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Auto-brewery Syndrome: A Comprehensive Review of an Endogenous Ethanol Production Disorder

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Article Info	ABSTRACT
Article history:	Auto-brewery Syndrome (ABS), or gut fermentation syndrome, is a rare condition where
Received: 19/08/2024 Received in revised format:	yeast or other microorganisms in the gut produce ethanol, leading to alcohol intoxication
09/09/2024	without alcohol consumption. Symptoms range from mild dizziness to severe intoxication,
Accepted: 16/09/2024 Available online: 05/10/2024	posing significant medical and psychosocial challenges. Due to its rarity and non-specific
Keywords: Auto-brewery	symptoms, ABS is often under diagnosed. Diagnosing ABS involves measuring blood ethanol
Syndrome; gut fermentation syndrome; endogenous ethanol	levels when no alcohol has been consumed and identifying fermenting organisms in the gut.
production; yeast overgrowth;	Treatment typically includes dietary modifications, antifungal therapy, and probiotics to
gastrointestinal disorders; alcohol intoxication	restore gut flora balance. A multidisciplinary approach is crucial for proper diagnosis and
Corresponding Author details:	management. Increased awareness among healthcare professionals is needed to avoid
<i>Email:</i> abhishekpimpale9823@gmail.com	misdiagnosis and ensure effective treatment. Further research is required to better understand
(K.P. Rathod)	ABS and establish standardized diagnostic and therapeutic protocols.
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INTRODUCTION

Review Article

Auto-brewery Syndrome (ABS), also known as gut fermentation syndrome, is a rare medical condition where ethanol is produced endogenously within the gastrointestinal tract, leading to symptoms of alcohol intoxication without the consumption of alcoholic beverages. This syndrome arises from the abnormal proliferation of yeast or other microorganisms in the gut, which ferment carbohydrates into ethanol. While it has been primarily reported in individuals with underlying gastrointestinal disorders or after antibiotic use, ABS can manifest in various ways, leading to significant psychosocial and medical implications for those affected. The clinical presentation of Auto-brewery Syndrome can vary DOI: 10.62946/IJMPHS/1.3.106-114 widely, from mild symptoms such as dizziness and fatigue to more severe intoxication episodes. Because of its rarity and the often non-specific nature of symptoms, ABS is frequently misdiagnosed or overlooked, leading to delayed or inappropriate treatment. The condition has gained increasing attention due to its complex pathophysiology, diagnostic challenges, and the psychosocial impact on patients, many of whom may face skepticism from healthcare providers and society ^[1].

This review aims to provide a comprehensive overview of Auto-brewery Syndrome, discussing its pathophysiology, clinical manifestations, diagnostic methods, and treatment approaches. By synthesizing the available literature, this review seeks to offer insights into the mechanisms underlying ABS and to propose strategies for its effective management [2]

EPIDEMIOLOGY AND PREVALENCE

Auto-brewery Syndrome (ABS) is an exceedingly rare and often underreported condition, which makes determining its epidemiology and prevalence challenging. The limited data available on ABS primarily comes from case reports and small studies, rather than large-scale epidemiological research ^[3]. Below is a summary of what is known about the epidemiology and prevalence of Auto-brewery Syndrome:

I. Incidence and Prevalence

• **Rarity**: Auto-brewery Syndrome is considered extremely rare, with only a few documented cases in the medical literature. Due to the scarcity of reports and the potential for misdiagnosis, the true prevalence of ABS is unknown.

• Underreporting: The condition may be underdiagnosed due to its non-specific symptoms and the lack of awareness among healthcare professionals. Some individuals may be suffering from ABS without a formal diagnosis, especially in cases where symptoms are mild or intermittent.

• **Case Reports**: Most documented cases have been reported from countries such as the United States, Japan, and the United Kingdom. However, it is likely that cases exist globally but go unrecognized or misattributed to other conditions.

II. Demographics

• Age: ABS has been reported in both children and adults, with a slight predominance in middle-aged adults. There is no clear age group that is disproportionately affected, although case reports suggest that adults with a history of gastrointestinal issues may be more susceptible.

• Gender: There is no strong gender predilection in ABS, as cases have been reported in both men and women.

However, some studies suggest a slight male predominance, potentially due to differences in gut microbiota or metabolic factors.

