WBCmm^3 if aged <1 month of cases in which CSF cell count and type was reported.
**RSV detected in any CNS specimen (CSF or brain tissue) of cases where testing was reported.

to-severe hyponatremia were subcategorized into their own group.

For all cases, seizure was the most reported neurologic feature (127/150, 85%). Where seizure type was specified, 77% (72/93) were generalized, 15% (14/93) were focal, and 8% (7/93) were mixed. Non-seizure neurologic features were reported for 60% (93/155) of cases. Of these, reduced level of consciousness (64/93, 69%) and encephalopathy (58/93, 62%) were most common. Motor abnormality was reported in 31% (29/93) and included paralysis, weakness, ataxia, and esotropia. Non-neurologic features reported included gastrointestinal symptoms (14), cyanosis (10), cardiopulmonary arrest (7), shock (7), hepatic dysfunction (6), and coagulopathy (4).

Level of intensive care support was infrequently specified but where reported, 98% (42/43) of cases were admitted to the ICU and 73% (41/56) of cases received mechanical ventilation. Pharmacologic treatment was reported for some cases and included steroids (20), intravenous immunoglobulin (6), and ribavirin (2). Outcome was reported for 122 cases. Of these, complete recovery occurred in 66% (81) and partial recovery in 27% (33). Partial recovery ranged from mild residual dysfunction to persistent cognitive impairment and physical disability. Death was reported in 8 cases.[4,15,22,43,60,79]

Of 25 cases subcategorized into the hyponatremic group, all were aged less than 6 months and all but 1 reported seizure. Compared with other cases, children in this group were younger (median age of 1.6 vs 12.5 months), had a greater frequency of severe respiratory symptoms (96% vs 39%), and had a lower frequency of fever (27% vs 77%). A history of prematurity was reported in 10 cases.

Across all cases, there was substantial heterogeneity in the reporting of investigations (neuroimaging, electroencephalogram, pathogen testing, cerebrospinal fluid [CSF] analysis,

Table III. Characteristics of cases with RSV detected in the CNS (n = 12)

						Presenting clinical features				Laboratory and neurologic investigations					
Authors	Year	Age, y	Sex	Country	Medical history	Fever	Resp	Neurologic	Other	RSV detection	CSF pleocytosis*	MRI*	CT*	EEG*	Outcome
Kakimoto et al[22]	2016	1.6	F	Japan	None	Yes	Yes	Coma	Cardiopulmonary arrest	RSV in a brain biopsy (IH), RSV-B in a respiratory sample (PCR)†	ND	ND	Yes	ND	Death
Kawashima et al[27]	2018	0.3	M	Japan	Unilateral kidney	Yes	Yes	General seizure, encephalopathy	DIC, cardiopulmonary arrest, renal/liver failure	RSV-A in a CSF and respiratory sample (PCR)	No	ND	Yes	Yes	Spastic paraplegia
Kawashima et al[28]	2019	0.9	F	Japan	None	Yes	Yes	Mixed seizure, encephalopathy, eye deviation	Nil	RSV-A in a CSF and respiratory sample (PCR)	Yes	Yes	ND	Yes	"Mental retardation" and delay
Kawashima et al[28]	2019	1.9	M	Japan	None	Yes	Yes	General seizure, encephalopathy	Nil	RSV-A in a CSF and respiratory sample (PCR)	Yes	ND	Yes	U	Complete recovery
Kawashima et al[29]	2012	3.0	M	Japan	Febrile seizure	Yes	Yes	General seizure, SE, encephalopathy	Nil	RSV-A in a CSF and respiratory sample (PCR)	No	No	No	Yes	Complete recovery
Kawashima et al[29]	2012	1.0	F	Japan	None	Yes	Yes	General seizure, encephalopathy	Nil	RSV-A in a CSF and respiratory sample (PCR)	No	No	Yes	Yes	Complete recovery
Kawashima et al[29]	2012	3.0	M	Japan	CHARGE syndrome	Yes	Yes	Focal seizure, encephalopathy	DIC, low serum carnitine	RSV-A in a CSF and respiratory sample (PCR)	No	Yes	Yes	Yes	Not reported
Park et al[21]	2014	3.9	M	Korea	Recurrent otitis media	U	U	Mixed seizure, encephalopathy	Nil	RSV in a CSF sample (PCR)	Yes	Yes	U	Yes	Mild motor impairment
Shirota et al[24]	2011	0.2	M	Japan	None	Yes	Yes	Nil	Nil	RSV-B in a CSF sample (PCR)	Yes	No	U	No	Complete recovery
Tison-Chambellan et al[25]	2013	7.0	M	France	U	Yes	Yes	Encephalopathy, hypotonia, extrapyramidal & cerebellar signs	Nil	RSV-A in a CSF and respiratory sample (PCR)	Yes	Yes	No	U	Partial recovery (not further specified)
Zlateva et al[26]	2004	0.3	M	Belgium	None	Yes	Yes	General seizure, reduced LOC	Mild hyponatremia (133mmoL/L)	RSV-B in a CSF ad respiratory sample (PCR and culture)	U	U	U	U	Complete recovery
ACE study		1.6	M	Australia	None	Yes	Yes	Lethargy, cerebellar dysfunction, urinary retention	Hypernatremia (154 mmol/L)	RSV in a CSF and respiratory sample (PCR)	Yes	Yes	ND	ND	Complete recovery

CHARGE, coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness; *DIC*, disseminated intravascular coagulation; *F*, female; *IH*, immunohistochemistry; *LOC*, level of consciousness; *M*, male; *ND*, not done; *PCR*, polymerase chain reaction; *Resp*, respiratory symptoms; *SE*, status epilepticus; *U*, unknown.

*Yes = abnormal findings, no = normal findings, ND = investigation not done, U = unknown if the investigation was performed.

†For case 1, RSV was detected in macrophages in the brain by immunohistochemistry at autopsy and RSV-B was detected by PCR in lung tissue at autopsy.

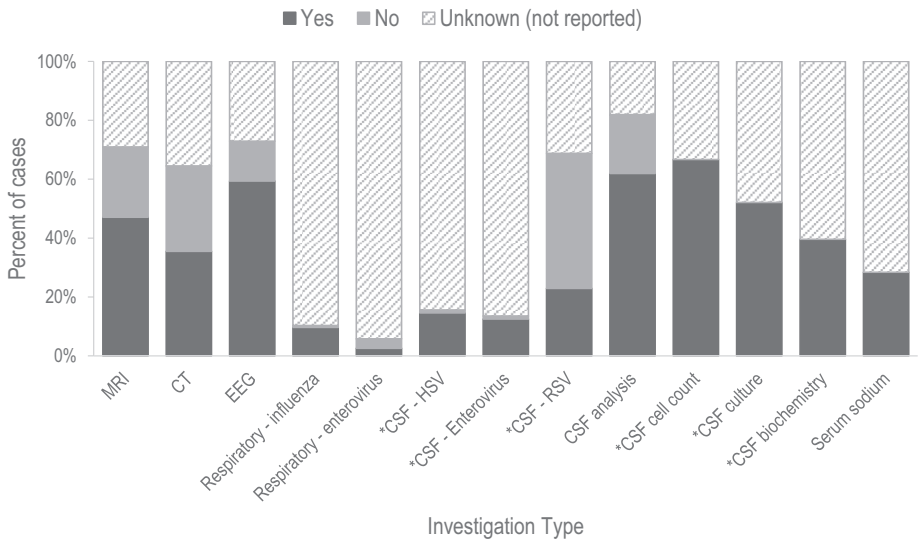

Figure 4. Investigations performed in included cases (n = 155). *For specific CSF investigations, the denominator is the number of cases in which CSF analysis was reported (n = 96). *CT*, computed tomography; *EEG*, electroencephalogram; *HSV*, herpes simplex virus; *MRI*, magnetic resonance imaging.

and serum sodium analysis) (**Figure 4**). In many cases, it was unclear whether the sought investigations were performed. Only 2 studies explicitly reported performing the prespecified investigations required to meet the Causality Domain (CSF analysis, testing for common neuropathogens, and neuroimaging).[17,41]

Quality and Risk of Bias

For included articles, we assessed quality and risk of bias across 4 domains (**Table I**; **Table IV** [available at www.jpeds.com]). A total of 43 (43%) articles satisfied at least 3 domains and were rated "Higher Quality"; the majority of these were cross-sectional and cohort studies.

Discussion

This systematic review and aggregated cases series demonstrate that RSV-associated severe acute neurologic disease in children has been widely reported and encompasses a broad spectrum of syndromes ranging from proven encephalitis to acute encephalopathy syndromes, complex seizures, hyponatremic seizures, and immune-mediated disorders. Assessment of the published literature uncovered considerable heterogeneity in the design, reporting and quality of existing studies. Nonetheless, the novel synthesis of data in our study establishes that acute neurologic disease is a clinically important complication amongst the larger burden of RSV respiratory disease in children.

The literature suggests that 1%-7% of all children hospitalized with RSV infection will experience a form of neurologic complication,[4,33-37,46,47] a substantial burden when considering that RSV is estimated to cause 3.2 million annual hospitalizations globally.[1] Key studies provide evidence that RSV is an important contributor to defined severe acute neurologic syndromes including acute childhood encephalitis/encephalopathy,[13,40-45] complex seizures, and status epilepticus.[14,23,46,81] Notably, the most severe syndromes, such as proven encephalitis, are likely rare among the large volume of children hospitalized with RSV infection, less than 0.1% in 1 study.[21] RSV-associated neurologic disease in the presence of hyponatremia emerged as a distinct group in our review and was characterized by young age, severe respiratory symptoms, a low frequency of fever, and a high frequency of prematurity.[49-51,53,56-59,71-75,77,82]

Clinicians should consider RSV infection as a possible cause in children presenting with acute neurologic and respiratory symptoms, especially during seasonal RSV epidemics. In addition, clinicians should consider the potential for hyponatremia in infants hospitalized with RSV respiratory disease. This presentation, possibly related to the syndrome of inappropriate antidiuretic hormone secretion, is common in infants with RSV bronchiolitis in the ICU and is associated with increased disease severity.[49,83] Its diagnosis may have a role in predicting the disease course and guiding fluid management to prevent severe outcomes including associated acute neurologic complications.[49,83]

The age distribution of RSV-associated neurologic disease may differ from that of severe RSV respiratory disease. Following the removal of the hyponatremic subgroup, only 29% of cases in our study were aged younger than 6 months. In contrast, around 45% of all RSV

hospitalizations occur in this age group.[1] RSV-specific interventions, directed at reducing the burden of respiratory disease, may have an additional benefit of preventing RSV-associated neurologic disease, as suggested for influenza vaccines and associated childhood encephalitis.[6] The older age distribution observed in our study contributes to the rationale for considering RSV-specific prevention in older children as well as infants.

