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Cholelithiasis Prevalence and Risk Factors in Individuals with Severe or Profound Intellectual and Motor Disabilities

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Data are available upon request from the corresponding author

Ethics approval statement (for studies involving animal subjects and/or human participants)

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Cholelithiasis Prevalence and Risk Factors in Individuals with Severe or Profound Intellectual and Motor Disabilities

Abstract

Background: The prevalence and risk factors of cholelithiasis in individuals with severe or profound intellectual and motor disabilities (SPIMD) are poorly characterised. Thus, we aimed to investigate the prevalence and risk determinants of cholelithiasis in a cohort with SPIMD under medical care in a residential facility.

Method: We categorised 84 patients in a residential hospital for persons with SPIMD into groups: those with (Group CL) and without (Group N) cholelithiasis. Gallstones were detected via computed tomography, ultrasonography, or both. We evaluated gastrostomy status, nutritional and respiratory support, constipation, and bladder and kidney stones. Data were significantly analysed using univariate and multivariate logistic regression analyses.

Results: The prevalence rate of cholelithiasis in our SPIMD cohort was 27%. Sex, age, weight, height, or Gross Motor Function Classification System scores between the groups. However, more patients received enteral nutrition (39.13% *vs*. 6.56%, P = .000751) and were on ventilator support (56.52% *vs*. 19.67%, P = .00249) in Group CL than in Group N. Enteral nutrition (odds ratio [OR] 10.4, 95% confidence interval [CI] 1.98–54.7) and ventilator support (OR 20.0, 95% CI 1.99–201.0) were identified as independent risk factors for the prevalence of cholelithiasis in patients with SPIMD.

Conclusions: Patients with SPIMD demonstrated an increased prevalence of cholelithiasis, with a notable association between nutritional tonic use and respiratory support. Therefore, to emphasise the need for proactive screening, it is crucial to devise diagnostic and therapeutic strategies specific to patients with SPIMD. Further investigation is essential to validate our findings and explore causative factors.

Keywords: gallstones; severe or profound intellectual and motor disabilities; prevalence; risk factor

Background

Cholelithiasis is a significant health issue with well-established risk factors, such as obesity, rapid weight loss, dietary habits, age, sex, familial background, ethnicity, and certain diseases in the general population, including diabetes and cirrhosis (Fujita et al. 2023, Amorim-Cruz et al. 2023, Song et al. 2020, Littlefield and Lenahan 2019, Di Ciaula et al. 2019, Mayumi et al. 2018, Zhang et al. 2017, Pak and Lindseth 2016, Lammert et al. 2016, Wong and Ko 2013, Kitamura and Ogino 2011, Sanders and Kingsnorth 2007, Shaffer 2006, Halldestam et al. 2004). The estimated prevalence of cholelithiasis varies geographically and with populations. For example, the prevalence of gallstones is 14%–20% in Europe and the USA, but lower in East Asia, particularly in Japan, where it is 4%–10% (Unalp-Arida et al. 2023, Ferkingstad et al. 2018, Higashizono et al. 2022, Fujita et al. 2021, Index of Health 1993).

The global prevalence of cholelithiasis among children aged <18 years has increased to 1.9%–4%. This might be linked to an increased rate of childhood obesity as well as dietary factors and the extensive use of ultrasound for diagnostic purposes (Jeanty et al. 2015, Parra-Landazury et al. 2021, Krawczyk et al. 2023, Zdanowicz et al. 2022, Fujita et al. 2021). However, the specific prevalence and risk factors of cholelithiasis in individuals with severe or profound intellectual and motor disabilities (SPIMD) defined as a combination of severe physical disability and severe mental retardation due to conditions including cerebral palsy (CP) and neuromuscular disorders, are largely unknown (Zuo et al. 2022, van Timmeren et al. 2017).

Patients with SPIMD have a high incidence of gastrointestinal disorders and respiratory-related complications, such as pneumonia, and are particularly prone to severe and prolonged infections that require a more detailed diagnosis and treatment (van Timmeren et al. 2016, Hermans and Evenhuis 2014, van Schrojenstein Lantman-de Valk and Walsh 2008). Additionally, patients with SPIMD are prone to multiple comorbidities that complicate their condition (van Timmeren et al. 2016). Therefore, each disease needs to be detected early to ensure appropriate intervention.

Cholelithiasis is a potential disease for patients with SPIMD but may be difficult to accurately diagnose due to physical abnormalities such as scoliosis and a limited ability to clearly express or understand physical symptoms (Zuo et al. 2022). Furthermore, implementing appropriate surgical or endoscopic treatment is difficult because of the risk of complications associated with sedation, general anaesthesia, or physical abnormalities such as severe scoliosis (Khalid and Al-Salamah 2006). Therefore, there is an urgent need to clarify the epidemiology and risk factors of cholelithiasis in patients with SPIMD to prevent the disease and assist in early detection. However, to the best of our knowledge, only one study has focused on patients with SPIMD (Zuo et al. 2022). Thus, we aimed to determine the prevalence of cholelithiasis in this unique population, identify risk factors, and assess the prevalence of symptoms and complications among patients with severe mental and physical disabilities residing in welfare facilities.