• **Risk Factors**: The condition is often associated with underlying gastrointestinal disorders, such as Crohn's disease, short bowel syndrome, or chronic antibiotic use, which may alter gut microbiota and promote the overgrowth of ethanol-producing microorganisms.

III. Geographic Distribution

• **Global Occurrence:** ABS has been reported across various regions, including North America, Europe, and Asia. The condition does not appear to be limited to any specific geographic area, but the availability of healthcare and diagnostic facilities may influence the likelihood of detection.

• **Cultural and Dietary Factors**: In some regions, dietary habits that involve high carbohydrate intake may predispose individuals to the development of ABS, especially if they also have other risk factors like gut dysbiosis.

IV. Challenges in Epidemiological Research

• **Diagnostic Difficulty**: Due to the lack of standardized diagnostic criteria, many cases of ABS may go undetected. The episodic nature of the condition and the fact that symptoms can mimic alcohol intoxication also contribute to diagnostic challenges.

• Lack of Large-scale Studies: Most of the available data comes from isolated case reports, which limits the ability to generalize findings to larger populations. More robust epidemiological studies are needed to accurately estimate the prevalence and incidence of ABS.

V. Potential for Increased Awareness

• **Increased Reporting**: As awareness of ABS grows, more cases may be recognized and reported. This could lead to a better understanding of the condition's true prevalence.

• Focus on Gut Microbiome: With the growing interest in the gut microbiome and its impact on health, ABS may gain more attention in the medical community, leading to improved diagnostic techniques and epidemiological tracking ^[4-5].

CAUSES AND PATHOPHYSIOLOGY OF ABS

The causes and pathophysiology of ABS are complex and involve various factors, including microbial overgrowth, gut dysbiosis, and metabolic disturbances ^[6].

I. Microbial Overgrowth

• Yeast Overgrowth: The primary cause of ABS is the overgrowth of ethanol-producing microorganisms, particularly yeasts like *Saccharomyces cerevisiae* and *Candida* species, within the gastrointestinal tract. These yeasts ferment carbohydrates into ethanol and other byproducts. In a healthy gut, these microorganisms are usually present in small quantities, but when they proliferate abnormally, they can produce significant amounts of ethanol.

• **Other Microorganisms**: In addition to yeasts, certain bacteria, such as *Klebsiella pneumoniae*, have also been implicated in ABS. These bacteria can produce ethanol through fermentation processes similar to yeasts ^[6].

II. Gut Dysbiosis

• **Imbalance in Gut Microbiota**: Gut dysbiosis, an imbalance in the normal gut flora, plays a crucial role in the pathophysiology of ABS. Dysbiosis can result from various factors, including antibiotic use, poor diet, gastrointestinal infections, and underlying gastrointestinal diseases, Ex: IBD, constipation etc. When the normal balance of gut bacteria is disrupted, ethanol-producing microorganisms may proliferate, leading to ABS.

• Reduced Bacterial Competition: In a healthy gut, beneficial bacteria outcompete ethanol-producing microorganisms, preventing their overgrowth. However, in individuals with dysbiosis, this protective mechanism is compromised, allowing these microorganisms to thrive.

III. Carbohydrate Metabolism

• **Carbohydrate Fermentation**: The production of ethanol in ABS occurs when fermentable carbohydrates (such as sugars and starches) are consumed. These carbohydrates serve as substrates for yeast and bacterial fermentation, leading to the production of ethanol. High-carbohydrate diets can exacerbate the symptoms of ABS, as more substrates are available for fermentation.

• Impaired Carbohydrate Absorption: In some cases, individuals with ABS may have impaired carbohydrate absorption, leading to an increased availability of fermentable substrates in the gut. This can further fuel the production of ethanol by microorganisms.

IV. Underlying Gastrointestinal Conditions

• Short Bowel Syndrome: Individuals with short bowel syndrome, a condition where a significant portion of the small intestine is removed or non-functional, are at increased risk for ABS. The reduced length of the intestine can lead to malabsorption of nutrients and an altered gut microbiome, providing an environment conducive to ethanol production.

• Crohn's Disease and Other Inflammatory Conditions: Chronic inflammatory conditions like Crohn's disease can also predispose individuals to ABS by disrupting the normal gut flora and impairing the integrity of the gut barrier^[6].