Detection of RSV in the CSF of 12 cases reported from 7 unique studies[21-29] and in 1 case from the ACE study, is a key finding and establishes that RSV is capable of causing direct CNS infection as proven RSV encephalitis.[10] Although CSF is not routinely investigated for respiratory viruses,[84] RSV was found in the CNS of one-half of those tested, most of whom also had RSV detected in the respiratory tract. The potential mechanism of neurologic invasion of respiratory viruses is an active area of research and both hematogenous and retrograde neural pathways have been suggested with supportive evidence derived from animal and genomic studies.[3,85,86] The evidence for RSV neuroinvasion emphasizes the need to characterize the pathogenesis of severe acute neurologic disease associated with respiratory viruses to support the development of treatment approaches to prevent long-term morbidity.

The spectrum of acute childhood neurologic syndromes described in our study is broadly reflective of those associated with other respiratory viruses such as influenza virus, adenovirus and more recently SARS-CoV-2.[3,7,87,88] The pathogenesis of respiratory virus-associated encephalopathy is likely diverse and may include both direct and indirect pathways. A leading hypothesis is that a "cytokine storm" mediates immune cell over activation and cellular dysfunction within the CNS.[3,7] Host genetic susceptibility is another potentially important contributor to pathogenesis. In our study, we identified several children with inborn errors that were considered contributory to the acute neurologic presentation.[89-92] Further studies interrogating host genetic profiles may contribute to understanding of individual susceptibility to severe RSV disease including RSV-associated neurologic disease.[85]

Our study employed a systematic review framework to synthesize study and case level data and provide a novel, comprehensive description of the available evidence relating to RSV-associated neurologic disease. We have taken steps to reduce the inherent risk of bias. These include duplicate screening and quality assessment of articles, broad inclusion criteria that was not limited by date, language or study design, and involvement of content experts in the study design and analysis.

The most important limitation of this systematic review is the inclusion of low-quality studies, in particular case reports, which have a high risk of selection bias.[5] The bias for reporting and publishing severe or unusual cases may mean that severity is over-represented in our study. An additional important limitation is the variable reporting of clinical features, investigations, outcomes, and timelines across studies. Unclear or missing information may have resulted in the exclusion of important studies at the screening phase and the exclusion of important cases at the synthesis phase. Finally, there was substantial heterogeneity in study design, acute neurologic syndrome definitions and study inclusion criteria.

RSV-associated neurologic disease is a clinically important presentation, and RSV infection should be considered in children presenting with acute neurologic symptoms. The findings in this study can inform the investigation and management of RSV-associated neurologic complications in children. Further, this comprehensive description of associated severe acute neurologic disease defines an underappreciated burden of RSV that should be further considered in ongoing efforts to develop RSV-specific interventions. There is a need for multicenter cohort studies that employ universally accepted definitions of acute neurologic syndromes to improve the accuracy of frequency estimates. In addition, the improved conduct and reporting of standardized investigations can support evidence of a causal relationship among cases in which RSV is a possible cause. ■

We thank Miroslava Ross, Zhicheng Wang, and Ye Yin Joo for providing translation support for non-English literature. We thank the Acute Childhood Encephalitis (ACE) study team and members of the Paediatric Active Enhanced Disease Surveillance (PAEDS) network, who contributed to the conduct of the ACE study.

Submitted for publication Feb 15, 2021; last revision received May 30, 2021; accepted Jun 21, 2021.

Reprint requests: Gemma L. Saravanos, BN, BSc(Hons), National Centre of Immunisation Research and Surveillance, The Children's Hospital at Westmead, Corner of Hawkesbury Road & Hainsworth Street, Locked Bag 4001, Westmead, NSW 2145 Australia. E-mail: gemma.saravanos@health.nsw.gov.au

References

1. Shi T, McAllister DA, O'Brien KL, Simoes EAF, Madhi SA, Gessner BD, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in young children in 2015: a systematic review and modelling study. Lancet 2017;390:946-58.
2. Eisenhut M. Extrapulmonary manifestations of severe respiratory syncytial virus infection—a systematic review. Crit Care 2006;10:R107.
3. Bohmwald K, Galvez NMS, Rios M, Kalergis AM. Neurologic alterations due to respiratory virus infections. Front Cell Neurosci 2018;12:386.
4. Millichap JJ, Wainwright MS. Neurological complications of respiratory syncytial virus infection: case series and review of literature. J Child Neurol 2009;24:1499-503.
5. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. BMJ Evid Based Med 2018;23:60-3.
6. Britton PN, Dale RC, Blyth CC, Clark JE, Crawford N, Marshall H, et al. Causes and clinical features of childhood encephalitis: a multicenter, prospective cohort study. Clin Infect Dis 2020;70:2517-26.
7. Britton PN, Dale RC, Blyth CC, Macartney K, Crawford NW, Marshall H, et al. Influenza-associated Encephalitis/Encephalopathy

Identified by the Australian Childhood Encephalitis Study 2013-2015. Pediatr Infect Dis J 2017;36:1021-6.
8. International League Against Epilepsy. Guidelines for epidemiologic studies on epilepsy. Commission on epidemiology and prognosis, international league against epilepsy. Epilepsia 1993;34:592-6.
9. Vandenbroucke JP, von Elm E, Altman DG, Gotzsche PC, Mulrow CD, Pocock SJ, et al. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): explanation and elaboration. Int J Surg 2014;12:1500-24.
10. Granerod J, Cunningham R, Zuckerman M, Mutton K, Davies NW, Walsh AL, et al. Causality in acute encephalitis: defining aetiologies. Epidemiol Infect 2010;138:783-800.
11. Luu R, DeWitt PE, Reiter PD, Dobyns EL, Kaufman J. Hyponatremia in children with bronchiolitis admitted to the pediatric intensive care unit is associated with worse outcomes. J Pediatr 2013;163:1652-6.e1.
12. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377-81.
13. Hoshino A, Saitoh M, Oka A, Okumura A, Kubota M, Saito Y, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev 2012;34:337-43.
14. Uda K, Kitazawa K. Febrile status epilepticus due to respiratory syncytial virus infection. Pediatr Int 2017;59:878-84.
15. Mayordomo-Colunga J, Concha Torre A, Menendez Cuervo S, Rey Galan C. Haemorrhagic shock syndrome and encephalopathy (I). An Pediatr (Barc) 2008;69:489-91 [in Spanish].
16. Ince E, Kuloglu Z, Akinci Z. Hemorrhagic shock and encephalopathy syndrome: neurologic features. Pediatr Emerg Care 2000;16:260-4.
17. Al-Maskari N, Mohsin J, Al-Maani A, Al-Macki N, Al-Ismaili S. Atypical presentations of respiratory syncytial virus infection: case series. Sultan Qaboos Univ Med J 2016;16:e86-91.
18. Erdogan S, Yakut K, Kalin S. Acute encephalitis and myocarditis associated with respiratory syncytial virus infections. Turk J Anaesthesiol Reanim 2019;47:348-51.
19. Ong SCL, Nur Azidawati AH, Liew YH, Anita S. Acute necrotising encephalopathy of childhood: a review of two cases. Med J Malaysia 2017;72:311-3.
20. Li G, Li S, Qi F, Mei G. Mild encephalitis/encephalopathy in children with a reversible splenial lesion. Radiol Infect Dis 2018;5:118-22.
21. Park A, Suh SI, Son GR, Lee YH, Seo HS, Eun BL, et al. Respiratory syncytial virus-related encephalitis: magnetic resonance imaging findings with diffusion-weighted study. Neuroradiology 2014;56:163-8.
22. Kakimoto Y, Seto Y, Ochiai E, Satoh F, Osawa M. Cytokine Elevation in sudden death with respiratory syncytial virus: a case report of 2 children. Pediatrics 2016;138:12.
23. Rantala H, Uhari M, Tuokko H. Viral infections and recurrences of febrile convulsions. J Pediatr 1990;116:195-9.
24. Shirota G, Morozumi M, Ubukata K, Shiro H. Infantile meningitis caused by respiratory syncytial virus. Kansenshogaku Zasshi 2011;85:682-5 [in Japanese].
25. Tison-Chambellan C, Cheuret E, Cances C, Karsenty C, Le Camus C, Sevely A, et al. Respiratory syncytial virus brainstem encephalitis in a 7-year-old boy. Arch Pediatr 2013;20:657-60 [in French].
26. Zlateva KT, Van Ranst M. Detection of subgroup B respiratory syncytial virus in the cerebrospinal fluid of a patient with respiratory syncytial virus pneumonia. Pediatr Infect Dis J 2004;23:1065-6.
27. Kawashima H, Ioi H, Hasegawa Y, Yamanaka G, Takekuma K, Mori M, et al. Life-threatening extrapulmonary manifestations associated with respiratory syncytial virus infection in Japan. J Tokyo Med Univ 2008;66:549-52.
28. Kawashima H, Ioi H, Ushio M, Yamanaka G, Matsumoto S, Nakayama T. Cerebrospinal fluid analysis in children with seizures from respiratory syncytial virus infection. Scand J Infect Dis 2009;41:228-31.
29. Kawashima H, Kashiwagi Y, Ioi H, Morichi S, Oana S, Yamanaka G, et al. Production of chemokines in respiratory syncytial virus infection with central nervous system manifestations. J Infect Chemother 2012;18:827-31.
30. Morichi S, Kawashima H, Ioi H, Ushio M, Yamanaka G, Kashiwagi Y, et al. Cerebrospinal fluid NOx (nitrite/nitrate) in RSV-infected children with CNS symptoms. J Infect 2009;59:299-301.
31. Morishima Y, Kawashima H, Yamanaka G, Oana S, Ioi H, Takekuma K, et al. A case of acute encephalopathy with biphasic seizures and late reduced diffusion on respiratory syncytial virus infection. J Tokyo Med Univ 2010;68:231-4.
32. Morichi S, Kawashima H, Ioi H, Yamanaka G, Kashiwagi Y, Hoshika A, et al. Classification of acute encephalopathy in respiratory syncytial virus infection. J Infect Chemother 2011;17:776-81.
33. Sweetman LL, Ng YT, Butler IJ, Bodensteiner JB. Neurologic complications associated with respiratory syncytial virus. Pediatr Neurol 2005;32:307-10.
34. Ng YT, Cox C, Atkins J, Butler IJ. Encephalopathy associated with respiratory syncytial virus bronchiolitis. J Child Neurol 2001;16:105-8.
35. Yoon SW, Kim HJ, Yum MK, Seol IJ. Neurologic complications associated with respiratory syncytial virus infection in childhood. J Pediatr New Econ 2008;16:206-12.
36. Cha T, Choi YJ, Oh JW, Kim CR, Park DW, Seol IJ, et al. Respiratory syncytial virus-associated seizures in Korean children, 2011-2016. Korean J Pediatr 2019;62:131-7.
37. Savic N, Jankovic B, Minic P, Vasiljevic Z, Sovtic A, Pejic K, et al. Clinical characteristics of respiratory syncytial virus infection in neonates and young infants. Vojnosanit Pregl 2011;68:220-4.
38. Kho N, Kerrigan JF, Tong T, Browne R, Knilans J. Respiratory syncytial virus infection and neurologic abnormalities: retrospective cohort study. J Child Neurol 2004;19:859-64.
39. Watabe S. Examination of risk factors for severe RS virus infection in intensive care unit. Eur J Pediatr 2016;175:1786.
40. Aizaki K, Tsuru T, Okumura K, Ikehara H, Hiramoto R. Group A coxsackie virus-associated encephalitis/encephalopathy: a retrospective hospital-based study in Japan. Dev Med Child Neurol 2012;4:15-6.
41. Fowler A, Stodberg T, Eriksson M, Wickstrom R. Childhood encephalitis in Sweden: etiology, clinical presentation and outcome. Eur J Paediatr Neurol 2008;12:484-90.
42. Hon KL, Tsang YC, Chan LC, Tsang HW, Wong KY, Wu YH, et al. Outcome of encephalitis in pediatric intensive care unit. Indian J Pediatr 2016;83:1098-103.
43. Kawasaki Y, Suyama K, Go H, Hosoya M. Clinical manifestations of respiratory syncytial virus-associated encephalopathy in Fukushima, Japan. Pediatr Int 2019;61:802-6.
44. Loh R, Grimwood K, Malone S. Paediatric febrile encephalopathy and encephalitis - experience in Brisbane, Australia. Dev Med Child Neurol 2012;4:22-3.
45. Wong AM, Lin JJ, Toh CH, Bilaniuk LT, Zimmerman RA, Chang YC, et al. Childhood encephalitis: relationship between diffusion abnormalities and clinical outcome. Neuroradiology 2015;57:55-62.
46. Chung B, Wong V. Relationship between five common viruses and febrile seizure in children. Arch Dis Child 2007;92:589-93.
47. Miyama S, Goto T. Afebrile seizures associated with respiratory syncytial virus infection: a situation-related seizure disorder in early infancy. Pediatr Int 2011;53:113-5.
48. Gouyon JB, Fantino M, Couillault G, Durand C, Pothier P, Alison M. Respiratory syncytial virus infections in newborn infants. Arch Fr Pediatr 1986;43:93-7 [in French].
49. Hanna S, Tibby SM, Durward A, Murdoch IA. Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. Acta Paediatr 2003;92:430-4.

