Effects of the COVID-19 Pandemic on Brief Resolved Unexplained Events (BRUEs) in Children: A Comparative Analysis of Pre-Pandemic and Pandemic Periods

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Article

Effects of the COVID-19 Pandemic on Brief Resolved Unexplained Events (BRUEs) in Children: A Comparative Analysis of Pre-Pandemic and Pandemic Periods

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Abstract: Background: Brief Resolved Unexplained Events (BRUEs), formerly known as Apparent Life-Threatening Events (ALTE), are concerning episodes of short duration (typically < 1 min) characterized by a change in breathing, consciousness, muscle tone, and/or skin color. In some cases, SARS-CoV-2 infection has been associated with episodes of BRUEs in previously healthy children.This study aimed to compare the demographic, respiratory, perinatal, and infectious characteristics in children affected by BRUE before the COVID-19 pandemic and after the spread of SARS-CoV-2. Methods: We conducted a retrospective observational study covering January 2018 to March 2020 (pre-COVID-19) and April 2023 (during the ongoing COVID-19 pandemic). Collected variables included clinical information during pregnancy and neonatal details of children with BRUE. Results: The number of children in the pre-COVID-19 period was 186 (41%); after the emergence and spread of SARS-CoV-2, it was 268 (59%). The risk of infection at birth for children developing BRUE was higher during the pandemic. Children were less likely to have ongoing symptomatic infection during BRUE during the pandemic (coefficient B = 0.783; p=0.009). Respiratory symptoms during BRUE were more frequent during the pandemic (coefficient B = 0.654; p=0.052). Fever during BRUE was less likely during the pandemic (coefficient B = -0.465, p=0.046). Conclusions: The study suggests that the COVID-19 pandemic has significantly impacted children with BRUE, potentially due to changes in hygiene practices and maternal-fetal infections.

Keywords: apparent life-threatening events; brief resolved unexplained event; COVID-19; infant; newborn; polysomnography; pregnancy; SARS-CoV-2

1. Introduction

Brief Resolved Unexplained Events (BRUEs), formerly known as Apparent Life-Threatening Events (ALTE), are concerning episodes of short duration (typically < 1 min) characterized by a change in breathing, consciousness, muscle tone (hyper- or hypotonia), and/or skin colour (cyanosis or pallor) [1,2]. The American Academy of Pediatrics (AAP) introduced the term BRUE to describe episodes in which a child exhibits one or more of the following symptoms: apnea (breathlessness), cyanosis (change in skin colour to blue or purple), alteration of muscle tone, or alteration in response to the environment [3]. Italian guidelines distinguish between BRUE and ALTE, reserving the latter for severe cases [4].

The incidence of BRUE varies in the literature. Prospective studies indicate an incidence ranging from 0.58 to 2.46 per 1000 live births [4]. The most common diagnosis (63%) was no diagnosis. Of the

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37% who were discharged with a diagnosis, the most commonly made diagnoses were gastroesophageal reflux and choking/gagging. Only 4.1% of the diagnoses were classified as severe [2,5].

Identifying the causes of BRUEs is a challenge. About 39.1% of BRUEs have been attributed to lower respiratory tract infections [6]. Other associated causes include respiratory tract anomalies [5]. For infants who have experienced a BRUE, respiratory infection may be considered if there is a fever or persistent respiratory symptoms [4,7].

Viruses most frequently implicated in BRUEs are respiratory syncytial virus (RSV), influenza viruses, and parainfluenza viruses [4,8]. In some BRUE cases, an infection with the HCoV-229E coronavirus may be an underlying cause [9]. Clinical cases have been reported, including a previously healthy infant infected with the SARS-CoV-2 virus at 8 months of age, developing recurrent episodes of BRUE [10], and another previously healthy infant experiencing a severe episode of BRUE [11]. A case has been described of a healthy 2-week-old newborn with apnea and coinfection with SARS-CoV-2 and influenza B [12].