V. Immunosuppression

• Immunosuppressive Conditions: Individuals with weakened immune systems, such as those with HIV/AIDS or those undergoing chemotherapy, may be more susceptible to ABS. Immunosuppression can lead to an overgrowth of pathogenic microorganisms, including ethanol-producing yeasts and bacteria.

VI. Antibiotic Use

• **Disruption of Gut Flora**: The use of broadspectrum antibiotics like Ampicillin, cefepime can disrupt the normal gut microbiota, eliminating beneficial bacteria and allowing opportunistic microorganisms, such as yeasts, to overgrow. This disruption can create a favorable environment for ethanol production, leading to ABS symptoms.

• **Post-antibiotic Overgrowth**: After a course of antibiotics, some individuals may experience a rebound overgrowth of yeasts or bacteria, further contributing to the development of ABS^[6].

VII. Liver Function

• **Reduced Ethanol Metabolism**: In some cases, impaired liver function may exacerbate the effects of ABS by reducing the body's ability to metabolize and clear ethanol. This can lead to higher blood alcohol levels and more pronounced symptoms of intoxication.

• Liver Disease: Individuals with pre-existing liver conditions may be more susceptible to the effects of endogenous ethanol production, as their ability to process and detoxify ethanol is compromised.

VIII. Genetic Predisposition

• Genetic Factors: Although not well-studied, there may be a genetic predisposition to ABS. Certain individuals may have genetic variations that affect their gut microbiome composition, immune response, or carbohydrate metabolism, making them more prone to developing ABS.

PATHOPHYSIOLOGY OF ABS

The pathophysiology of Auto-brewery Syndrome can be summarized in the following key processes:

1. **Fermentation of Carbohydrates**: When individuals with ABS consume carbohydrates, these are fermented by overgrown yeasts or bacteria in the gut, leading to the production of ethanol. This process occurs primarily in the small intestine, where the microbial load is usually lower but can increase due to dysbiosis or other factors.

2. **Ethanol Absorption**: The ethanol produced in the gut is absorbed into the bloodstream, leading to elevated blood alcohol levels. This absorption occurs primarily in the small intestine and can mimic the effects of alcohol consumption.

3. **Systemic Effects:** Once absorbed, ethanol exerts its typical effects on the central nervous system, leading to symptoms such as dizziness, confusion, slurred speech, and in severe cases, overt intoxication. These symptoms can occur even in the absence of alcohol consumption, leading to significant challenges in diagnosis and management.

4. **Psychosocial Impact**: The recurrent and unexplained symptoms of intoxication lead to significant psychosocial distress for individuals with ABS. Patients may

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face skepticism from healthcare providers and society, leading to stigmatization & isolation. ^[7]

DIAGNOSIS

Diagnosing Auto-brewery Syndrome (ABS) can be challenging due to its rarity and the non-specific nature of its symptoms. Accurate diagnosis requires a thorough clinical evaluation, careful patient history, and specialized testing to confirm endogenous ethanol production.^[8] Below is an outline of the key steps and methods used in diagnosing ABS:

1. Clinical History and Symptom Evaluation

• **Symptom Presentation**: The diagnosis often begins with a detailed assessment of the patient's symptoms. Common symptoms include episodes of dizziness, confusion, slurred speech, and other signs of alcohol intoxication without any reported alcohol consumption. These symptoms may appear sporadically, often after meals, particularly those rich in carbohydrates.

• Dietary and Lifestyle Assessment: Since ABS is related to carbohydrate fermentation, a careful examination of the patient's diet is essential. A history of consuming carbohydrate-rich meals, combined with the onset of symptoms, can provide clues.

• Gastrointestinal and Antibiotic History: A history of gastrointestinal issues (such as Crohn's disease, irritable bowel syndrome, or short bowel syndrome) or recent antibiotic use, which could have disrupted gut microbiota, may increase suspicion of ABS.

2. Exclusion of Other Conditions

• Rule out Alcohol Consumption: It is crucial to rule out the possibility of covert alcohol consumption or alcohol use disorder. In some cases, patients may need to undergo monitored periods of observation to confirm that no alcohol is being ingested.

• **Differential Diagnosis**: Other conditions that can mimic ABS, such as metabolic disorders, neurological conditions, and psychiatric disorders, should be considered and ruled out through appropriate testing.