50. Al Shibli A, Abukhater D, Al Kuwaiti N, Noureddin MB, Al Harbi M, Al Kaabi A, et al. Hyponatraemia and neurological complications in children admitted with bronchiolitis. Paediatr Int Child Health 2016;36:175-80.
51. Albinski M, Gamperli L, Regamey N, Stettler J, Tomaske M. Hyponatraemia in paediatric bronchiolitis—a harmful complication not to be ignored. Klin Padiatr 2016;228:275-6.
52. Arrowsmith WA, Smithells RW, Congdon PJ. Letter: temporary paralysis after infection by respiratory syncytial virus. Lancet 1975;1:743.
53. Ben Jaballah N, Mnif K, Hedfi L, Hammami A, Khaldi F, Bennaceur B. Clinical, therapeutic and developmental aspects of acute bronchiolitis in Tunisia. Cah Anesthesiol 1996;44:423-8 [in French].
54. Brown WD, Caruso JM. Extrapontine myelinolysis with involvement of the hippocampus in three children with severe hypernatremia. J Child Neurol 1999;14:428-33.
55. Brunatti P, Giacchetti L, Pezzoli V, Kottanattu L, Ramelli GP. RSV associated acute encephalitis with basal ganglia involvement: a pediatric case report. Swiss Medical Weekly 2017;147:23S.
56. Cheriathu J. Hyponatremic seizures and shock: an unusual presentation of respiratory syncitial virus infection. Eur J Pediatr 2016;175:1870-1.
57. Claeys T, Van De Voorde P, Willems J, Oosterlynck L. Convulsions in a 6-week-old boy with RSV bronchiolitis: don't forget the salt!. Tijdschrift voor Geneeskunde 2011;67:1041-4 [in Dutch].
58. Della Paolera S, Soffritti S, Sandri F. The syndrome of inappropriate antidiuretic hormone (ADH) secretion in bronchiolitis. Medico e Bambino 2016;35:463-4 [in Italian].
59. Duran Carvajal J, Pena Zarza JA, Figuerola Mulet J. Bronchiolitis and convulsions: not always due to apnoeas. An Pediatr (Barc) 2012;77:284-6 [in Spanish].
60. Griffin N, Keeling JW, Tomlinson AH. Reye's syndrome associated with respiratory syncytial virus infection. Arch Dis Child 1979;54:74-6.
61. Healy L, Forbes E, Rice J, Leonard J, Crushell E. Reye-like syndrome and severe carnitine deficiency in a boy with autism spectrum disorder and restricted diet. Arch Dis Child 2019;104:A187.
62. Hirayama K, Sakazaki H, Murakami S, Yonezawa S, Fujimoto K, Seto T, et al. Sequential MRI, SPECT and PET in respiratory syncytial virus encephalitis. Pediatr Radiol 1999;29:282-6.
63. Inoue S, Nakazawa T, Kantake M, Kaneko K, Shimojima T. Early infantile patients of RS viral bronchiolitis with afebrile convulsions. No To Hattatsu 2003;35:347-9 [in Japanese].
64. Jimenez-Legido M, Cantarin-Extremera V, Almodovar-Martin JL, Bernardino-Cuesta B. Neurological complications in cases of bronchiolitis due to respiratory syncytial virus: febrile status and other neurological manifestations. Rev Neurol 2019;68:489-91 [in Spanish].
65. Miyamoto K, Fujisawa M, Hozumi H, Tsuboi T, Kuwashima S, Hirao J, et al. Systemic inflammatory response syndrome and prolonged hypoperfusion lesions in an infant with respiratory syncytial virus encephalopathy. J Infect Chemother 2013;19:978-82.
66. Mizuno Y. A three-year-old girl with acute encephalopathy with biphasic seizures associated with respiratory syncytial virus infection. Pediatr Crit Care Med 2011;1:A121.
67. Morichi S, Morishita N, Ishida Y, Oana S, Yamanaka G, Kashiwagi Y, et al. Examination of neurological prognostic markers in patients with respiratory syncytial virus-associated encephalopathy. Int J Neurosci 2017;127:44-50.
68. Moriyama K, Takahashi Y, Shiihara T. Another case of respiratory syncytial virus-related limbic encephalitis. Neuroradiology 2014;56:435-6.
69. Nakamura K, Kato M, Sasaki A, Shiihara T, Hayasaka K. Respiratory syncytial virus-associated encephalopathy complicated by congenital myopathy. Pediatr Int 2012;54:709-11.
70. Otake Y, Yamagata T, Morimoto Y, Imi M, Mori M, Aihara T, et al. Elevated CSF IL-6 in a patient with respiratory syncytial virus encephalopathy. Brain Dev 2007;29:117-20.
71. Paul SP, Hicks SS, Sanjeevaiah MK, Heaton PA. Where did the salt go? Turk J Pediatr 2017;59:345-8.
72. Piastra M, Caresta E, Tempera A, Langer A, Zorzi G, Pulitano S, et al. Sharing features of uncommon respiratory syncytial virus complications in infants. Pediatr Emerg Care 2006;22:574-8.
73. Picone S, Mondi V, Di Palma F, Martini L, Paolillo P. Neonatal encephalopathy and SIADH during RSV infection. Am J Perinatol 2019;36:S106-9.
74. Pop Jora D, de Suremain N, Arnaud C, Greteau S, Guellec I, Renolleau S, et al. VRS bronchiolitis with severe hyponatremia leading to acute seizures: a report of three cases. Arch Pediatr 2014;21:1359-63 [in French].
75. Rivers RP, Forsling ML, Olver RP. Inappropriate secretion of antidiuretic hormone in infants with respiratory infections. Arch Dis Child 1981;56:358-63.
76. Sato A, Mizuguchi M, Mimaki M, Takahashi K, Jimi H, Oka A, et al. Cortical gray matter lesions in acute encephalopathy with febrile convulsive status epilepticus. Brain Dev 2009;31:622-4.
77. Seto M, Shiomi M, Togawa M, Lee SS, Yabiku M, Sugita T. Thirty seven cases of respiratory syncytial virus infection hospitalised and 7 severe cases with apneic attacks. Kansenshogaku Zasshi 1994;68:226-33 [in Japanese].
78. Tang Y, Suddarth B, Du X, Matsumoto JA. Reversible diffusion restriction of the middle cerebellar peduncles and dentate nucleus in acute respiratory syncytial virus cerebellitis: a case report. Emerg Radiol 2014;21:89-92.
79. Xu L, Gao H, Zeng J, Liu J, Lu C, Guan X, et al. A fatal case associated with respiratory syncytial virus infection in a young child. BMC Infect Dis 2018;18:217.
80. Simpson H, Matthew DJ, Habel AH, George EL. Acute respiratory failure in bronchiolitis and pneumonia in infancy. Modes of presentation and treatment. Br Med J 1974;2:632-6.
81. Carman KB, Calik M, Karal Y, Isikay S, Kocak O, Ozcelik A, et al. Viral etiological causes of febrile seizures for respiratory pathogens (EFES Study). Hum Vaccin Immunother 2019;15:496-502.
82. Van Steensel-Moll HA, Van der Voort E, Bos AP, Rothbarth PH, Neijens HJ. Respiratory syncytial virus infections in children admitted to the intensive care unit. Pediatrie 1989;44:583-8.
83. Hasegawa K, Stevenson MD, Mansbach JM, Schroeder AR, Sullivan AF, Espinola JA, et al. Association between hyponatremia and higher bronchiolitis severity among children in the ICU with bronchiolitis. Hosp Pediatr 2015;5:385-9.
84. Britton PN, Eastwood K, Brew BJ, Nagree Y, Jones CA. Consensus guidelines for the investigation and management of encephalitis. Med J Aust 2015;202:576-7.
85. Salas A, Pardo-Seco J, Cebey-Lopez M, Gomez-Carballa A, Obando-Pacheco P, Rivero-Calle I, et al. Whole exome sequencing reveals new candidate genes in host genomic susceptibility to respiratory syncytial virus disease. Sci Rep 2017;7:15888.
86. Espinoza JA, Bohmwald K, Cespedes PF, Gomez RS, Riquelme SA, Cortes CM, et al. Impaired learning resulting from respiratory syncytial virus infection. Proc Natl Acad Sci U S A 2013;110:9112-7.
87. Lindan CE, Mankad K, Ram D, Kociolek LK, Silvera VM, Boddaert N, et al. Neuroimaging manifestations in children with SARS-CoV-2 infection: a multinational, multicentre collaborative study. Lancet Child Adolesc Health 2021;5:167-77.
88. Schwartz KL, Richardson SE, MacGregor D, Mahant S, Raghuram K, Bitnun A. Adenovirus-associated central nervous system disease in children. J Pediatr 2019;205:130-7.
89. Kumar A, Asghar S, Kavanagh R, Wicklund M. A unique presentation of rapidly fluctuating symptoms in a child diagnosed with congenital myasthenic syndrome due to RAPSN mutation. Neurology Conference: 70th Annual Meeting of the American Academy of Neurology, AAN90.
90. Schmitt-Mechelke T. Neonatal star gazing: tonic upward gaze as a manifestation of atypical non-ketotic hyperglycinemia. Neuropediatrics Conference: 38th Annual Meeting of the Society of Neuropediatrics Munster Germany Conference Publication43.

