Childhood Separation Anxiety Disorder and Panic Disorder:

Differences Between Respiratory and Nonrespiratory Subtypes

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Abstract

Objective: The association between childhood separation anxiety disorder (CSAD) and panic disorder (PD) has been demonstrated, although some findings are contradictory. The separation anxiety hypothesis postulates that both CSAD and PD encompass a heightened sensitivity to carbon dioxide (CO_2). Patients with the respiratory subtype (RS) of PD are known to be more sensitive to CO_2 than those from the nonrespiratory subtype (NRS). Therefore, the primary objective centered on the comparative analysis of CSAD prevalence between RS and NRS groups, with secondary objectives focusing on the comparative assessment of RS and NRS groups and the control group.

Methods: Sixty RS-PD patients, 60 NRS-PD patients, and 60 controls were assessed for retrospective diagnosis of CSAD between March 2020 and August 2023 using a diagnostic categorical instrument, *DSM-5* criteria, and a dimensional one, the Separation Anxiety Symptom Inventory.

Results: RS patients had a significantly greater history of CSAD (55%) compared to the NRS (23%) and control (17%) groups ($P < .001$), which shows stronger association with the RS group. As seen in logistic regression, RS patients had 3.02 more chances of having CSAD when compared the NRS group and 5.11 when compared to the control group, which shows stronger association with the RS group.

Conclusion: This study supports the hypothesis that RS-PD is associated with CSAD, while there is a weak association between NRS-PD and CSAD. It is advisable for clinicians to screen individuals with RS-PD for symptoms of separation anxiety, as these symptoms may have a negative impact on the prognosis of PD.

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Anxiety disorders are prevalent on a global scale, as indicated by epidemiologic data, with a lifetime prevalence of up to 33.7%.[1] Typically beginning early in life, these disorders represent a notable burden on the health care system, quantified at an estimated annual cost of $33.71 billion to the United States in 2010.[2] Effort has been made to elucidate the pathophysiological underpinnings of these disorders and to enhance diagnostic systems and preventive strategies. Notably, there is an ongoing investigation into the potential interconnection between separation anxiety disorder and panic disorder (PD).

Separation anxiety is an innate mechanism observed in all mammals, and, in humans, it typically reaches its peak between the ages of 10 to 36 months.[3] It becomes a disorder when fear or anxiety involving separation of attachment figures is excessive or developmentally inappropriate.[4] What we call PD today was described by Donald Klein in 1964, while observing patients with sudden attacks of intense fear, associated with cognitive and somatic features such as "rapid breathing, palpitations, weakness, unsteadiness, and a feeling of impending death."[5(p397)] His observations and descriptions influenced the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-III*), published in 1980, in which the term *panic disorder* appears for the first time in an official psychiatric classification.[6] He also observed that some of these patients had a history of inappropriate childhood separation anxiety.[5]

In 1993, Klein[7] integrated childhood separation anxiety disorder (CSAD) with PD under his false suffocation alarm theory because he believed there was substantial shared pathophysiology between the 2 disorders. This resulted in the separation anxiety hypothesis of PD, which underwent comprehensive

Clinical Points

- The respiratory subtype of panic disorder (PD) demonstrates a stronger association with childhood separation anxiety disorder when compared to the nonrespiratory subtype.
- Clinicians may be aware of preventive strategies aimed at mitigating symptoms of separation anxiety in children, thereby averting potential adverse outcomes.
- Clinicians may additionally investigate for historical or concurrent manifestations of separation anxiety symptoms, as these may worsen the prognosis of PD.

exploration in subsequent studies,[8–11] indicating shared pathophysiology between PD and CSAD. In 2013, Kossowsky and colleagues[12] conducted a systematic review and meta-analysis of 25 studies to investigate the association between CSAD and PD. Their findings suggested that CSAD predicted PD with an odds ratio (OR) of 3.45 (95% CI, 2.4–5.0). Other anxiety disorders pooled together had a less robust association (OR = 2.19).[12] However, some studies presented conflicting results.[13–20] One possible explanation could be the varying prevalence of CSAD among different subgroups of PD patients. For instance, when comparing PD patients with and without agoraphobia, those with agoraphobia displayed a higher occurrence of CSAD.[21]