This study aims to compare the demographic, respiratory, perinatal, and infectious characteristics of children affected by BRUE before the SARS-CoV-2 pandemic and after the onset and spread of the virus. The primary objective is to contribute to identifying any impacts that occurred after the emergence of SARS-CoV-2 and assess whether there have been variations in the manifestation of such events with the spread of the virus.

2. Materials and Methods

We conducted a retrospective observational study at the University of Insubria Pediatric Clinic in Italy. The Institutional Ethics Committee of the University of Insubria approved the research protocol with approval number 110/2017, focusing on hospitalization for BRUE events. The period under consideration ranges from January 2018 to March 2020 (pre-COVID-19) and extends from April 2020 to April 2023, considering the onset and spread of SARS-CoV-2.

Study population

We reviewed the medical records of newborns admitted to our hospital for BRUE events. Inclusion criteria were children aged between 1 month and 2 years. We applied the Italian guidelines for diagnosing BRUE [4].

Data extraction from medical records

Data extraction from medical records included information related to the newborn [Birth weight, Age, Gender, date of BRUE event], variables related to pregnancy [infection during pregnancy, SARS-CoV-2 infections during pregnancy, other infections during pregnancy, infectious risk at birth], variables associated with symptoms and contagious agents [respiratory symptoms, fever, identified infectious agent: SARS-CoV-2, RSV, rhinovirus, SBEB], variables related to monitoring parameters (AHI, minimum SpO_2, average SpO_2), and variables related to clinical signs [abnormal breathing, desaturations, short apneas, prolonged apneas (>15 seconds), and periodic breathing].

Nap Polysomnography

Upon arrival, newborns underwent a polysomnography (PSG) during their naps. PSG was conducted using a Compumedics P/L E-series instrument based in Melbourne, Australia. The device recorded nasal flow pressure (measured via nasal cannulas), nasal flow (via a thermistor), thoracic and abdominal movement (using Compumedics P/L inductive bands), oxygen saturation (SpO_2) at a sampling rate of 1 sample per second, and electrocardiogram (ECG) with a sampling rate set at 500 Hz. Sleep staging was based on electroencephalogram (EEG) data. The sleep device included video and audio recordings and a position sensor. Nap PSG was conducted between two feeding sessions, starting no sooner than 30 minutes after the last meal [13]. The infant lay on their back in their bed. If the recording was less than 2 hours, the study continued until the next feeding session. Upon

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discharge, newborns were equipped with home monitoring of apnea events using a portable recording device (VitaGuard® V 3100, Getemed Medizin, Teltow, Germany).

Statistical analysis

We performed statistical analysis using SPSS Statistics 22.0® software (SPSS Inc., Chicago, IL, USA) for Windows (Microsoft Corp., Redmond, WA, USA). Measures included the Total Number of Cases, Mann-Whitney U, Wilcoxon W, Test Statistic, Standard Error, Standardized Test Statistic, and Asymptotic Significance of the two-way test. Compared categorical variables are expressed in terms of percentage frequencies. The Chi-square test (Pearson) assesses the association between variables, with corresponding asymptotic significance (two-sided). Binary logistic regression was used to examine the contribution of independent variables in predicting the presence or absence of a specific event or outcome. The statistical significance level was set at $P<0.05$.

3. Results

In total, the enrolled children were 454 (53.7% males). The number of children in the pre-SARS-CoV-2 period was 186 (41%); after the emergence and spread of SARS-CoV-2, they were 268 (59%).

The results presented in Table 1 represent differences in the measured variables between the children affected by BRUE during the pre-SARS-CoV-2 period and the group after the onset and spread of SARS-CoV-2. Birth weight showed an average of 3094 ± 609 grams. In the group of children who developed BRUE after the beginning of SARS-CoV-2, the mean was 3072 ± 643 grams. The two-way test did not reveal significant differences between the groups ($p = 0.588$). In the pre-SARS-CoV-2 group, the mean age was 101 days ± 101 days. In the group of children who developed BRUE after the onset of SARS-CoV-2, the mean age decreased to 98.5 ± 84.3 days. The two-way test did not detect significant differences between the groups ($p = 0.764$). In the pre-SARS-CoV-2 group, the average monitoring duration was 124 hours ± 148 hours. In the group of children who developed BRUE after the onset of SARS-CoV-2, the average time was 106 ± 100 hours. The two-way test did not find significant differences between the groups ($p = 0.128$).