91. Maitre A, Maw A, Ramaswami U, Morley SL. Relapsing acute axonal neuropathy in hereditary fructose intolerance. Pediatr Neurol 2016;64:92-3.

92. Kayfan S, Yazdani RM, Castillo S, Wong K, Miller JH, Pfeifer CM. MRI findings of hypomyelination in adenylosuccinate lyase deficiency. Radiol Case Rep 2019;14:255-9.

50 Years Ago in *The Journal of Pediatrics*

Molecular Diagnostics Determine Underlying Genetic Etiologies for Well-Described Clinical Syndromes

Johanson A, Blizzard R. A syndrome of congenital aplasia of the alae nasi, deafness, hypothyroidism, dwarfism, absent permanent teeth, and malabsorption. J Pediatr 1971;79:982-7.

In 1971, Drs Johanson and Blizzard described 3 unrelated individuals with a syndrome of aplastic alae nasi, dwarfism, scalp defects, microcephaly, deafness, hypothyroidism, pancreatic insufficiency, absent permanent teeth, and intellectual disability. Since its initial description 50 years ago, there are more than 60 patients in the literature with what is now known as Johanson–Blizzard syndrome (JBS) (OMIM 243800). Until 2005, the underlying genetic etiology of JBS was unknown.

With continuously evolving molecular diagnostics, Zenker et al performed a genome-wide linkage scan to identify a region of homozygosity on chromosome 15q shared by individuals with JBS. They further analyzed this region using microsatellite markers from the human genome sequence and refined a candidate region. Then, through direct sequencing of DNA from individuals with a clinical diagnosis of JBS, they detected molecular variants in the *UBR1* gene located on chromosome 15q15-21.3. *UBR1* encodes 1 of at least 4 functionally overlapping E3 ubiquitin ligases of the N-end rule pathway, a conserved proteolytic system whose substrates include proteins with destabilizing N-terminal residues.[1]

In an era before molecular diagnostics, Drs Johanson and Blizzard employed comprehensive physical examinations and pattern recognition to accurately describe the clinical features of a new genetic syndrome ("phenotype-first" approach). This allowed for identification of a larger cohort of affected individuals, improved counseling and management, and ultimately for determination of the underlying genetic etiology.

As the field of molecular diagnostics continues to grow rapidly, we are in a new era of genetics in which we are able to sequence the entire human genome and determine the genetic cause of countless syndromes ("genotype-first" approach). However, more work is required to better understand the function of much of the human genome. Comprehensive dysmorphology examinations and pattern recognition of associated anomalies will continue to allow for cohort identification, which in conjunction with improved molecular diagnostics, can allow for more individualized prognosis, management, and the potential for future targeted molecular therapeutics.

K. Taylor Wild, MD
Ian D. Krantz, MD
Roberts Individualized Medical Genetics Center
Children's Hospital of Philadelphia
Philadelphia, Pennsylvania

Reference

1. Zenker M, Mayerle J, Lerch MM, Tagariello A, Zerres K, Durie PR, et al. Deficiency of UBR1, a ubiquitin ligase of the N-end rule pathway, causes pancreatic dysfunction, malformations and mental retardation (Johanson-Blizzard syndrome). Nat Genet 2005;37:1345-50.

Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current>
Search Strategy:

---

1 exp Respiratory Syncytial Virus, Human/
2 exp Respiratory Syncytial Virus Infections/
3 (respiratory adj syncytial).tw.
4 rsv.tw.
5 exp Bronchiolitis/
6 bronchiolitis.tw.
7 1 or 2 or 3 or 4 or 5 or 6
8 exp Neurologic Manifestations/
9 neuro$.tw.
10 exp Encephalitis/
11 encephal$.tw.
12 exp Central Nervous System Viral Diseases/
13 mening$.tw.
14 exp Neuroimaging/
15 exp Magnetic Resonance Imaging/
16 (magnetic adj1 resonance adj1 imag$).tw.
17 mri.tw.
18 (brain adj1 biops$).tw.
19 exp Encephalomyelitis, Acute Disseminated/
20 (acute adj1 disseminated adj1 encephalomyelitis).tw.
21 adem.tw.
22 exp Ataxia/
23 ataxi$.tw.
24 exp Leukoencephalopathies/
25 (acute$ adj1 h?emorrhagic adj1 leu#oencephal$).tw.
26 AHL.tw.
27 exp Guillain-Barre Syndrome/
28 (guillain-barre$ or guillain barre$ or GBS).tw.
29 exp Myelitis, Transverse/
30 (transver$ adj1 myeliti$).tw.
31 TM.tw.
32 exp Opsoclonus-Myoclonus Syndrome/
33 (opsoclon$ adj1 myoclon$).tw.
34 exp Seizures/
35 seizure$.tw.
36 (fit or fits).tw.
37 convuls$.tw.
38 exp Paralysis/
39 paralys$.tw.
40 exp Cerebrospinal Fluid/
41 (cerebrospinal adj1 fluid).tw.
42 csf.tw.
43 ((visual$ or vision) adj1 disturbance$).tw.
44 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43
45 7 and 44
46 Animals/ not (Animals/ and Humans/)
47 45 not 46
48 limit 47 to "all child (0 to 18 years)"
49 exp Adolescent/
50 exp Child/
51 exp Infant/
52 (baby or babies or infant$ or toddler$ or child$ or paediatric$ or pediatric$ or adolescen$ or teenage$).tw.
53 49 or 50 or 51 or 52
54 47 and 53
55 48 or 54

Figure 1. OVID Medline search strategy. Database: MEDLINE(R) All including Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versions(R) <1946-current> search strategy.

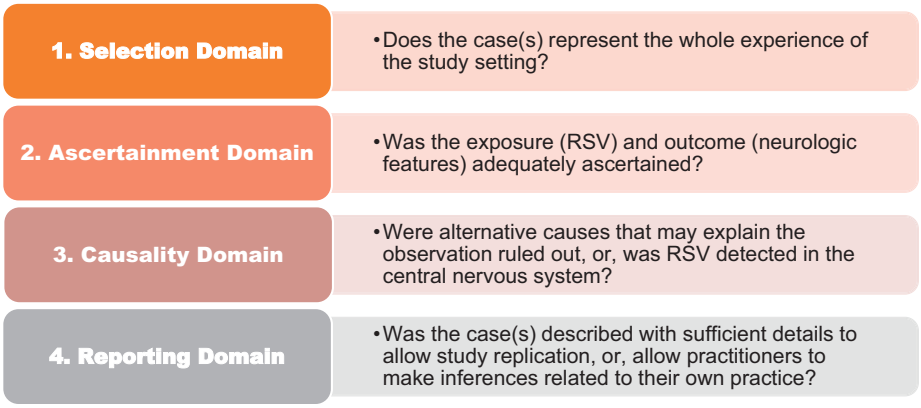

Figure 2. Quality assessment domains. The Causality Domain was informed by published guidelines for the investigation and causality of childhood encephalitis.[10,84] To meet this domain, authors must have reported on prespecified investigations to exclude common alternate causes of acute neurologic symptoms. Sought investigations were analysis of CSF including cell count, cell type, and culture; CSF testing for enterovirus and herpes simplex virus; respiratory sample testing for enterovirus and influenza virus; and neuroimaging using either magnetic resonance imaging or computed tomography. Reports that demonstrated the detection of RSV in the CNS met the causality domain regardless of other reported investigations. Articles that met 3 or more domains were classified "higher quality" and all others were classified "lower quality."

