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The Cause of Hirschsprung's Disease in Bardet Biedl Syndrome in Children

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Abstract

Hirschsprung's disease (HSCR) is a developmental disorder characterized by the absence of ganglion cells in the distal colon, leading to functional obstruction. Bardet-Biedl syndrome (BBS) is a rare ciliopathy associated with various clinical features, including HSCR. This review article aims to explore the underlying causes of HSCR in children with BBS, focusing on the genetic and developmental factors contributing to the pathogenesis of both conditions. We reviewed relevant literature, including peer-reviewed journal articles and case reports, to provide a comprehensive overview of the current understanding of the relationship between HSCR and BBS. Our findings highlight the complex interplay of genetic mutations, signaling pathways, and developmental processes involved in the pathogenesis of HSCR in BBS. Further research is needed to elucidate the precise mechanisms underlying this association and to develop targeted therapeutic strategies for children with HSCR and BBS.

Keywords

Hirschsprung's Disease, Bardet-Biedl Syndrome, Ciliopathy, Genetics, Developmental Disorder

1. Introduction

Hirschsprung's disease (HSCR) is a congenital disorder characterized by the absence of ganglion cells in the distal colon, leading to functional intestinal obstruction [1] [2]. While HSCR is often an isolated condition, it can also be associated with various chromosomal abnormalities, congenital anomalies, and syndromes, including Bardet-Biedl syndrome (BBS) [3]. BBS is a rare, multisystemic ciliopathy with diverse clinical features, such as obesity, retinal dystrophy, polydactyly, renal abnormalities, and developmental delays [4].

The association between HSCR and BBS has been documented in several

studies, suggesting a potential link between these two seemingly distinct conditions. Day, Avila, and Novak [5] reported two cases of HSCR in siblings with BBS, highlighting the challenges in diagnosis and management. Their study underscores the importance of recognizing the potential for HSCR in children with BBS and emphasizes the need for further research to elucidate the underlying mechanisms connecting these complex disorders [6].

This review article aims to explore the current understanding of the relationship between HSCR and BBS, focusing on the genetic, developmental, and clinical aspects of these conditions. We will examine the prevalence, pathogenesis, clinical presentation, and management of HSCR in children with BBS, drawing upon the latest research findings and clinical experience. Additionally, we will discuss the potential implications of this association for future research and clinical practice.

2. Bardet-Biedl Syndrome: An Overview

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive disorder characterized by a wide range of clinical features [7]-[10]. As a ciliopathy, BBS arises from dysfunction of primary cilia, which are microtubule-based organelles involved in cellular signaling and sensory perception [11] [12]. This dysfunction affects multiple organ systems, leading to the diverse manifestations of the syndrome [13].

2.1. Genetic Basis

BBS is genetically heterogeneous, with mutations identified in over 20 genes, including BBS1, BBS2, ARL6, BBS4, BBS5, and others [14] [15]. While a direct correlation between specific mutations and disease severity remains elusive, some trends have been observed. For instance, certain mutations in the BBS1 gene appear to be associated with milder ophthalmologic involvement [16]. Conversely, mutations in BBS10 may predispose individuals to obesity and insulin resistance [17].

2.2. Clinical Features

The clinical spectrum of BBS is broad, encompassing both major and minor features. Major features are those that occur with higher frequency and are often considered cardinal manifestations of the syndrome. Minor features, while less prevalent, contribute to the overall clinical picture and can significantly impact patient management. See **Table 1** to see the diverse clinical features and their approximate frequencies.

2.3. Caring for Children with Bardet-Biedl Syndrome

Bardet-Biedl syndrome (BBS) presents unique challenges for affected children and their families. Given the rarity and complexity of this multisystem disorder, parents often feel unprepared to navigate the associated medical, developmental, and psychosocial issues [18]. Therefore, healthcare professionals play a crucial role in providing comprehensive support and guidance.

Table 1. Bardet-Biedl Syndrome features, frequency, and foundation.