Table 1. Comparative overview of continuous variables between the pre-COVID-19 period and the onset of the SARS-CoV-2 pandemic. The table displays each variable's mean and standard deviation (S.D.), including the total number of patients, birth weight, age at the BRUE event, and the duration of home monitoring. Additionally, it provides the asymptotic significance value for a two-way test.

Continuous Variable	Mean ± S.D.	Mean S.E.	Mean ± S.D.	Mean S.E.	Sign. Asymptotic
	pre-COVID-19		Start-SARS-COV-2		
Total number of patients (% males)	186 (51.6)		268 (42.5)	-	0.056
Birth weight (grams)	3,094 ±609	44.6	3072 ±643	39.3	0.588
Age (days) at the event BRUE	101.3 ±100.6	7.4	98.5 ±84.3	5.2	0.764
Duration of home monitoring (days)	123.6 ± 148.0	10.9	105.9 ± 99.6	6.1	0.128

Legend: S.E., standard error.

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Table 2. Overview of dichotomous variables related to infections and respiratory conditions during pregnancy and BRUE events. The table displays the number of cases and the percentage for each variable, including specific diseases, respiratory symptoms, detection of particular viruses, and the outcome of home monitoring.

Dichotomous variable	No. of cases (%)
Infections in pregnancy	30 (6.6)
CMV Infection in Pregnancy	0
SARS-CoV-2 infection in pregnancy	17 (3.7)
Infectious risk at birth	61 (13.4)
Ongoing symptomatic infection of BRUE	344 (75.8)
Ongoing respiratory symptoms of BRUE	53 (11.7)
COVID detected in BRUE	2 (0.4)
RSV Detected in BRUE	3 (0.7)
Rhinovirus detected in BRUE	4 (0.9)
SBEB * detected in BRUE	2 (0.4)
Ongoing fever of BRUE	135 (29.7)
Pathologic breathing in the course of BRUE	336 (74)
Periodic breathing in the course of BRUE	146 (32.2)
Desaturations detected with GATEMED (yes)	249 (54.8)
Short apnea (yes)	347 (76.4)
Long apnea (yes)	2 (0.4)
O_2 therapy (yes)	52 (11.5)

* Group B Beta Hemolytic Streptococcus.

Breafly, out of 170 cases, 60% exhibited ongoing respiratory symptoms, 62% displayed pathologic breathing, and 62% experienced desaturations. Additionally, 21% cases involved COVID detection, 21% involved RSV detection, and 1% involved long apnea.

Table 3 presents the results of the binary logistic regression, where the dependent categorical variable corresponds to the two periods: the pre-COVID-19 period and the period of emergence and spread of SARS-CoV-2. Mothers of children with BRUE have shown a lower risk of infection during pregnancy in the period of SARS-CoV-2 spread (coefficient B -1.839; P=0.001). The infectious risk at birth of children who will develop BRUE is higher in the period of SARS-CoV-2 spread (coefficient B = 0.783; p=0.009). Asymptomatic infection during BRUE was less likely during the SARS-CoV-2 spread (coefficient B = -0.413; p=0.092). Respiratory symptoms during BRUE were more frequent during the SARS-CoV-2 spread (coefficient B = 0.654; p=0.052). Fever during BRUE was less likely during the SARS-CoV-2 spread (coefficient B = -0.465, p=0.046). In particular, there is a 37.2% decrease in fever during the SARS-CoV-2 spread, keeping all other variables constant. Finally, the average minimum SpO_2 was less severe or higher during the SARS-CoV-2 spread (coefficient B = 0.055, p<0.001). In addition, Table 3 presents the binary logistic regression results, where the dependent categorical variable corresponds to symptomatic infection, respiratory symptoms, or fever in the child with BRUE. In particular, the probability of symptomatic disease during the spread of SARS-CoV-2 is about 37.1% less compared to the pre-COVID-19 period (p=0.048), the possibilities of respiratory symptoms during the spread of SARS-CoV-2 are about 82.4% more compared to the pre-COVID-19 period (p=0.070), and the probabilities of fever during the spread of SARS-CoV-2 are about 39.6% less compared to the pre-COVID-19 period (p=0.034)