Considering the diagnosis of PD itself, various subtypes have been proposed, such as nocturnal and vestibular, for instance,[22] or based on its response to tricyclic antidepressants or benzodiazepines.[7] The most extensively studied subtype of PD is the respiratory subtype (RS), and it has been linked to high sensitivity to carbon dioxide (CO_2). In 1993, Briggs and colleagues[23] clustered symptoms into RS and nonrespiratory subtypes (NRS) of PD. Patients from the RS group tend to display more symptoms during panic attacks in general but particularly breathlessness, choking sensation, numbness, chest pain or discomfort, and fear of dying compared to those from the NRS group. The RS probably represents a more severe form of PD.[24,25]

Since both CSAD and RS-PD are associated with abnormal sensitivity to CO_2, one would expect that they share biological underpinnings, but the literature is scant on this topic. Specifically, there is an absence of studies examining the history of CSAD in individuals diagnosed with PD and exhibiting prominent respiratory symptoms. Considering this, our working hypothesis postulates that there is a robust connection between RS-PD and CSAD, whereas NRS-PD is not connected to CSAD. To empirically investigate this hypothesis, we examined the history of CSAD among individuals diagnosed with RS-PD, NRS-PD, and a control group. This examination was undertaken using both categorical and dimensional approaches. Our primary objective centered on the comparative analysis of CSAD prevalence between RS and NRS groups, with secondary objectives focusing on the comparative assessment of RS and NRS groups against the control group.

METHODS

Sample and Assessment

The current study enrolled 180 subjects, aged between 18 and 60 years. Patients coming for initial assessment or already in follow-up in the Anxiety Disorders Clinic from the Institute of Psychiatry of the Federal University of Rio de Janeiro were invited to participate in the current study. The Anxiety Disorders Clinic, which accepts patients from Rio de Janeiro city and metropolitan area referred for treatment for anxiety disorders, has the capacity to attend to approximately 120 patients per month. We assigned participants between March 2020 and August 2023 to the 3 study groups employing a first-come, first-served approach until each group reached a total of 60 individuals. This sample size was calculated based on the prevalence of separation anxiety in the general population and in individuals with PD. All individuals were assessed using the Brazilian-Portuguese version[26] of the Mini International Neuropsychiatric Inventory 5.0[27] for the diagnosis of psychiatric disorders. Those with organic mental disorders, neurodevelopmental disorders, substance use disorder, bipolar disorder, eating disorder, or personality disorder were excluded. Patients with unipolar depression and other anxiety disorders were included only if PD was identified as the primary diagnosis. To be included in the control group, individuals were required to have no current or past diagnosis of PD but could present with unipolar depression or other anxiety disorders. This inclusion criterion facilitated the establishment of comparability across the 3 groups concerning comorbidities. The categorization of individuals into RS and NRS followed the criteria established by Briggs et al[23]; thus, patients answered the Brazilian-Portuguese version of the Diagnostic Symptom Questionnaire, a self-reported instrument that assesses symptoms of a panic attack.[28]

Patients underwent evaluation by a senior psychiatrist, blind to their diagnosis, who assessed their history of CSAD in a clinical interview conducted in accordance with *DSM-5* criteria.[4] As a concluding step, patients answered the Brazilian-Portuguese version of the Separation Anxiety Symptom Inventory (SASI).[29]

This study was carried out in accordance with the Declaration of Helsinki. All subjects provided written consent, and the study was approved by our local ethics committee in March 2020 under the number CAAE 28920620.0.0000.5263.