Feature Category	Specific Feature	Approximate Frequency	Clinical Significance
Major Features	Retinal cone-rod dystrophy	94%	Progressive vision loss, often leading to legal blindness. Requires regular ophthalmological monitoring and management [19] [20].
	Postaxial polydactyly	79%	Extra digits on the hands or feet. May require surgical intervention for functional or cosmetic reasons [19] [21].
	Central obesity	89%	Significant weight gain, typically beginning in childhood. Contributes to metabolic complications and requires dietary and lifestyle interventions [19] [22].
Minor Features	Gastrointestinal abnormalities (including HSCR)	2.80%	Hirschsprung's disease, along with other gastrointestinal issues, can cause significant morbidity. Requires specialized care and may necessitate surgical treatment [19].
	Genitourinary abnormalities	Variable	Structural or functional abnormalities of the kidneys and urinary tract. Can lead to renal insufficiency and require nephrological management [19].
	Endocrine and metabolic abnormalities	Variable	Includes diabetes mellitus type 2 (15.8%), hypothyroidism (19.4%), and metabolic syndrome (54%). Requires careful monitoring and management to prevent long-term complications [19].
	Developmental delay	Variable	Cognitive impairment and learning difficulties. Requires educational support and intervention [19].
	Speech delay	Variable	Delayed acquisition of language skills. May benefit from speech therapy [19].
	Behavioral and psychiatric abnormalities	Variable	Includes anxiety, depression, and autism spectrum disorder. Requires psychological assessment and support [19].

Note: The frequencies presented in this table are approximate and may vary across different studies and populations.

Effective care for children with BBS requires a multidisciplinary approach, involving collaboration amongst various specialists, including geneticists, ophthalmologists, endocrinologists, nephrologists, and developmental pediatricians [23]. Early diagnosis and intervention are essential to optimize outcomes and improve quality of life.

2.4. Supporting Families

- Education and Counseling: Providing families with accurate and up-to-date information about BBS is paramount. This includes explaining the genetic basis of the disorder, its potential complications, and available management strategies. Genetic counseling can help families understand inheritance patterns and recurrence risks [8] [24].
- Psychosocial Support: Families may benefit from psychological support to cope with the emotional and social challenges associated with raising a child with BBS. Support groups and online resources can connect families with others facing similar experiences [8] [25].
- Care Coordination: Given the multisystem nature of BBS, care coordination is crucial to ensure that children receive appropriate and timely interventions from various specialists. A designated care coordinator can help families navigate the

healthcare system and advocate for their child's needs [8].

3. Hirschsprung's Disease: An Overview

The aganglionic segment in Hirschsprung's disease (HSCR) can vary in length, typically affecting the rectum and sigmoid colon in short-segment HSCR [1]. In some cases, it may extend further to involve longer sections of the colon (long-segment HSCR) or even the entire colon and small intestine, known as total colonic aganglionosis [26].

3.1. Clinical Presentation

- Infants with HSCR typically present within the first two months of life with symptoms such as failure to pass meconium, constipation, abdominal distension, vomiting, and poor feeding [27].
- Older children may experience chronic constipation, abdominal pain, and failure to thrive [27].

3.2. Genetic and Environmental Factors

- HSCR is a complex disorder with contributions from both genetic and environmental factors [28].
- Mutations in several genes, including RET, EDNRB, and SOX10, have been implicated in the pathogenesis of HSCR [28].
- The inheritance pattern can be autosomal dominant, autosomal recessive, or multigenic, depending on the specific gene involved [29].
- While genetic predisposition plays a significant role, environmental factors may also contribute to the development of HSCR [28] [29].

3.3. The Link between Hirschsprung's Disease and Bardet-Biedl Syndrome

Hirschsprung's disease (HSCR) and Bardet-Biedl syndrome (BBS) are seemingly distinct genetic disorders. HSCR affects the development of the enteric nervous system, leading to intestinal obstruction, while BBS is a multisystem ciliopathy with a wide range of clinical manifestations, including obesity, retinopathy, polydactyly, and renal dysfunction. However, a growing body of evidence suggests a potential link between these two conditions.