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Table 3. Comparative overview of continuous variables between the pre-COVID-19 period and the onset of the SARS-CoV-2 pandemic. The table displays each variable's mean and standard deviation (S.D.), including the total number of patients, birth weight, age at the BRUE event, and the duration of home monitoring. Additionally, it provides the asymptotic significance value for a two-way test.

Binary logistic regression	B	S.E.	Wald	P	Exp(B)	95% C.I.per EXP(B)
Dependent variable (pre-COVID-19=0, SARS-CoV-2 pandemic =1) *						
Infection in pregnancy	-1.839	0.551	11.157	0.001	0.159	0.054 - 0.468
Infectious risk at birth #	0.783	0.302	6.747	0.009	2.189	1.212 - 3.954
Ongoing symptomatic infection of BRUE	-0.413	0.245	2.847	0.092	0.662	0.409 - 1.069
Ongoing respiratory symptoms of BRUE	0.654	0.336	3.789	0.052	1.922	0.996 - 3.712
Ongoing fever of BRUE	-0.465	0.232	4.000	0.046	0.628	0.398 - 0.991
SpO_2 min (%)	0.055	0.015	13.467	<0.001	1.057	1.026 - 1.089
Dependent variable (Symptomatic infection in the course of BRUE, 1=si) **						
Pre-COVID-19=0, spread of SARS-CoV-2 =1	-0.464	0.234	3.926	0.048	0.629	0.397 - 0.995
Infection in pregnancy	1.646	0.406	16.431	0.000	5.184	2.339 - 11.487
Age (days)	-0.004	0.001	8.414	0.004	0.996	0.994 - 0.999
AHI (events/hour)	-0.019	0.008	5.339	0.021	0.981	0.965 - 0.997
Dependent variable (Respiratory symptoms during BRUE, 1=yes **						
Pre-COVID-19=0, spread of SARS-CoV-2 =1	0.601	0.332	3.273	0.070	1.824	0.951 - 3.498
Infection in pregnancy	-1.213	0.500	5.900	0.015	0.297	0.112 - 0.791
Age (days)	0.009	0.002	30.256	0.000	1.009	1.006 - 1.012
SpO_2 min (%)	-0.033	0.017	3.774	0.052	0.967	0.935 - 1.000
Dependent variable (Fever in the course of BRUE, 1=yes) **						
Pre-COVID-19=0, spread of SARS-CoV-2 =1	-0.504	0.238	4.487	0.034	0.604	0.379 - 0.963
Age (days)	0.010	0.002	47.178	0.000	1.010	1.007 - 1.013
SpO_2 min (%)	-0.030	0.015	4.146	0.042	0.971	0.943 - 0.999

Positive vaginal swab for GBS, PROM > 18h, maternal fever in labour, foul-smelling stained amniotic fluid. * Variables entered in phase 1: birth weight (grams); infections during pregnancy (yes=1, dichotomous variable); infectious risk at birth (yes=1, dichotomous variable), symptomatic infection (yes=1, dichotomous variable), respiratory symptoms at the event (yes=1, dichotomous variable); fever at the event (yes=1, dichotomous variable); pathological breathing (yes=1, dichotomous variable); AHI (events/h., continuous variable); minimum SpO_2 (%, continuous variable); average SpO_2 (%, continuous variable). ** Variables entered in phase 1: birth weight (grams), Age (days, continuous variable), infection during pregnancy (1=yes, dichotomous variable), infectious risk at birth AHI (events/hour, continuous variable), minimum SpO_2 (%, continuous variable); average SpO_2 (%, continuous variable).