Table I. Included articles (n = 100)

ID*	Authors (citation) [ID†]	Year	Country	Design‡	Neurologic features and syndromes	Eligible§	Extract¶	Quality Assessment** 1	2	3	4	Grade
1	Abernethy[1]	2014	Unknown	Case report	Encephalopathy, seizure, blindness	1	1 (0)	N	Y	N	N	Lower quality
2	Aizaki et al[2]	2012	Japan	Cohort	Encephalitis/encephalopathy	4	NA	Y	Y	N	Y	Higher quality
3	Al Shibli et al[3]	2016	United Emirates	Cross-sectional	Hyponatremic seizure, hypertonia, hyper-reflexia, apnea	1	1	Y	Y	N	Y	Higher quality
4	Al-Maskari et al[4]	2016	Oman	Case series	Encephalopathy, acute necrotizing encephalopathy	2	2	N	Y	Y	Y	Higher quality
5	Albinski et al[5]	2016	Switzerland	Case series	Hyponatremic seizure, apnea	1	1	N	Y	N	Y	Lower quality
6	Antonucci et al[6]	2010	Italy	Cohort	Encephalopathy, seizure, change in consciousness, tone abnormality	5	NA	Y	Y	N	Y	Higher quality
7	Arrowsmith et al[7]	1975	England	Case report	Paralysis	1	1	N	Y	N	Y	Lower quality
8	Bray et al[8]	2016	Unknown	Case report	Botulism-like (weakness, hypotonia, respiratory failure)	1	1 (0)	N	Y	N	N	Lower quality
9	Brown et al[9]	1999	USA	Case series	Extrapontine myelinolysis, ataxia, myoclonic spasm	1	1	N	Y	N	Y	Lower quality
10†	Brunatti et al[10] [33†]	2017	Switzerland	Case report	Acute encephalitis	1	1	N	Y	U	Y	Lower quality
11	Carman et al[11]	2019	Turkey	Cohort	Complex febrile seizures	12	NA	Y	Y	N	Y	Higher quality
12	Cha et al[12]	2019	South Korea	Cross-sectional	Seizure (complex febrile, afebrile), meningitis, encephalopathy	22	22 (14)	Y	Y	N	Y	Higher quality
13	Cheriathu[13]	2016	Unknown	Case report	Hyponatremic seizure	1	1	N	Y	N	Y	Lower quality
14††	Cheung and Hon[14] [23†]	2016	Hong Kong	Cross-sectional	Acute encephalitis	UD	NA	Y	Y	N	Y	Higher quality
15	Erdogan et al[15]	2019	Turkey	Case report	ANE	1	1	N	Y	N	Y	Lower Quality
17	Fowler et al[16]	2008	Sweden	Cross-sectional	Acute encephalitis	6	NA	Y	Y	Y	Y	Higher Quality
18	Francisco and Arnon[17]	2007	USA	Cross-sectional	Botulism-like	1	NA	Y	Y	N	Y	Higher quality
19	Fukasawa et al[18]	2015	Japan	Case report	Acute cerebellopathy	1	1 (0)	N	Y	N	Y	Lower Quality
20	Hanna et al[19]	2003	United Kingdom	Cross-sectional	Hyponatremic seizure, apnea	4	4	Y	Y	N	Y	Higher quality
21	Hinson et al[20]	2017	Unknown	Case report	Botulism-like (weakness, hypotonia, respiratory failure)	1	1 (0)	N	Y	N	N	Lower quality
22	Hirayama et al[21]	1999	Japan	Case report	Acute encephalitis	1	1	N	Y	N	Y	Lower quality
23††	Hon et al[22] [14††]	2016	Hong Kong	Cohort	Acute encephalitis	2	NA	Y	Y	U	Y	Higher quality
24	Jimenez et al[23]	2019	Spain	Case series	Seizure, status epilepticus	2	2	N	Y	N	Y	Lower quality
25	Kakimoto et al[24]	2016	Japan	Case series	Coma, RSV in CNS	2	2	N	Y	Y	Y	Higher quality
26	Kawasaki et al[25]	2019	Japan	Cohort	Acute encephalitis/encephalopathy	6	6	N	Y	N	Y	Lower quality
27††	Kawashima et al[26] [28, 37, 38, 39†]	2008	Japan	Cross-sectional	Encephalopathy, seizures, apnea, RSV in CNS	4	4	N	Y	Y	Y	Higher quality
28††	Kawashima et al[27] [27, 37, 38, 39, 40†]	2009	Japan	Case series	Seizures (partial and complex), involuntary movement, RSV in CNS	3 (2)	2	N	Y	Y	Y	Higher quality
29**	Kawashima et al[28] [27, 28, 37, 38, 39†]	2012	Japan	Case series	Encephalopathy, seizures, cerebellitis, RSV in CNS	8 (6)	6	N	Y	Y	Y	Higher quality
30	Kho et al[29]	2004	USA	Cross-sectional	Encephalopathy, seizure, motor dysfunction, apnea	UD	NA	Y	Y	N	Y	Higher quality
31	Li et al[30]	2018	China	Cross-sectional	Mild encephalitis with a reversible splenial lesion	1	NA	Y	Y	N	Y	Higher Quality
32	Loh et al[31]	2012	Australia	Cohort	Encephalopathy/encephalitis	1	NA	Y	Y	N	Y	Higher quality
33††	Lorenzo[32] [10†]		Switzerland	Case report	Encephalitis	1 (0)	0	N	Y	N	Y	Lower quality
34	Millichap et al[33]	2009	USA	Cohort	Seizure, hypertonia, apnea	7	7	Y	Y	N	Y	Higher quality
35	Miyamato et al[34]	2013	Japan	Case report	Encephalopathy, hypotonia, apnea	1	1	N	Y	N	Y	Lower quality
36	Mizuno[35]	2011	Unknown	Case report	Acute encephalopathy, seizure	1	1	N	Y	N	Y	Lower quality
37††	Morichi et al[36] [27, 28, 29, 38†]		Japan	Case series	Encephalopathy, seizure, apnea, RSV in CNS	8 (3)	3	N	Y	Y	Y	Higher quality
38††	Morichi et al[37] [27, 28, 29, 37†]	2011	Japan	Case series	Encephalopathy, seizure, RSV in CNS	9 (0)	0	U	Y	Y	Y	Higher quality
39††	Morichi et al[38] [27, 28, 29, 37, 38†]	2017	Japan	Cohort	Encephalopathy, seizure	11 (2)	2	U	Y	N	Y	Lower quality
40††	Morishima et al[39] [28†]	2010	Japan	Case report	Encephalopathy, seizure, RSV in CNS	1 (0)	0	N	Y	Y	Y	Higher quality
41	Morton et al[40]	1981	United Kingdom	Case series	Encephalopathy, tone abnormality, seizure, apnea	3	NA	N	Y	N	Y	Lower quality
43	Nakamura et al[41]	2012	Japan	Case report	Encephalopathy, convulsions	1	1	N	Y	N	Y	Lower quality
44	Ng et al[42]	2001	USA	Cohort	Encephalopathy, seizure, apnea, status epilepticus	8	8	Y	Y	N	Y	Higher quality
45	Ong et al[43]	2017	Malaysia	Case series	ANE	1	1	N	Y	N	Y	Lower quality
46	Otake et al[44]	2007	Japan	Case report	Encephalopathy, hemiplegia, seizure	1	1	N	Y	N	Y	Lower quality
47	Park et al[45]	2014	Korea	Cohort	Acute encephalitis, ADEM, seizure, RSV in CNS	6	6 (5)	Y	Y	Y	Y	Higher quality
48	Piastra et al[46]	2006	Italy	Case series	Hyponatremic seizure, apnea	1	1	N	Y	N	Y	Lower quality
49	Picone et al[47]	2019	Italy	Case report	Hyponatremic seizures, encephalopathy, hypotonia	1	1	N	Y	N	Y	Lower quality
50	Quinn et al[48]	2013	USA	Case report	Botulism-like (weakness, hypotonia, respiratory failure, facial paralysis)	1	1 (0)	N	Y	N	Y	Lower quality

(*continued*)