3. Laboratory Testing

• **Blood Alcohol Levels**: Measuring blood alcohol levels during symptomatic episodes is a key diagnostic tool. Elevated blood alcohol levels without a history of alcohol consumption strongly suggest ABS. Blood samples should be taken at multiple time points, ideally after a carbohydrate-rich meal, to capture fluctuations in alcohol levels.

• **Carbohydrate Challenge Test**: In a controlled clinical setting, a carbohydrate challenge test can be performed. The patient is given a carbohydrate-rich meal or drink, and blood alcohol levels are monitored over time. A significant rise in blood alcohol levels after the carbohydrate challenge supports the diagnosis of ABS.

• **Breathalyzer Test**: Breath alcohol testing can be used in conjunction with blood alcohol testing. Serial breathalyzer tests after a carbohydrate load can provide noninvasive evidence of ethanol production.

4. Stool and Microbiological Analysis

• **Stool Culture and Analysis:** Stool samples can be analyzed to identify the presence of ethanol-producing microorganisms, such as *Saccharomyces cerevisiae* or *Candida* species. A stool culture that shows overgrowth of these microorganisms may support the diagnosis of ABS.

• Gut Microbiome Analysis: Advanced microbiome sequencing like Shotgun sequencing can be employed to analyze the composition of the gut microbiota. This can help identify imbalances or overgrowth of ethanol-producing organisms. While not a routine test, it can provide valuable insights in complex cases.

5. Imaging and Endoscopy (if indicated)

• Endoscopy: In some cases, endoscopy may be used to assess the gastrointestinal tract for signs of inflammation, overgrowth of microorganisms, or other underlying conditions that may contribute to ABS.

• Imaging: Imaging studies, such as abdominal ultrasound or CT scan, may be considered to rule out structural abnormalities that could predispose a patient to ABS, such as bowel obstructions or diverticula.

6. Psychosocial and Behavioral Evaluation

• Assessment of Psychological Impact: Given the social and psychological implications of ABS, a mental health evaluation may be necessary. Patients often face skepticism and may suffer from anxiety or depression due to the unexplained nature of their symptoms.

• **Behavioral Monitoring**: To rule out potential covert alcohol use, patients may need to undergo periods of monitored behavior, particularly if there are concerns about alcohol abuse or malingering.

7. Response to Treatment

• Trial of Dietary and Antifungal Therapy: As part of the diagnostic process, a trial of dietary modification (e.g., reducing carbohydrate intake) and antifungal treatment (e.g., fluconazole) can be initiated. A positive response to these interventions may further support the diagnosis of ABS.

8. Consultation with Specialists

• Multidisciplinary Approach: Due to the complexity of ABS, consultation with specialists such as gastroenterologists, infectious disease experts, and dietitians may be necessary to confirm the diagnosis and develop a comprehensive management plan.

SYMPTOMS AND SIGNS

1. Intoxication-like Symptoms

• **Dizziness and Lightheadedness**: Individuals with ABS often experience dizziness, lightheadedness, or a sensation of spinning (vertigo). These symptoms may appear suddenly, particularly after consuming a meal rich in carbohydrates.

• Impaired Coordination: Difficulty with balance, clumsiness, and poor coordination are common symptoms, similar to those seen in alcohol intoxication. Patients may appear unsteady on their feet and have trouble walking or performing fine motor tasks.

• **Slurred Speech**: Speech may become slow and slurred, resembling the effects of alcohol consumption. This symptom can be particularly troubling for patients, as it may lead to misunderstandings or suspicions of alcohol use.

• **Blurred Vision**: Visual disturbances, such as blurred or double vision, can occur during symptomatic episodes, further contributing to the feeling of intoxication ^[9].

2. Cognitive and Neurological Symptoms

• **Confusion and Disorientation**: ABS can cause significant mental fog, confusion, and disorientation. Patients may struggle to concentrate, recall information, or navigate familiar environments.

• **Memory Impairment**: Short-term memory loss or difficulty recalling recent events is sometimes reported. This may be linked to the effects of ethanol on the brain, similar to alcohol-induced blackouts.

• Fatigue and Drowsiness: The feeling of extreme tiredness or sudden drowsiness can be a sign of ABS. Patients may feel an overwhelming need to sleep, even during the day.

• **Headaches**: Some individuals with ABS experience headaches or migraines, which may be triggered by fluctuations in blood alcohol levels.