Table 1.
Sociodemographic Features of the Groups

Feature	Respiratory subtype group	Nonrespiratory subtype group	Control group	χ^2/Kruskal–Wallis (*P*)
Sex, n (%)				
Female	48 (80)	48 (80)	48 (80)	
Male	12 (20)	12 (20)	12 (20)	
Any psychiatric comorbidity, n (%)				
Yes	20 (33)	19 (32)	17 (28)	$\chi^2 = 0.363$ (.834)
No	40 (67)	41 (68)	43 (72)	
Age, median (interquartile range), y	43.00 (20.00)	43.00 (16.25)	40.50 (20.50)	Kruskal–Wallis = 1.268 (.531)

Statistical Analysis

The analyses were performed using JASP (version 0.17.2).[30] The normality of the distribution of numerical variables was tested using the Shapiro–Wilk test,[31] in which significant results point to a deviation from normality. The χ^2-square test was used for categorical variables association,[32] and the Kruskal–Wallis test was used for comparing the nonparametric quantitative data,[33] with Dunn post hoc analysis.[34] Binary logistic regression was used to evaluate the association between the groups and the clinical diagnosis of CSAD.[35]

RESULTS

Demographic Characteristics

Groups were matched in terms of age and sex. Age in the control group deviated from normality, as measured by the Shapiro–Wilk test. For this reason, we used median and interquartile range (IQR) as central tendency and dispersion measure, respectively, and the Kruskal–Wallis test for comparing groups. There was no statistically significant difference between the groups. Also, groups were no different in terms of anxious and mood disorders comorbidity. These data are summarized in Table 1.

CSAD Diagnosis

Groups were compared using the categorical approach of *DSM-5* diagnostic criteria for the history of CSAD. RS had a higher prevalence of CSAD (55%) when compared to the NRS (23%) and control (17%) groups. These data are summarized in Table 2. Logistic regression pointed to a significant relationship between the 3 groups (Akaike information criterion = 207.837, Bayesian information criterion = 217.416, $\chi^2_{177} = 22.923$, $P < .001$, and $R^2 = 0.168$). RS patients had 5.11 times more chances of having CSAD than the control group (B = 1.810, Wald = 17.490, $P < .001$). CSAD diagnosis association with NRS patients did not show a statistically significant difference when compared to the control group (B = 0.420, Wald = 0.827, $P = .363$). When compared to the NRS group, the RS group had 3.02 times more chances of having CSAD (B = 1.390, Wald = 12.042, $P < .001$). This logistic regression model could predict correctly in 71.67% of the cases.

SASI Scores

Considering the SASI total score, the Shapiro–Wilk test showed deviation from normality for the RS (0.961, $P = .050$) and NRS groups (0.967, $P = .101$). For this reason, we again used median and IQR as central tendency and dispersion measure, respectively, and the Kruskal–Wallis test for comparing groups. These data are summarized in Table 2 and Figure 1. Dunn post hoc comparisons showed that the RS group had significantly higher scores than the NRS ($P = .001$) and control ($P < .001$) groups, but scores for NRS were not different from that of the control group ($P = .132$).

DISCUSSION

As hypothesized, RS patients had a significantly greater history of CSAD measured both in a categorical approach, using the *DSM-5* criteria, and by a dimensional instrument, the SASI, when compared to the NRS and control groups. History of CSAD in the NRS group showed a slight tendency of being greater than that in the control group, but this was not statistically significant. It could be expected for NRS to be in an intermediate position between the RS and control groups in terms of CSAD; however, NRS is more like the control group than RS. As seen in logistic regression, RS patients had 3.02 more chances of having CSAD when compared to the NRS group and 5.11 when compared to the control group, which shows greater vulnerability in the RS group.

