

CLINICAL PHENOTYPING ASSOCIATED WITH COMORBIDITIES (ADHD, EPILEPSY, ANXIETY, GASTROINTESTINAL DISORDERS) <https://doi.org/10.63330/aurumpub.034-012>**Victor Lucas Mendes Garcia¹ and Forsyth Vasconcelos e Silva²****Abstract**

Clinical phenotyping has emerged as a fundamental approach to understanding the heterogeneity of neurodevelopmental disorders, particularly when associated with common comorbidities such as attention-deficit/hyperactivity disorder (ADHD), epilepsy, anxiety, and gastrointestinal disorders. This chapter aims to analyze the relevance of clinical phenotyping in identifying clinical profiles associated with these comorbidities, contributing to more accurate diagnoses and individualized therapeutic strategies. The methodology consists of a narrative literature review, including clinical, observational, and systematic review studies published in recognized scientific databases, encompassing both pediatric and adult populations. The results demonstrate that the presence of multiple comorbidities significantly influences clinical presentation, prognosis, and treatment response, highlighting the need for a multidimensional assessment. Additionally, gastrointestinal disorders and anxiety were found to exacerbate neurological and behavioral symptoms, while epilepsy showed a direct impact on cognitive development. It is concluded that clinical phenotyping associated with comorbidities is a key tool for both clinical practice and research, enabling an integrated, patient-centered, and evidence-based approach.

Keywords: Anxiety, Clinical phenotyping, Epilepsy, Gastrointestinal disorders, ADHD.

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INTRODUCTION

Clinical phenotyping has consolidated itself as an essential approach to understanding the complexity of neurodevelopmental disorders and associated neurological conditions, as it allows the detailed characterization of individuals' clinical, cognitive, behavioral, and physiological manifestations. The heterogeneity of these disorders, combined with the high prevalence of comorbidities such as attention-deficit/hyperactivity disorder (ADHD), epilepsy, anxiety disorders, and gastrointestinal disorders, poses significant challenges to diagnosis and clinical management, especially when symptoms are analyzed in isolation. In this context, it becomes essential to understand how these comorbidities interact with one another and influence patients' clinical expression, prognosis, and therapeutic response.

Despite scientific advances in neurology and psychiatry, a gap remains in the systematic use of clinical phenotyping as an integrative tool in care practice. Fragmentation of care, often centered on single diagnoses, limits the identification of specific clinical profiles and hinders the implementation of individualized therapeutic strategies. Thus, the problem guiding this chapter is to analyze how clinical phenotyping can contribute to the identification and integrated management of comorbidities associated with ADHD, epilepsy, anxiety disorders, and gastrointestinal disorders, considering the complexity and variability of clinical manifestations.

Given this context, the overall objective of this chapter is to analyze the importance of clinical phenotyping in understanding neurological, psychiatric, and gastrointestinal comorbidities, while the specific objectives include describing the conceptual foundations of clinical phenotyping, identifying the main comorbidities associated with the clinical profiles studied, analyzing the influence of these conditions on clinical course and response to treatment, and discussing the relevance of a multidimensional approach to patient care. The justification for developing this work is grounded in the need to move beyond reductionist clinical models and promote an integrated view of the individual, considering that the coexistence of multiple comorbidities directly impacts quality of life, cognitive development, and psychosocial well-being.

The scientific literature indicates that clinical phenotyping enables the identification of more homogeneous subgroups within clinically diverse populations, favoring more precise diagnoses and personalized interventions. Evidence shows that individuals with ADHD have high rates of comorbidity with anxiety disorders and epilepsy, which may aggravate behavioral symptoms and compromise cognitive performance. In addition, recent studies highlight the relationship between gastrointestinal disorders and neurological and behavioral changes, mediated by neuroimmunological mechanisms and the gut–brain axis. In this way, integrating these findings reinforces the importance of clinical phenotyping as a strategic tool for both clinical practice and research, contributing to a more precise, humane, and evidence-based approach.

METHODOLOGY

TYPE OF RESEARCH

This chapter is characterized as qualitative research with a descriptive and exploratory approach, grounded in a narrative review of the scientific literature. This modality was chosen because it allows a broad and in-depth analysis of concepts related to clinical phenotyping and associated comorbidities, enabling the integration of different theoretical and clinical perspectives. The narrative review is appropriate for complex and multidimensional themes in which the heterogeneity of studies requires an interpretive and contextualized analysis.

SEARCH PROCEDURES AND STUDY SELECTION

The literature search was conducted in recognized scientific databases, including PubMed, SciELO, Web of Science, and PsycINFO. Controlled and uncontrolled descriptors were used, combined with Boolean operators, such as “clinical phenotyping,” “ADHD,” “epilepsy,” “anxiety disorders,” and “gastrointestinal disorders.” Study selection considered publications in Portuguese and English, prioritizing original articles, systematic reviews, and meta-analyses published in recent years in order to ensure the timeliness and scientific relevance of the evidence analyzed.

Inclusion and exclusion criteria

Studies were included if they addressed clinical phenotyping associated with at least one of the comorbidities investigated, involving pediatric and/or adult populations. Works discussing clinical, diagnostic, or therapeutic implications were also considered. Studies with insufficient data, duplicate publications, isolated case reports, and articles whose focus was not directly related to the proposed objective were excluded.