3.4. Genetic Interaction between BBS and HSCR

Studies have identified mutations in BBS genes among patients diagnosed with both BBS and HSCR, suggesting a possible genetic interaction. Zhang *et al.* [30] investigated two families with both conditions. In one family of Caucasian origin (F1), three siblings affected by a short-segment HSCR harbored two heterozygous missense mutations in a BBS gene. In another family of Moroccan origin (F2), two out of five siblings with BBS also had confirmed HSCR, with all five siblings exhibiting a homozygous 1-bp deletion in the BBS4 gene. Additionally, a sporadic

case (SB25) was identified with an infant born to healthy parents of Caucasian origin presenting with both HSCR and BBS, who inherited a heterozygous missense BBS4 mutation from their father [31].

Further analysis revealed that patients with BBS and HSCR are often carriers of the RET allele, a gene known to be associated with HSCR. Kuil [32] suggests sequencing patients for RET mutations to identify potential BBS and HSCR links. In the F1 family, all three affected siblings were homozygous for the intronic hypomorphic T allele of RET, while in the F2 family, only the two siblings with both BBS and HSCR were homozygous for this allele. This suggests that epistasis, or gene-gene interaction, between RET and BBS mutations, may contribute to the development of HSCR.

3.5. BBS and HSCR: Shared Molecular Pathways

BBS is a genetically heterogeneous disorder with at least 12 loci and 10 genes identified [24]. It is characterized by defects in primary cilia, which play critical roles in various cellular processes, including signal transduction and development. Interestingly, recent research has implicated cilia dysfunction in the pathogenesis of HSCR. This raises the possibility that shared molecular pathways involving cilia dysfunction may underlie the link between BBS and HSCR.

4. Clinical Overlap and Case Reports

The McKusick-Kaufman syndrome (MKKS) is a rare disorder allelic to BBS, characterized by postaxial polydactyly, congenital heart defects, and, in some cases, HSCR (Alvarez-Satta, Castro-Sanchez and Valverde 2017). The clinical overlap between BBS, MKKS, and HSCR further supports a connection between these conditions. Case reports, such as the one described by Kapor, Smith, and Ambartsumyan [33] involving a 3-year-old child with BBS presenting with HSCR, provide additional evidence for this association.

4.1. Effects of HSCR and BBS in Children

Both HSCR and BBS can significantly impact a child's quality of life. HSCR can lead to complications such as intestinal obstruction, constipation, enterocolitis, and potentially life-threatening infections. BBS, with its multisystem involvement, can result in vision loss, obesity, renal dysfunction, developmental delays, and behavioral issues.

4.2. Prevalence and Clinical Presentation

The prevalence of BBS varies geographically, ranging from 1 in 140,000 to 1 in 160,000 newborns in North America and Europe [34]. HSCR is more common in males and can present with symptoms such as abdominal distention, constipation, and vomiting. Children with BBS may exhibit a range of behavioral issues, including internalizing problems like anxiety and depression [35]. **Table 2** summarizes the key features and overlapping manifestations found in both HSCR and BBS.

Table 2. Summary of key features and overlapping manifestations of HSCR and BBS.

Feature	Hirschsprung's Disease (HSCR)	Bardet-Biedl Syndrome (BBS)	Overlapping Manifestations
Primary Defect	Abnormal development of the enteric nervous system	Dysfunction of primary cilia	Potentially shared molecular pathways involving cilia dysfunction
Genetic Heterogeneity	Associated with RET gene and other loci	At least 12 loci and 10 genes identified	Some BBS genes may interact with RET, increasing HSCR risk
Clinical Manifestations	Intestinal obstruction, constipation, enterocolitis	Obesity, retinopathy, polydactyly, renal dysfunction, developmental delays	HSCR observed in some BBS patients, particularly those with MKKS
Prevalence	More common in males	Varies geographically	
Treatment	Surgical intervention	Symptomatic management, supportive care	

4.3. Further Research

While the link between HSCR and BBS is becoming increasingly evident, further research is needed to fully elucidate the underlying mechanisms. Investigating the role of cilia dysfunction in both conditions, identifying additional genetic interactions, and exploring potential shared signaling pathways may provide valuable insights for diagnosis, treatment, and genetic counseling.