To our knowledge, this is the first study comparing PD and CSAD regarding RS. Our findings are in accordance with current literature, which integrates CSAD and PD. These 2 diagnoses seem to share the same neurobiological features,[36] in particular the hypersensitivity to CO_2.[37] RS seems to be a more severe subtype of PD due to greater familial risk, more comorbidities, longer duration of illness, less favorable prognosis,[38] and, according to our data, being associated with CSAD. This represents a different diathesis when

Table 2.

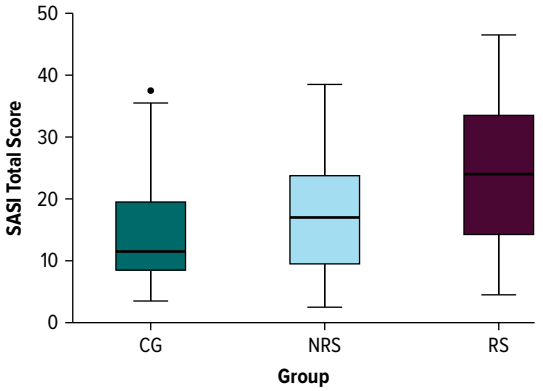
CSAD Diagnosis and SASI Total Score Between Groups

Variable	Respiratory subtype group	Nonrespiratory subtype group	Control group	χ^2/Kruskal–Wallis (*P*)
CSAD diagnosis, n (%)				
Yes	33 (55)	14 (23)	10 (17)	χ^2 = 23.261 (<.001)
No	27 (45)	46 (77)	50 (83)	
SASI total score, median (interquartile range)	21.50 (19.25)	14.50 (14.25)	9.00 (11.00)	Kruskal–Wallis = 23.323 (<.001)

Abbreviations: CSAD = childhood separation anxiety disorder, SASI = Separation Anxiety Symptom Inventory.

Figure 1.

Comparison of SASI Total Scores by Group



Abbreviations: CG = control group, NRS = nonrespiratory subtype group, RS = respiratory subtype group, SASI = Separation Anxiety Symptom Inventory.

compared to NRS. Since not only SAD but also separation anxiety symptoms, as a continuum, might be associated with PD, we evaluated the individuals using a dimensional instrument, the SASI. Its scores were significantly higher in RS when compared both to the NRS group and controls.

Among children without comorbidities, CSAD was the only diagnosis to predict panic symptoms in response to a 5% CO_2 challenge.[39] Children with separation anxiety disorder also displayed increased psychophysiological response to voluntary hyperventilation as observed by elevated heart rate, respiratory variability, and musculus corrugator supercilii, when compared to children with other anxiety disorders and healthy controls. It is important to acknowledge the vulnerability of children with CSAD to CO_2 hypersensitivity. Our study supports the diathesis-stress model, in which children with CSAD may exhibit heightened vulnerability to the onset of PD.[37]

The current study is constrained by several limitations. First, the use of a clinical sample curtails the inferential capacity of the study findings; therefore, employing an epidemiologic sample in future research could yield results of greater generalizability. Second, the classification of individuals into RS and NRS groups relies solely on symptom self-reports from patients, introducing potential subjectivity. Additionally, there is an inherent limitation related to memory bias when participants recall childhood separation anxiety experiences, which is characteristic of retrospective study designs.

To address these limitations and enhance the robustness of future investigations, it is recommended to undertake cohort studies that longitudinally track individuals with CSAD alongside healthy children. Such studies should systematically compare the developmental trajectories of both RS and NRS-PD. Furthermore, exploring novel forms of categorization within these subtypes could contribute to a more nuanced understanding of the complex interplay between childhood separation anxiety symptoms and subsequent PD manifestations.

This study supports the hypothesis that RS-PD is associated with CSAD, while there is a weak association between NRS-PD and CSAD. For future directions, we believe this association should be taken into consideration when preventing, diagnosing, and treating CSAD and PD. All RS-PD patients should be asked about their past history of CSAD, and separation anxiety symptoms should be searched in their offspring so that preventive strategies could take place, such as parental guidance and family-based cognitive-behavioral therapy.[40]

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