Table I. Continued

ID*	Authors (citation) [ID†]	Year	Country	Design‡	Neurologic features and syndromes	Eligible§	Extract¶	Quality Assessment** 1	2	3	4	Grade
51	Rantala et al[49]	1990	Finland	Cohort	Complex febrile seizure, RSV in CNS	4	NA	Y	Y	Y	Y	Higher quality
52	Sakai et al[50]	2013	Japan	Case report	Acute encephalopathy, febrile convulsive status epilepticus	1	1 (0)	N	Y	N	Y	Lower quality
53	Sato et al[51]	2009	Japan	Case report	Encephalopathy, febrile convulsive status epilepticus	1	1	N	Y	N	Y	Lower Quality
54	Savic et al[52]	2011	Serbia	Cohort	Encephalopathy	1	NA	Y	Y	N	Y	Higher Quality
55	Shirota et al[53]	2011	Japan	Case report	Meningitis, RSV in CNS	1	1	N	Y	Y	Y	Higher quality
56	Srivastava et al[54]	2018	Canada	Case report	Encephalopathy, ataxia, reversible splenial lesion syndrome	1	1 (0)	N	Y	N	Y	Lower quality
57	Sweetman et al[55]	2005	USA	Cross-sectional	Encephalopathy, complex febrile seizures, status epilepticus	12	12	Y	Y	N	Y	Higher quality
58	Tang et al[56]	2014	USA	Case report	Cerebellitis, altered consciousness, ataxia, hypotonia	1	1	N	Y	N	Y	Lower quality
59	Tison-Chambellan et al[57]	2013	France	Case report	Encephalitis, ataxia, meningitis, RSV in CNS	1	1	N	Y	Y	Y	Higher Quality
60	Uda and Kitazawa[58]	2017	Japan	Cohort	Febrile status epilepticus, AESD, HSES, paresis	19	19	Y	Y	N	Y	Higher quality
61††	Watabe[59] [62, 63†]	2010	Japan	Cross-sectional	Encephalopathy	5	NA	Y	Y	N	Y	Higher quality
62††	Watabe[60] [61, 63†]	2011	Japan	Cross-sectional	Encephalopathy	5 (0)	NA	Y	Y	N	Y	Higher quality
63†	Watabe[61] [61, 62†]	2016	Japan	Cross-sectional	Encephalopathy	5 (0)	NA	Y	Y	N	Y	Higher quality
64	Xu et al[62]	2018	China	Case report	Encephalopathy, brain edema	1	1	N	Y	N	Y	Lower quality
65	Zlateva and Van Ranst[63]	2004	Belgium	Case report	Febrile seizure, RSV in CNS	1	1	N	Y	Y	Y	Higher quality
66**	Babiker[64] [77†]	2010	Unknown	Case report	Encephalopathy, acute motor neuropathy	1 (0)	0	N	Y	N	Y	Lower quality
67††	Feria et al[65] [70, 71†]	2018	Unknown	Case report	Congenital myasthenic syndrome	1 (0)	0	N	Y	N	Y	Lower quality
68	Gallagher et al[66]	2009	Unknown	Case report	Chorea	1	1 (0)	N	Y	N	Y	Lower quality
69	Healy et al[67]	2019	Unknown	Case report	Encephalopathy, ataxia (Reye-like syndrome)	1	1	N	Y	N	Y	Lower quality
70††	Kumar et al[68] [67, 71†]	2018	Unknown	Case report	Congenital myasthenic syndrome (weakness, hypotonia, respiratory failure)	1 (0)	0	N	Y	N	Y	Lower quality
71†	Kumar[69] [67, 70†]	2018	USA	Case report	Congenital myasthenic syndrome (weakness, hypotonia, respiratory failure)	1	1 (0)	N	Y	N	Y	Lower quality
72	Schmitt-Mechelke et al[70]	2012	Unknown	Case report	Acute choreoathetotic encephalopathy	1	1 (0)	N	Y	N	N	Lower quality
73	Wong et al[71]	2015	Taiwan	Cohort	Encephalitis	1	NA	Y	Y	N	Y	Higher quality
74	Miranda[72]	2016	USA	Case report	Hemiparesis, weakness, incontinence, ataxia	1	1 (0)	N	Y	N	Y	Lower quality
75	Erez[73]	2014	Israel	Cohort	Encephalopathy, seizure	3	NA	U	Y	N	Y	Lower quality
76	Griffin et al[74]	1979	United Kingdom	Case report	Reye syndrome, loss of consciousness, cerebral edema, hypertonia	1	1	N	Y	N	Y	Lower quality
77††	Maitre et al[75] [66†]	2016	United Kingdom	Case report	Relapsing and remitting neuropathy (profound global hypotonia, hyporeflexia)	1	1 (0)	N	Y	N	Y	Lower quality
78	Miyama et al[76]	2011	Japan	Cohort	Afebrile seizure	6	NA	Y	Y	N	Y	Higher quality
79	Higuchi[77]	2010	Japan	Case series	Worsening of seizures	2	2 (0)	N	Y	N	Y	Lower quality
81	Chinoy[78]	2017	Unknown	Case series	Hypocalcemia seizure	1	1 (0)	N	Y	N	Y	Lower quality
82	Paul et al[79]	2017	United Kingdom	Case report	Hyponatremic seizure	1	1	N	Y	N	Y	Lower quality
83	Chung et al[80]	2007	China	Cohort	Complex febrile seizures	22	NA	Y	Y	N	Y	Higher quality
84	Simpson et al[81]	1974	United Kingdom	Cross-sectional	Convulsions and apnea	1	1	Y	Y	N	Y	Higher quality
85	Lloreda-Garcia[82]	2013	Spain	Case report	Cerebritis, apnea, hypotonia	1	1 (0)	N	Y	N	Y	Lower quality
86	Claeys et al[83]	2011	Belgium	Case report	Hyponatremic seizures	1	1	N	Y	N	Y	Lower quality
87	Della Paolera et al[84]	2016	Italy	Case report	Leukoencephalopathy, hyponatremic seizures, apnea	1	1	N	Y	N	Y	Lower quality
88	Nozawa[85]	2019	Japan	Cross-sectional	Encephalopathy	1	NA	Y	Y	N	Y	Higher quality
89	Ben Jaballah et al[86]	1996	Tunisia	Cross-sectional	Hyponatremic seizure	1	1	Y	Y	N	Y	Higher quality
90	Duran Carvajal et al[87]	2012	Spain	Case report	Hyponatremic seizure, tone abnormality, apnea	1	1	N	Y	N	Y	Lower quality
91	Pop Jora et al[88]	2014	France	Case series	Hyponatremic seizure, apnea	3	3	N	Y	N	Y	Lower quality
92	Seto et al[89]	1994	Japan	Cross-sectional	Hyponatremic seizure, seizure, apnea	4	4	Y	Y	N	Y	Higher quality
93	Mayordomo-Colunga et al[90]	2008	Spain	Case series	Hemorrhagic shock and encephalopathy syndrome	1	1	N	Y	N	Y	Lower quality
94	Inoue et al[91]	2003	Japan	Case series	Afebrile seizure, status epilepticus	2	2	N	Y	N	Y	Lower quality
95	Kayfan et al[92]	2019	USA	Case report	Seizure, hypotonia	1	1 (0)	N	Y	N	Y	Lower quality
96	Ince et al[93]	2000	Turkey	Case series	HSES, seizures, hypotonia	1	1	N	Y	N	Y	Lower quality
97	Hoshino et al[94]	2012	Japan	Cross-sectional	Acute encephalopathy including AESD, MERS, HSES	17	NA	N	Y	N	Y	Lower quality
98	Fernandez-Menendez et al[95]	2014	Spain	Case series	Febrile status epilepticus	1	1 (0)	N	Y	N	Y	Lower quality
99	Gouyon et al[96]	1986	France	Cohort	Afebrile seizure, apnea	3	3	Y	Y	N	Y	Higher quality
100	Rivers et al[97]	1981	United Kingdom	Case series	Hyponatremic seizure, apnea	2	2	N	Y	N	Y	Lower quality

(*continued*)

Table I. Continued

ID*	Authors (citation) [ID†]	Year	Country	Design‡	Neurologic features and syndromes	Eligible§	Extract¶	Quality Assessment** 1	2	3	4	Grade
101	Yoon et al[98]	2008	Korea	Cohort	Febrile and afebrile seizure	6	6	Y	Y	N	Y	Higher quality
102	Moriyama et al[99]	2014	Japan	Case report	Limbic encephalitis, complex seizure	1	1	N	Y	N	Y	Lower quality
103	Van Steensel-Moll et al[100]	1989	The Netherlands	Cross-sectional	Hypoxic and hyponatremic convulsions	2	NA	U	Y	N	Y	Lower quality

AESD, acute encephalopathy with biphasic seizures and late reduced diffusion; *ANE*, acute necrotizing encephalopathy; *HSES*, hemorrhagic shock and encephalopathy syndrome; *MERS*, mild encephalopathy with a reversible splenial lesion; *N*, no, quality domain was not met; *NA*, no available extractable case data; *U*, unclear whether quality domain was met; *UD*, undetermined number of eligible cases, ie, unable to disaggregate eligible cases; *Y*, yes, quality domain was met.

*Article identifier.

†[ID†] denotes articles describing duplicate study or case data and corresponding article/s. Articles 27, 28, 29, 37, 38, 39 and 40 report overlapping studies.

‡For cross-sectional and cohort studies, study design was determined according to the STROBE definitions.

§Number of cases described in the article which met eligibility criteria. Where provided, numbers in parentheses indicate the remaining number of eligible cases once duplicate case reports were removed.

¶Number of cases extracted. Duplicate case reports were not extracted. Where provided, numbers in parentheses indicate the remaining number of cases eligible for inclusion in the quantitative case synthesis after additional exclusion criteria where applied.

**Articles were assessed across 4 domains (Selection, Ascertainment, Causality, Reporting) and were graded "higher quality" if 3 or more domains were met.

††Duplicate study removed or overlapping study collapsed for purposes of narrative synthesis.

Table IV. Quality assessment of included articles by study design

Quality measures	Case report (%) n = 42	Case series (%) n = 20	Cross-sectional (%) n = 19	Cohort (%) n = 19	Total (%) N = 100
Higher quality*	4 (10)	6 (30)	17 (90)	16 (84)	43 (43)
Lower quality	38 (91)	16 (80)	2 (11)	3 (16)	58 (58)
1. Selection Domain	0 (0)	0 (0)	16 (84)	16 (84)	32 (32)
2. Ascertainment Domain	42 (100)	20 (100)	19 (100)	19 (100)	100 (100)
3. Causality Domain	4 (10)	6 (30)	2 (11)	2 (11)	14 (14)
4. Reporting Domain	38 (91)	20 (100)	19 (100)	19 (100)	96 (96)

*Higher-quality articles met 3 or more quality domains.