3. Behavioral and Emotional Symptoms

• **Mood Changes**: Sudden shifts in mood, including irritability, anxiety, depression, or euphoria, can occur during ABS episodes. These mood swings may be directly related to the effects of ethanol on the central nervous system.

• Aggression or Agitation: In more severe cases, patients may exhibit aggressive or agitated behavior, similar to alcohol-induced rage or frustration.

• Social Withdrawal: Due to the unpredictable nature of their symptoms and the potential stigma, some individuals with ABS may withdraw from social interactions and become isolated.

4. Gastrointestinal Symptoms

• **Abdominal Pain and Bloating**: Some patients with ABS may experience gastrointestinal discomfort, including bloating, cramping, and abdominal pain, particularly after eating carbohydrate-rich foods.

• Nausea and Vomiting: Episodes of nausea and, in some cases, vomiting may occur, particularly when blood alcohol levels rise rapidly.

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5. Cardiovascular Symptoms

• **Palpitations**: Some individuals with ABS report experiencing palpitations or a racing heart during symptomatic episodes. This may be linked to the effects of ethanol on the cardiovascular system.

• Flushing: A sensation of warmth or redness in the face and neck (flushing) can also occur, mimicking the physical signs of alcohol consumption.

6. Respiratory Symptoms

• **Breath Odor**: Although less common, some individuals with ABS may develop a noticeable odor of alcohol on their breath, even without consuming any alcoholic beverages.

7. Legal and Social Consequences

• **DUI-like Situations**: Due to the nature of ABS, individuals may find themselves in situations where they are mistakenly suspected of driving under the influence (DUI) or other alcohol-related legal issues, despite not having consumed any alcohol.

• **Misunderstanding in Social Situations**: The signs of intoxication, such as slurred speech and impaired coordination, can lead to misunderstandings in social or professional settings, often resulting in embarrassment or social stigma.

8. Chronic Symptoms and Long-term Effects

• Chronic Fatigue: Over time, the repeated episodes of ABS can lead to chronic fatigue and a general feeling of being unwell.

• **Psychosocial Impact**: The ongoing, unexplained symptoms can have a profound psychological impact, leading to anxiety, depression, or a sense of helplessness, especially if the condition remains undiagnosed for a long time.

• Weight Loss or Nutritional Deficiencies: If dietary restrictions (e.g., avoiding carbohydrates) are necessary for symptom management, some individuals may experience weight loss or nutritional deficiencies.

9. Triggers

• **Carbohydrate-rich Meals**: Symptoms are often triggered or exacerbated after consuming meals high in carbohydrates, as these provide the substrate for microbial fermentation in the gut.

• **Stress**: Emotional or physical stress may worsen symptoms, as stress can affect gut motility and microbial balance.

LEGAL AND SOCIAL IMPLICATIONS

Legal Implications

• Driving Under the Influence (DUI) Charges: One of the most serious legal implications of ABS is the potential for being charged with driving under the influence (DUI). Since individuals with ABS can produce ethanol endogenously, they may have elevated blood alcohol levels despite not consuming any alcohol. If stopped by law enforcement and subjected to a breathalyzer or blood test, they could face DUI charges, even though they have not been drinking. Successfully defending against such charges can be challenging without proper medical documentation of ABS.

• Employment and Workplace Issues: Individuals with ABS may face legal issues related to their employment. If symptoms of intoxication appear during work hours, they could be accused of violating workplace policies regarding alcohol use, leading to disciplinary actions, termination, or legal disputes with employers. Even if ABS is diagnosed, explaining the condition and its implications to employers can be difficult.

• Child Custody and Family Law: In family law matters, individuals with ABS may face challenges in child custody disputes if their condition is misinterpreted as alcohol abuse. The perceived inability to control alcohol-related behavior, despite not consuming alcohol, could negatively impact custody decisions.

• Social Security and Disability Claims: For those severely affected by ABS, applying for disability benefits may be necessary. However, the rarity and misunderstanding of the condition may lead to denials of claims, necessitating legal representation to appeal decisions and provide adequate medical evidence of the disorder.

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Social Implications

• Stigma and Misunderstanding: One of the most profound social implications of ABS is the stigma associated with alcohol intoxication. People with ABS may be misunderstood by friends, family, colleagues, and the public, leading to social isolation and damaged relationships. The perception that someone is intoxicated, especially in inappropriate situations, can lead to judgment, ridicule, and exclusion from social or professional activities.