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4. Discussion

This study conducted an in-depth examination of cases of children hospitalized following an episode of BRUE, comparing the period before the arrival of COVID-19 with that following the spread of SARS-CoV-2. These results could have important implications for understanding the impact of the COVID-19 pandemic on maternal and child health and the clinical management of BRUE. The fact that mothers of children with BRUE have shown a lower risk of infection during pregnancy during the period of SARS-CoV-2 spread could suggest that the protective measures adopted during the pandemic (such as social distancing, the use of masks and hand hygiene) may have reduced the risk of exposure to pathogens.

Before exploring the implications of SARS-CoV-2 infection during pregnancy, it is essential to consider the overall picture. In most cases, women who received a diagnosis of SARS-COV-2 during pregnancy had favourable pregnancy outcomes [14]. This could be partly due to the protective measures adopted during the pandemic, which reduced exposure to pathogens and the risk of infection during pregnancy.

Even though most pregnancies in women diagnosed with SARS-COV-2 have favourable outcomes, exposure to SARS-CoV-2 during pregnancy could pose a higher risk of mortality, spontaneous abortion, preterm birth and low birth weight [15], pneumonia and thromboembolic disease [16], and admission to intensive care [17,18]. These factors could affect the health of newborns and potentially increase the risk of BRUE.

Maternal infection with SARS-CoV-2 induces a fetal immune response even without placental infection or symptoms in the newborn [19,20]. The SARS-CoV-2 virus seems to primarily infect syncytiotrophoblast cells and other cells of the maternal-fetal interface. Fetuses or newborns with SARS-CoV-2 infection may present involvement of various organs 2021 [20]. It is unknown whether SARS-COV-2 infection during pregnancy is directly related to an increased risk of BRUE. Therefore, it is crucial to consider that conditions associated with the infection could theoretically contribute to respiratory problems or other disorders in neonatal health, potentially raising the risk of BRUE.

In this context, it is essential to underline that viral infections and pertussis are among the possible etiological causes of BRUE [21]. In parallel, univariate BRUE predictors include prematurity, resuscitation attempt, apnea, cyanosis, and upper respiratory tract infection [22]. This intricate network of factors requires an in-depth analysis to fully understand the causal relationships and impacts on neonatal health.

The higher risk of infection at birth for children who will develop BRUE during the period of SARS-CoV-2 spread could indicate an increase in exposure to pathogens in the perinatal period, possibly due to variations in hospital practices and increased newborn exposure. The fact that a symptomatic infection during an episode of BRUE was less likely during the period of SARS-CoV-2 spread could reflect a change in the causes of BRUE or diagnostic practices. This is consistent with significant variations in common respiratory and bacterial diseases globally caused by the SARS-CoV-2 pandemic [23].

Lockdown measures and social distancing have influenced the incidence of diseases [24], slowing down the circulation of pathogens and the development of immunity in the population. This could have contributed to the lower likelihood of fever during a BRUE episode, reflecting a change in the causes of BRUE or children's immune responses. Infections from respiratory viruses, such as influenza and respiratory syncytial virus, have decreased significantly at the beginning of the pandemic and have continued to vary during the successive waves of SARS-CoV-2 infections [25]. This could have influenced the average minimum SpO_2, which was less severe or higher, during the SARS-CoV-2 spread, indicating a general improvement in the therapeutic management of pathogens in patients with BRUE.

A study highlighted that respiratory tract infection symptoms were more frequent in the group with BRUE recurrences than in the group without repetitions (44% vs. 14%, $p = 0.005$). The multivariate analysis confirmed that respiratory tract infection symptoms represent independent risk factors for the recurrence of BRUE (OR, 5.02; 95% CI, 1.48-16.98) [26]. From the same perspective, the most commonly encountered symptoms during BRUE episodes include apnea (73.3%), cyanosis

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(60.0%) and cough (20.0%). These data further underline the complexity of the interactions that influence the susceptibility and recurrence of BRUE, requiring a comprehensive evaluation of the multiple factors involved [27]. In the group with recurrence of BRUE, respiratory tract infection symptoms were more frequent than in the group without repetition (44% vs. 14%, p = 0.0055). Respiratory tract infection symptoms were an independent risk factor for the recurrence of BRUE, with an odds ratio (OR) of 5.02 [26]. The results of our study indicate an O.R. value of 1.922 (C.I. 95% 0.996 - 3.712; p=0.052) for respiratory symptoms at the diagnosis of BRUE.