ANALYSIS TECHNIQUES AND INSTRUMENTS

The analysis of the selected studies was carried out through critical reading and qualitative interpretation of the content, with an emphasis on identifying clinical patterns, relationships between comorbidities, and implications for clinical practice. As a data-organization instrument, an analytical matrix was used, allowing the categorization of information according to variables such as type of comorbidity, clinical manifestations, impacts on prognosis, and therapeutic strategies. This technique facilitated comparison across studies and synthesis of the most relevant findings.

SAMPLE AND CHARACTERIZATION OF STUDIES

The sample of this research consisted of the studies selected after applying the inclusion and exclusion criteria, encompassing different methodological designs and clinical contexts. The diversity of investigated populations made it possible to obtain a comprehensive view of phenotypic expression associated with the comorbidities analyzed, considering age-related, clinical, and contextual variations. This heterogeneity contributed to a broader understanding of the phenomena studied without compromising analytical coherence.

METHODOLOGICAL DISCUSSION AND RATIONALE

The choice of a narrative review is grounded in the complexity of the topic and the need to integrate evidence from different fields of knowledge, such as neurology, psychiatry, and gastroenterology. Although it does not follow rigid protocols of systematic reviews, this approach allows greater analytical flexibility and conceptual depth, fostering an understanding of the interactions between clinical phenotyping and comorbidities. Thus, the adopted methodology is consistent with the chapter's objectives, enabling a critical and contextualized analysis capable of supporting more integrated and evidence-based clinical practices.

RESULTS AND DISCUSSION

The results obtained from the literature analysis show that clinical phenotyping plays a central role in understanding the complexity of neurological and neurodevelopmental conditions when associated with multiple comorbidities. The analyzed studies demonstrate that individuals with ADHD, epilepsy, anxiety disorders, and gastrointestinal disorders present heterogeneous clinical profiles in which the coexistence of these conditions significantly modifies symptom expression, clinical course, and therapeutic response. It was observed that identifying clinical subphenotypes allows greater diagnostic precision and favors individualized interventions.

Table 1 presents the main associated comorbidities and their clinical impacts described in the analyzed studies.

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Table 1

Main associated comorbidities and clinical implications

Comorbidity	Main manifestations	Observed associated clinical impacts
ADHD	Attention deficit	Functional impairment, academic difficulties, and impulsivity, social hyperactivity
Epilepsy	Seizures, cognitive changes	Developmental delay, increased risk of psychiatric comorbidities.
Anxiety	Excessive fear, irritability	Exacerbation of behavioral and somatic symptoms, leading to a reduction in quality of life.
Gastrointestinal disorders	Abdominal pain, constipation, diarrhea	Worsening of neurological and behavioral symptoms.

Source: Author's own elaboration.

The findings indicate that anxiety and gastrointestinal disorders are among the comorbidities most frequently associated with neurodevelopmental disorders, acting as modulatory factors of clinical severity. The literature indicates that alterations in the gut–brain axis and neuroimmunological mechanisms may explain the association between gastrointestinal symptoms and behavioral manifestations, reinforcing the need for integrated assessments. In the case of epilepsy, studies highlight its direct impact on cognitive and emotional development, especially when associated with ADHD.

Another relevant finding concerns the influence of comorbidities on treatment response. As presented in Table 2, individuals with multiple associated conditions tend to show a lower response to standardized interventions, requiring personalized therapeutic strategies.

Table 2

Relationship between number of comorbidities and therapeutic response

Number of comorbidities	Response to treatment	Need for an integrated approach
One comorbidity	Good to moderate	Average
Two comorbidities	Moderate	High
Three or more comorbidities	Low	Very high

Source: Author's own elaboration.

CONCLUSION

This chapter aimed to analyze the importance of clinical phenotyping in understanding and managing comorbidities associated with attention-deficit/hyperactivity disorder, epilepsy, anxiety

disorders, and gastrointestinal disorders. Returning to this objective makes it possible to highlight that detailed characterization of clinical profiles represents an essential tool for understanding the heterogeneity of neurological, behavioral, and physiological manifestations, as well as their interactions throughout the clinical course.

The main results demonstrated that the coexistence of multiple comorbidities significantly influences symptom expression, prognosis, and response to treatment, reinforcing the limitations of fragmented clinical approaches. It was observed that anxiety disorders and gastrointestinal disorders act as modulatory factors of clinical severity, often exacerbating neurological and behavioral symptoms, whereas epilepsy has a direct impact on cognitive and emotional development. In this sense, clinical phenotyping proved effective in identifying more homogeneous subphenotypes, favoring more precise diagnoses and individualized therapeutic strategies.

The contributions of this research focus on strengthening an integrated and multidimensional approach to healthcare by highlighting the relevance of clinical phenotyping as a foundation for clinical practice and scientific research. The chapter also contributes to expanding knowledge regarding the interaction among neurological, psychiatric, and gastrointestinal conditions, supporting patient-centered and evidence-based models of care.

As a suggestion for future research, empirical and longitudinal studies are recommended to deepen the investigation of the biological and psychosocial mechanisms underlying the comorbidities analyzed, as well as to validate clinical phenotyping models applicable to different population contexts. Such investigations may expand understanding of clinical subphenotypes and contribute to advancing increasingly personalized diagnostic and therapeutic strategies.

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