5. Counseling

In interrelationship marriages, individuals should receive counseling on the features, impacts, and effects of their situation, including the genetic implications. Hirschsprung's disease (HSCR) is a congenital malformation with a 4% overall recurrence risk in the proband's siblings (relative risk = 200). In isolated HSCR, the sex and aganglionic segment of the proband, as well as the gender of the sibling, provide adequate relative risk estimates. Many instances of HSCR are linked to other genetic abnormalities, and the severity of these associated malformations impacts the long-term prognosis. A Mendelian inheritance pattern is observed in many diseases, underscoring the importance of a comprehensive examination of all babies with HSCR by a genetic counselor [36].

5.1. Genetic Conclusion

In interrelationship marriages, individuals should be counseled on the features, impacts, and effects of their situation, including the genetic implications. HSCR is a congenital malformation with a 4% overall recurrence risk in the proband's siblings (relative risk = 200). In isolated HSCR, the sex and aganglionic segment

of the proband, as well as the gender of the sibling, provide adequate relative risk estimates. Many instances of HSCR are linked to other genetic abnormalities, and the severity of these associated malformations impacts the long-term prognosis. This highlights the significance of a genetic counselor's comprehensive examination of all infants with HSCR [37].

5.2. Diagnosis

Hirschsprung disease (HSCR) can be treated surgically by removing the colon segment lacking nerve cells. In contrast, Bardet-Biedl syndrome (BBS) has no definitive treatment and focuses on managing specific signs and symptoms. According to Bergmann [38], BBS is associated with various classical features, and some patients may not receive a precise diagnosis for several years. Ogundele [39] noted that diagnosis difficulties often arise when a child has learning disabilities and weight management issues but no congenital abnormalities, making the diagnosis uncertain.

Retinal disease diagnosis may require consultation with ophthalmologists and a definitive examination, such as an electroretinogram (ERG). Esposito [40] suggested that genetic testing could aid in diagnosing patients with BBS1 and BBS10 gene mutations, although Caudle *et al.* [41] pointed out that such tests may not be available in all laboratories. Primary treatment for BBS involves addressing specific symptoms, and kidney transplantation may be necessary for severe kidney disease [38].

Recent progress in HSCR stem cell-based medicinal research has been significant, though many essential questions remain unanswered. This review provides a brief background on HSCR, outlines future approaches to stem cell-based treatment, reviews key recent articles, and discusses ethical and technical challenges before clinical translation [42].

In HSCR, surgical treatment aims to restore normal bowel function and remove the tonic contraction of the internal anal sphincter [43]. Various surgical procedures, including the Soave and Duhamel procedures, are used. One-stage procedures are applicable for short-segment diseases, while long-segment diseases may require total colonic ganglions and temporary enterostomy before definitive surgery. Ghorbanpour *et al.* [44] proposed laparoscopic and transanal pull-through techniques for HSCR diagnosis. **Table 3** covers the complications and outcomes of HSCR Surgery.

Table 3. Complications and outcomes of HSCR surgery.

Complication Type	Short-term Complications	Long-term Complications
Examples	Diarrhea, constipation, fever, rectal bleeding, fistula, enterocolitis	Chronic constipation, soiling
Mortality Rate	Less than 6% (mainly related to short-term complications and malformations)	-

In the United States, approximately 90% of initial HSCR diagnoses occur within the first year of life, with 10% during childhood and less than 1% during adolescence or adulthood [45]. Postoperative treatment should include measures to minimize complications, such as regular physical examinations, kidney and urinary bladder function evaluations, and monitoring of vital signs. If all signs are normal, patients can be sent home with instructions for bowel irrigation three times a day at the operation site. Children with a history of HSCR are at higher risk of developing enterocolitis, characterized by explosive diarrhea, lethargy, and abdominal distension [46].

6. Conclusion

This review article explored the complex relationship between Hirschsprung's disease (HSCR) and Bardet-Biedl syndrome (BBS), highlighting the genetic, developmental, and clinical aspects of these conditions. We examined the prevalence, pathogenesis, clinical presentation, and management of HSCR in children with BBS, drawing upon the latest research findings and clinical experience. Our findings highlight the complex interplay of genetic mutations, signaling pathways, and developmental processes involved in the pathogenesis of HSCR in BBS. Further research is needed to elucidate the precise mechanisms underlying this association and to develop targeted therapeutic strategies for children with HSCR and BBS.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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