Reference List of Included Articles

1. Abernethy S, Smith D, Hague R, Horrocks IA. Cortical blindness following paracetamol ingestion. Dev Med Child Neurol 2014;1:50.
2. Aizaki K, Tsuru T, Okumura K, Ikehara H, Hiramoto R. Group A coxsackie virus-associated encephalitis/encephalopathy: a retrospective hospital-based study in Japan. Dev Med Child Neurol 2012;4:15-6.
3. Al Shibli A, Abukhater D, Al Kuwaiti N, Noureddin MB, Al Harbi M, Al Kaabi A, et al. Hyponatraemia and neurological complications in children admitted with bronchiolitis. Paediatr Int Child Health 2016;36:175-80.
4. Al-Maskari N, Mohsin J, Al-Maani A, Al-Macki N, Al-Ismaili S. Atypical presentations of respiratory syncytial virus infection: case series. Sultan Qaboos University Medical Journal 2016;16:e86-91.
5. Albinski M, Gamperli L, Regamey N, Stettler J, Tomaske M. Hyponatraemia in paediatric bronchiolitis - a harmful complication not to be ignored. Klin Padiatr 2016;228:275-6.
6. Antonucci R, Chiappe S, Porcella A, Rosatelli D, Fanos V. Bronchiolitis-associated encephalopathy in critically-ill infants: an underestimated complication? Matern Fetal Neonatal Med 2010;23:431-6.
7. Arrowsmith WA, Smithells RW, Congdon PJ. Letter: temporary paralysis after infection by respiratory syncytial virus. Lancet 1975;1:743.
8. Bray K, Spaeder M. Analysis of diaphragmatic electrical activity may aid in diagnosis of infantile botulism. Crit Care Med 2016;44:524.
9. Brown WD, Caruso JM. Extrapontine myelinolysis with involvement of the hippocampus in three children with severe hypernatremia. J Child Neurol 1999;14:428-33.
10. Brunatti P, Giacchetti L, Pezzoli V, Kottanattu L, Ramelli GP. RSV associated acute encephalitis with basal ganglia involvement: a pediatric case report. Swiss Medical Weekly 2017;147:23S.
11. Carman KB, Calik M, Karal Y, Isikay S, Kocak O, Ozcelik A, et al. Viral etiological causes of febrile seizures for respiratory pathogens (EFES Study). Hum Vaccin Immunother 2019;15:496-502.
12. Cha T, Choi YJ, Oh JW, Kim CR, Park DW, Seol IJ, et al. Respiratory syncytial virus-associated seizures in Korean children, 2011-2016. Korean J Pediatr 2019;62:131-7.
13. Cheriathu J. Hyponatremic seizures and shock: an unusual presentation of respiratory syncitial virus infection. European J Pediatr 2016;175:1870-1.
14. Cheung KL, Hon KLE. Severe acute encephalitis in a tertiary PICU in Hong Kong. Crit Care Med 2016;44:211.
15. Erdogan S, Yakut K, Kalin S. Acute encephalitis and myocarditis associated with respiratory syncytial virus infections. Turk J Anaesthesiol Reanim 2019;47:348-51.
16. Fowler A, Stodberg T, Eriksson M, Wickstrom R. Childhood encephalitis in Sweden: etiology, clinical presentation and outcome. Eur J Paediatr Neurol 2008;12:484-90.
17. Francisco AMO, Arnon SS. Clinical mimics of infant botulism. Pediatrics 2007;119:826-8.
18. Fukasawa T, Kubota T, Negoro T, Saitoh M, Mizuguchi M, Ihara Y, et al. A case of recurrent encephalopathy with SCN2A missense mutation. Brain Dev 2015;37:631-4.
19. Hanna S, Tibby SM, Durward A, Murdoch IA. Incidence of hyponatraemia and hyponatraemic seizures in severe respiratory syncytial virus bronchiolitis. Acta Paediatr 2003;92:430-4.
20. Hinson D, Hinojosa M, Varney S, Schaeffer T. What could it be, honey? Think outside the (botulism) box. Clin Toxicol 2017;55:727.
21. Hirayama K, Sakazaki H, Murakami S, Yonezawa S, Fujimoto K, Seto T, et al. Sequential MRI, SPECT and PET in respiratory syncytial virus encephalitis. Pediatr Radiol 1999;29:282-6.
22. Hon KL, Tsang YC, Chan LC, Tsang HW, Wong KY, Wu YH, et al. Outcome of encephalitis in pediatric intensive care unit. Indian J Pediatr 2016;83:1098-103.
23. Jimenez-Legido M, Cantarin-Extremera V, Almodovar-Martin JL, Bernardino-Cuesta B. Neurological complications in cases of bronchiolitis due to respiratory syncytial virus: febrile status and other neurological manifestations. Revista De Neurologia 2019;68:489-91.
24. Kakimoto Y, Seto Y, Ochiai E, Satoh F, Osawa M. Cytokine elevation in sudden death with respiratory syncytial virus: a case report of 2 children. Pediatrics 2016;138:12.
25. Kawasaki Y, Suyama K, Go H, Hosoya M. Clinical manifestations of respiratory syncytial virus-associated encephalopathy in Fukushima, Japan. Pediatr Int 2019;61:802-6.
26. Kawashima H, Ioi H, Hasegawa Y, Yamanaka G, Takekuma K, Mori M, et al. Life-threatening extrapulmonary manifestations associated with respiratory syncytial virus infection in Japan. J Tokyo Med Univ 2008;66:549-52.
27. Kawashima H, Ioi H, Ushio M, Yamanaka G, Matsumoto S, Nakayama T. Cerebrospinal fluid analysis in children with seizures from respiratory syncytial virus infection. Scand J Infect Dis 2009;41:228-31.
28. Kawashima H, Kashiwagi Y, Ioi H, Morichi S, Oana S, Yamanaka G, et al. Production of chemokines in respiratory syncytial virus infection with central nervous system manifestations. J Infect Chemother 2012;18:827-31.
29. Kho N, Kerrigan JF, Tong T, Browne R, Knilans J. Respiratory syncytial virus infection and neurologic abnormalities: retrospective cohort study. J Child Neurol 2004;19:859-64.
30. Li G, Li S, Qi F, Mei G. Mild encephalitis/encephalopathy in children with a reversible splenial lesion. Radiol Infect Dis 2018;5:118-22.
31. Loh R, Grimwood K, Malone S. Paediatric febrile encephalopathy and encephalitis - experience in Brisbane, Australia. Dev Med Child Neurol 2012;4:22-3.
32. Lorenzo G, Patrizia B, Elisabetta F, Lisa K, Valdo P, Paolo RG. Respiratory syncytial virus associated acute encephalitis with basal ganglia involvement: a paediatric case report. Arch Dis Child 2017;102:A63.
33. Millichap JJ, Wainwright MS. Neurological complications of respiratory syncytial virus infection: case series and review of literature. J Child Neurol 2009;24:1499-503.
34. Miyamoto K, Fujisawa M, Hozumi H, Tsuboi T, Kuwashima S, Hirao J, et al. Systemic inflammatory response syndrome and prolonged hypoperfusion lesions in an infant with respiratory syncytial virus encephalopathy. J Infect Chemother 2013;19:978-82.
35. Mizuno Y. A three-year-old girl with acute encephalopathy with biphasic seizures associated with respiratory syncytial virus infection. Pediatr Crit Care Med 2011A121.
36. Morichi S, Kawashima H, Ioi H, Ushio M, Yamanaka G, Kashiwagi Y, et al. Cerebrospinal fluid NOx (nitrite/nitrate) in RSV-infected children with CNS symptoms. J Infect 2009;59:299-301.
37. Morichi S, Kawashima H, Ioi H, Yamanaka G, Kashiwagi Y, Hoshika A, et al. Classification of acute encephalopathy in respiratory syncytial virus infection. J Infect Chemother 2011;17:776-81.
38. Morichi S, Morishita N, Ishida Y, Oana S, Yamanaka G, Kashiwagi Y, et al. Examination of neurological prognostic markers in patients with respiratory syncytial virus-associated encephalopathy. Int J Neurosci 2017;127:44-50.
39. Morishima Y, Kawashima H, Yamanaka G, Oana S, Ioi H, Takekuma K, et al. A case of acute encephalopathy with biphasic seizures and late reduced diffusion on respiratory syncytial virus infection. J Tokyo Med Univ 2010;68:231-4.
40. Morton RE, Dinwiddie R, Marshall WC, Matthew DJ. Respiratory syncytial virus infection causing neurological disorder in neonates. Lancet 1981;1:1426-7.
41. Nakamura K, Kato M, Sasaki A, Shiihara T, Hayasaka K. Respiratory syncytial virus-associated encephalopathy complicated by congenital myopathy. Pediatr Int 2012;54:709-11.
42. Ng YT, Cox C, Atkins J, Butler IJ. Encephalopathy associated with respiratory syncytial virus bronchiolitis. J Child Neurol 2001;16:105-8.
43. Ong SCL, Nur Azidawati AH, Liew YH, Anita S. Acute necrotising encephalopathy of childhood: a review of two cases. Med J Malaysia 2017;72:311-3.
44. Otake Y, Yamagata T, Morimoto Y, Imi M, Mori M, Aihara T, et al. Elevated CSF IL-6 in a patient with respiratory syncytial virus encephalopathy. Brain Dev 2007;29:117-20.