• Challenges in Relationships: Personal relationships can be strained by the symptoms of ABS. Partners, family members, or friends may struggle to understand the condition, leading to trust issues, frustration, and conflicts. The unpredictability of symptoms can further complicate social interactions and relationships.

• Impact on Mental Health: The social isolation and misunderstanding associated with ABS can contribute to mental health issues, such as anxiety, depression, and low self-esteem. The psychological burden of dealing with a rare and poorly understood condition can be significant, especially when individuals feel unsupported or stigmatized.

• **Public Embarrassment**: Episodes of ABS can lead to embarrassing situations in public, such as slurred speech, unsteady gait, or other signs of intoxication. These incidents can be humiliating and may deter individuals from engaging in social activities or public outings for fear of judgment.

• Loss of Professional Reputation: In professions where maintaining a clear and sober demeanor is essential, such as healthcare, law enforcement, or education, individuals with ABS may face challenges to their professional reputation. Unexplained symptoms of intoxication lead to doubts about their competence and reliability, potentially damaging their careers.^[10]

CHALLENGES IN DIAGNOSIS AND ADVOCACY

• **Difficulty in Proving the Condition**: Since ABS is rare and often misunderstood, individuals may struggle to convince others, including employers, legal authorities, or even healthcare providers, that their symptoms are due to a medical condition rather than voluntary alcohol consumption. This can lead to difficulties in obtaining the necessary support or accommodations.

• Need for Advocacy: Patients with ABS often need to become advocates for themselves, educating others about the condition and fighting for appropriate recognition and treatment. This can be exhausting and emotionally draining, especially when faced with skepticism or disbelief.^[11]

IMPACT ON DAILY LIFE

• Avoidance of Social Situations: Due to the unpredictable nature of ABS, individuals may avoid social gatherings, particularly those involving food, out of fear that symptoms will occur. This can lead to a diminished quality of life and a sense of isolation.

• **Dietary Restrictions**: Managing ABS often requires strict dietary modifications, such as avoiding carbohydrates or sugars that can trigger symptoms. These restrictions can make it challenging to participate in communal meals or cultural celebrations, further contributing to social isolation.

SUPPORT SYSTEMS

• Importance of Education and Awareness: Educating those around them, including family, friends, and colleagues, about ABS can help reduce stigma and foster understanding. Awareness campaigns and support groups may be beneficial in connecting individuals with ABS to others who share their experiences.

• Legal and Medical Support: Individuals with ABS may benefit from seeking legal counsel, particularly if they face legal challenges related to their condition. Additionally, working with healthcare providers who are knowledgeable about ABS can help in obtaining proper documentation and treatment.^[11]

CONCLUSIONS

Auto-brewery Syndrome (ABS) is a rare and complex condition characterized by the endogenous production of

ethanol within the body, leading to symptoms of alcohol intoxication without alcohol consumption. Despite its rarity, ABS can have profound medical, legal, and social implications, making it a challenging condition to diagnose and manage.

This comprehensive review has highlighted the multifaceted nature of ABS, from its elusive causes and pathophysiology to the difficulties in obtaining an accurate diagnosis. The condition's unpredictability and the wide range of symptoms it presents often lead to misdiagnosis and misunderstanding, both by healthcare providers and the public.

The legal and social implications of ABS are significant, impacting various aspects of an individual's life, including their personal relationships, professional reputation, and even their legal standing. The stigma associated with intoxication-like symptoms and the challenges of proving the condition in legal and social settings further complicate the lives of those affected by ABS.

Despite these challenges, awareness of ABS is growing, and advancements in medical understanding and diagnostic techniques offer hope for better management and support for individuals with this condition. Early recognition, accurate diagnosis, and a multidisciplinary approach to treatment are essential for improving outcomes.

Ultimately, greater education and awareness among healthcare providers, legal professionals, and the public are needed to reduce the stigma and misunderstandings associated with ABS. By fostering a more supportive environment and advocating for proper recognition of the condition, those affected by ABS can lead more fulfilling and less burdened lives. Further research into the causes, diagnosis, and treatment of ABS is crucial to better understand this rare condition and provide more effective care for patients.

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DECLARATION OF COMPETING INTEREST

The authors declare that they have no competing interests.

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