However, a statistically borderline difference (p=0.052) emerged in respiratory symptoms between the pre-COVID period and after the emergence and spread of SARS-COV-2. In particular, during the SARS-CoV-2 pandemic, there was an increased risk of presenting respiratory symptoms during a BRUE episode. On the contrary, a statistically significant difference was observed between the two periods for the presence of fever at the time of diagnosis. In particular, during the period of SARS-CoV-2 spread, there was a reduction in the likelihood of the risk of presenting rage during a BRUE episode (p=0.046).

These data further support the correlation between infections, particularly of the upper respiratory tract, and the onset of BRUE events [28], confirming the importance of considering respiratory diseases as a significant risk factor for BRUE in infants. In particular, 44.8% of infants had a cause of BRUE associated with respiratory diseases, confirming a substantial link between respiratory infections and BRUE [29]. According to one study, most infants with SARS-CoV-2 infection were asymptomatic or had mild symptoms, were generally left to breathe spontaneously, and had a good prognosis [30]. These results underline the need for a thorough clinical evaluation, as respiratory diseases have emerged as a significant risk factor for BRUE in infants, paving the way for careful consideration of the implications of potential hypoxia related to these conditions.

Infected infants, even if asymptomatic or with mild symptoms, may maintain variable levels of hypoxia before manifesting evident symptoms. Infants may act as silent carriers of the virus, and chronic airway inflammation could contribute to the remodelling and thickening of the same [31]. Our study shows a statistically significant difference in the minimum SpO_2 (%) in children with BRUE between the pre-COVID-19 period and the one following the emergence and spread of SARS-COV-2. In particular, the increase in the average minimum SpO_2 (%) seems to correlate with a higher likelihood of belonging to the period after the spread of SARS-CoV-2.

This data integrates with the variation in the incidence of apneas in infants with RSV infection, which can vary significantly, ranging between 10% and 26% [32]. Although viral infection is not commonly associated with BRUE, thorough microbiological investigations could clarify the aetiology of such events, even without manifest signs of respiratory disease, thus contributing to the overall understanding of the underlying factors [9,33]. In addition, factors such as symptoms of respiratory infection increase the likelihood of BRUE [28].

Our study has some limitations. First, the sample size is small and does not represent the general population. Second, the study did not consider other factors that could influence the results, such as the severity of SARS-CoV-2 infection or the patient's underlying health conditions. Further research is needed to confirm this study's findings and understand the mechanisms underlying these results. In particular, studies with larger samples and more representative of the general population are needed. In addition, studies are required to examine the association between the variables studied and other clinical outcomes, such as the disease duration, the need for hospitalization, or mortality.

Finally, our study revealed significant differences between children who experienced BRUE before and after the emergence of SARS-CoV-2. These results indicate that various factors can influence the likelihood that a child is affected by the SARS-CoV-2 pandemic compared to the pre-COVID-19 period. Improved personal hygiene during the spread of SARS-CoV-2 has significantly impacted the dynamics of other common respiratory microorganisms, highlighting the importance of hygiene management in preventing respiratory infections [34].

5. Conclusions

Our study has highlighted significant changes in children's experiences with BRUE episodes following the emergence of SARS-CoV-2. The lower incidence of maternal-fetal infections suggests the effectiveness of preventive measures, but the increased neonatal risk may reflect variations in hospital practices. The reduced likelihood of symptomatic disease during BRUE indicates possible changes in the causes or diagnostic procedures, while the decrease in fever suggests influences on the immune response. The increase in oxygenation could mean improvements in therapeutic management, but the increase in respiratory symptoms could be associated with the spread of SARS-CoV-2, requiring further investigations. The reduction of fever in the period of SARS-CoV-2 could be due to the effect of preventive measures. Finally, the complex dynamics related to the pandemic, such as the increase in oxygen saturation and symptomatic variations, underline the importance of personal hygiene in managing respiratory infections in children with BRUE.

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