45. Park A, Suh SI, Son GR, Lee YH, Seo HS, Eun BL, et al. Respiratory syncytial virus-related encephalitis: magnetic resonance imaging findings with diffusion-weighted study. Neuroradiology 2014;56:163-8.
46. Piastra M, Caresta E, Tempera A, Langer A, Zorzi G, Pulitano S, et al. Sharing features of uncommon respiratory syncytial virus complications in infants. Pediatr Emerg Care 2006;22:574-8.
47. Picone S, Mondi V, Di Palma F, Martini L, Paolillo P. Neonatal Encephalopathy and SIADH during RSV Infection. Am J Perinatol 2019;36: S106-9.
48. Quinn KK, Cherry JD, Shah NR, Christie LJ. A 3-month-old boy with concomitant respiratory syncytial virus bronchiolitis and infant botulism. Pediatr Neurol 2013;32:195.
49. Rantala H, Uhari M, Tuokko H. Viral infections and recurrences of febrile convulsions. J Pediatr 1990;116:195-9.
50. Sakai E, Yamanaka G, Kawashima H, Morishima Y, Ishida Y, Oana S, et al. A case of recurrent acute encephalopathy with febrile convulsive status epilepticus with carnitine palmitoyltransferase II variation. Neuropediatrics 2013;44:218-21.
51. Sato A, Mizuguchi M, Mimaki M, Takahashi K, Jimi H, Oka A, et al. Cortical gray matter lesions in acute encephalopathy with febrile convulsive status epilepticus. Brain & Development 2009;31:622-4.
52. Savic N, Jankovic B, Minic P, Vasiljevic Z, Sovtic A, Pejic K, et al. Clinical characteristics of respiratory syncytial virus infection in neonates and young infants. Vojnosanit Pregl 2011;68:220-4.
53. Shirota G, Morozumi M, Ubukata K, Shiro H. [Infantile meningitis caused by respiratory syncytial virus]. Kansenshogaku Zasshi 2011;85: 682-5 [in Japanese].
54. Srivastava R, Yaworski A, Jain S, Goez H, Kassiri J, Richer L. Episodic ataxia and encephalitis: A novel presentation of RESLES in a 3-year-old girl. Can J Neurol Sci 2018;45:S50.
55. Sweetman LL, Ng YT, Butler IJ, Bodensteiner JB. Neurologic complications associated with respiratory syncytial virus. Pediatr Neurol 2005;32:307-10.
56. Tang Y, Suddarth B, Du X, Matsumoto JA. Reversible diffusion restriction of the middle cerebellar peduncles and dentate nucleus in acute respiratory syncytial virus cerebellitis: a case report. Emerg Radiol 2014;21:89-92.
57. Tison-Chambellan C, Cheuret E, Cances C, Karsenty C, Le Camus C, Sevely A, et al. Respiratory syncytial virus brainstem encephalitis in a 7-year-old boy. Arch Pediatr 2013;20:657-60 [in French].
58. Uda K, Kitazawa K. Febrile status epilepticus due to respiratory syncytial virus infection. Pediatr Int 2017;59:878-84.
59. Watabe S. Examination of clinical characteristics of severe RSV infection. Paediatr Respir Rev 2010;1:S86.
60. Watabe S. Examination of respiratory syncytial virus (RSV) infection in the western part of Okayama prefecture in Japan. Paediatr Respir Rev 2011;12:S87.
61. Watabe S. Examination of risk factors for severe RS virus infection in intensive care unit. Eur J Pediatr 2016;175:1786.
62. Xu L, Gao H, Zeng J, Liu J, Lu C, Guan X, et al. A fatal case associated with respiratory syncytial virus infection in a young child. BMC Infect Dis 2018;18:217.
63. Zlateva KT, Van Ranst M. Detection of subgroup B respiratory syncytial virus in the cerebrospinal fluid of a patient with respiratory syncytial virus pneumonia. Pediatr Infect Dis J 2004;23:1065-6.
64. Babiker A, Lakshmanan A, Ramaswami U. Hereditary fructose intolerance e an unusual neurological presentation. Paediatr Child Health 2010;20:257-8.
65. Feria J, Kavanagh R. Congenital myasthenic syndrome as a cause for extubation failure in a child with rsv bronchiolitis. Crit Care Med 2018;46: 387.
66. Gallagher RC, Halbower AC, Baker CD, Thomas JA, Saenz M, Goodman SI, et al. NKX2.1 haploinsufficiency: a novel etiology of 3-methylglutaconic aciduria associated with chorea. Med J Malaysia 2009;98:99-100.
67. Healy L, Forbes E, Rice J, Leonard J, Crushell E. Reye-like syndrome and severe carnitine deficiency in a boy with autism spectrum disorder and restricted diet. Arch Dis Child 2019;104:A187.
68. Kumar A, Asghar S, Kavanagh R, Wicklund M. A unique presentation of rapidly fluctuating symptoms in a child diagnosed with congenital myasthenic syndrome due to RAPSN mutation. Neurology Conference: 70th Annual Meeting of the American Academy of Neurology, AAN90.
69. Kumar A, Asghar S, Kavanagh R, Wicklund MP. Unique presentation of rapidly fluctuating symptoms in a child with congenital myasthenic syndrome due to RAPSN mutation. Muscle Nerve 2018;58:E23-4.
70. Schmitt-Mechelke T. Neonatal star gazing: tonic upward gaze as a manifestation of atypical non-ketotic hyperglycinemia. Neuropediatrics Conference: 38th Annual Meeting of the Society of Neuropediatrics Munster Germany Conference Publication43.
71. Wong AM, Lin JJ, Toh CH, Bilaniuk LT, Zimmerman RA, Chang YC, et al. Childhood encephalitis: relationship between diffusion abnormalities and clinical outcome. Neuroradiology 2015;57:55-62.
72. Miranda SP, Kimmell KT, Silberstein HJ. Acute presentation of Chiari I malformation with hemiparesis in a pediatric patient. World Neurosurg 2016;85:366.e1-4.
73. Erez DL, Yarden-Bilavsky H, Mendelson E, Yuhas Y, Ashkenazi S, Nahum E, et al. Apnea induced by respiratory syncytial virus infection is not associated with viral invasion of the central nervous system. Pediatr Infect Dis J 2014;33:880-1.
74. Griffin N, Keeling JW, Tomlinson AH. Reye's syndrome associated with respiratory syncytial virus infection. Arch Dis Child 1979;54:74-6.
75. Maitre A, Maw A, Ramaswami U, Morley SL. Relapsing acute axonal neuropathy in hereditary fructose intolerance. Pediatr Neurol 2016;64:92-3.
76. Miyama S, Goto T. Afebrile seizures associated with respiratory syncytial virus infection: a situation-related seizure disorder in early infancy. Pediatr Int 2011;53:113-5.
77. Higuchi T, Fukuyama T, Motobayashi M, Misawa Y, Arai F, Inaba Y. Two cases of symptomatic West syndrome suffering from severe respiratory syncytial virus-induced bronchiolitis. No to Hattatsu 2010;42: 458-62 [in Japanese].
78. Chinoy A, Skae M, Babiker A, Kendall D, Mughal MZ, Padidela R. Impact of intercurrent illness on calcium homeostasis in children with hypoparathyroidism: a case series. Endocrine Connections 2017;6:589-94.
79. Paul SP, Hicks SS, Sanjeevaiah MK, Heaton PA. Where did the salt go? Turk J Pediatr 2017;59:345-8.
80. Chung B, Wong V. Relationship between five common viruses and febrile seizure in children. Arch Dis Child 2007;92:589-93.
81. Simpson H, Matthew DJ, Habel AH, George EL. Acute respiratory failure in bronchiolitis and pneumonia in infancy. Modes of presentation and treatment. Br Med J 1974;2:632-6.
82. Lloreda-Garcia JM, Martinez-Ferrandez C, Gil-Sanchez S, Susmozas-Sanchez J. Cerebritis and cerebral abscess due to Streptococcus pneumoniae in a newborn. Rev Neurol 2013;56:543-4 [in Spanish].
83. Claeys T, Van De Voorde P, Willems J, Oosterlynck L. Convulsions in a 6-week-old boy with RSV bronchiolitis: don't forget the salt!. Tijdschrift voor Geneeskunde 2011;67:1041-4 [in Dutch].
84. Della Paolera S, Soffritti S, Sandri F. The syndrome of inappropriate antidiuretic hormone (ADH) secretion in bronchiolitis. Medico e Bambino 2016;35:463-4 [in Italian].
85. Nozawa M, Terashima H, Tsuji S, Kubota M. A simplified electroencephalogram monitoring system in the emergency room. Pediatr Emerg Care 2019;35:487-92.
86. Ben Jaballah N, Mnif K, Hedfi L, Hammami A, Khaldi F, Bennaceur B. Clinical, therapeutic and developmental aspects of acute bronchiolitis in Tunisia. Cah Anesthesiol 1996;44:423-8 [in French].
87. Duran Carvajal J, Pena Zarza JA, Figuerola Mulet J. Bronchiolitis and convulsions: not always due to apnoeas. An Pediatr (Barc) 2012;77: 284-6 [in Spanish].
88. Pop Jora D, de Suremain N, Arnaud C, Greteau S, Guellec I, Renolleau S, et al. VRS bronchiolitis with severe hyponatremia leading to acute seizures: a report of three cases. Arch Pediatr 2014;21:1359-63 [in French].
89. Seto M, Shiomi M, Togawa M, Lee SS, Yabiku M, Sugita T. [Thirty seven cases of respiratory syncytial virus infection hospitalised and 7

severe cases with apneic attacks. Kansenshogaku Zasshi 1994;68:226-33 [in Japanese].
90. Mayordomo-Colunga J, Concha Torre A, Menendez Cuervo S, Rey Galan C. Haemorrhagic shock syndrome and encephalopathy (I). An Pediatr (Barc) 2008;69:489-91 [in Spanish].
91. Inoue S, Nakazawa T, Kantake M, Kaneko K, Shimojima T. Early infantile patients of RS viral bronchiolitis with afebrile convulsions. No to Hattatsu 2003;35:347-9 [in Japanese].
92. Kayfan S, Yazdani RM, Castillo S, Wong K, Miller JH, Pfeifer CM. MRI findings of hypomyelination in adenylosuccinate lyase deficiency. Radiol Case Rep 2019;14:255-9.
93. Ince E, Kuloglu Z, Akinci Z. Hemorrhagic shock and encephalopathy syndrome: neurologic features. Pediatr Emerg Care 2000;16:260-4.
94. Hoshino A, Saitoh M, Oka A, Okumura A, Kubota M, Saito Y, et al. Epidemiology of acute encephalopathy in Japan, with emphasis on the association of viruses and syndromes. Brain Dev 2012;34:337-43.
95. Fernandez-Menendez A, Buenache-Espartosa R, Coca-Perez A, Morillo-Carnero P, Martinez-San Millan J, Lorenzo-Sanz G. Refractory status epilepticus presenting as shaken baby syndrome. Rev Neurol 2014;58:548-52 [in Spanish].
96. Gouyon JB, Fantino M, Couillault G, Durand C, Pothier P, Alison M. Respiratory syncytial virus infections in newborn infants. Arch Fr Pediatr 1986;43:93-7 [in French].
97. Rivers RP, Forsling ML, Olver RP. Inappropriate secretion of antidiuretic hormone in infants with respiratory infections. Arch Dis Child 1981;56:358-63.
98. Yoon SW, Kim HJ, Yum MK, Seol IJ. Neurologic complications associated with respiratory syncytial virus infection in childhood. J Pediatr New Econ 2008;16:206-12.
99. Moriyama K, Takahashi Y, Shiihara T. Another case of respiratory syncytial virus-related limbic encephalitis. Neuroradiology 2014;56:435-6.
100. Van Steensel-Moll HA, Van der Voort E, Bos AP, Rothbarth PH, Neijens HJ. Respiratory syncytial virus infections in children admitted to the intensive care unit. Pediatrie 1989;44:583-8.