Methods

We retrospectively reviewed charts of patients from the Niko Niko House Medical Welfare Center, which is a residential facility that provides full-time care exclusively for persons with SPIMD resulting from diverse aetiologies. These include congenital conditions such as CP, as well as acquired infections and neurological disorders. The prevalence of gallstones was determined from medical records collected between 1 January 2020 and 1 January 2021 to better understand variations in gallstone diagnoses. Charts with insufficient medical record data were excluded.

Diagnoses of cholelithiasis were determined from a combination of CT and ultrasound examinations, which are more sensitive and specific for gallstone detection, between 1

January 2020 and 31 December 2020. This approach enhanced the accuracy of our prevalence data (Fujita et al. 2023, Mayumi et al. 2018, Lammert et al. 2016). Data from 84 residents (median age, 42.5 [5–76] years) were included and assigned to Group CL (n = 23; 27%) and Group N (n = 61; 73%). We assigned the residents to groups with (CL) and without (N) cholelithiasis to investigate potential risk factors. Individuals presenting solely with biliary sludge were included in Group N.

We analysed the following established factors that have been validated by similar studies: body mass index (BMI); Gross Motor Function Classification System (GMFCS) data; presence of epilepsy, minimal communication skills (van Timmeren et al. 2017), cardiac disease, diabetes, constipation (defined as the use of an enema at least once a day), bladder stones, kidney stones; and history of gastrostomy, fundoplication for gastroesophageal reflux, nutritional support, and respiratory support (tracheostomy, ventilator management, or non-invasive positive pressure ventilation) (Fujita et al. 2023, Amorim-Cruz et al. 2023, Pak et al. 2016). Oral intake was defined as the intake of food or beverages at least once a day, regardless of the form, amount, or frequency, with or without enteral nutrition use, total caloric intake (defined as daily caloric intake), and total fluid intake (defined as daily fluid intake).

This study was approved by the ethics review committee of the institution (protocol no. B210086). Written informed consent was obtained from parents., family members, or guardians.

Statistical analysis

Continuous variables are presented as mean ± standard deviation and were compared using the Mann–Whitney U test. Categorical data were analysed using Fisher’s exact tests. The risk factors for cholelithiasis in patients with SPIMD were analysed using univariate logistic regression to derive odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Variables with $p < .05$ in univariate analysis were included in multivariate models.

All statistical analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a modified version of R Commander (version 1.55) customised for biostatistics. Differences were considered statistically significant at $p < .05$.

Results

Patient demographics and clinical characteristics are shown in Table 1. The prevalence of cholelithiasis in our SPIMD cohort was 27%. One and four patients in Groups CL and N were aged <18 years, among whom 1 (20%) in Group CL had gallstones. The causes of SPIMD in the study population comprised neuromuscular diseases (n = 33), CP (n = 23), hypoxic encephalopathy (n = 14), and infections (n = 7). One patient in Group CL had Herpes encephalitis (n = 1). Group N contained one patient each with congenital Cytomegalovirus infection, and sequelae of purulent meningitis, measles encephalitis, and Japanese encephalitis; two had congenital Rubella syndrome (n = 2); and seven had chromosomal abnormalities. The causes of SPIMD did not significantly differ between the two groups. All patients underwent abdominal ultrasonography, abdominal CT, or both. Demographic parameters such as mean age (43.57 ± 15.62 *vs*. 42.64 ± 15.82 years; p =.80), mean weight (39.51 ± 8.04 *vs*. 36.78 ± 9.35 kg; p = .2), mean height (153.79 ± 12.46 *vs*. 149.61 ± 15.52 cm; p = .25), and mean BMI (16.69 ± 2.71 *vs*. 16.41 ± 3.83 kg/m^2; p = .75) did not significantly differ between the groups even when accounting for patients with a BMI of >25 kg/m^2 (classified as obese). Sex distribution between the groups (19 males and 4 females in Group CL vs. 37 males and 24 females in Group N) also did not significantly differ (p = .072).

Epilepsy was a prevalent comorbidity that did not significantly differ between Groups CL and N (n = 20 [86.96%] *vs*. 52 [85.3%]), (p = 1.0). Other comorbidities, such as impaired communication (p =.20), cardiac disease (p = 1.0), diabetes (p = .48), bladder stones (p = .60), and urinary stones (p=.50), also did not significantly different. However, there was a significant difference was observed in tracheostomy/laryngotracheal separation (p=.024) and ventilator support (p=.0025), both of which were significantly higher in Group CL than in Group N. Furthermore, patients in Group CL had a significantly higher reliance on enteral nutrition than those in Group N (39.1% *vs*. 6.56%; p = .00075).

Regarding gastrostomy and fundoplication procedures, no significant differences were found between the groups (n = 13 *vs*. 20, p = .34; and 21.7% *vs*. 24.6%, p = 1.0, respectively). Constipation was equally prevalent in both groups (78.3% in Group CL *vs*. 80.3% in Group N; p=1.0). Total calorie intake per weight and total water intake per weight did not differ significantly between the groups (28.82 ± 7.59 *vs*. 32.99 ± 10.91; p = .096 and 33.43 ± 15.72 *vs*. 31.07 ± 13.34; p = .49, respectively). Biliary inflammatory diseases, such as cholecystitis and cholangitis developed in 6 (26%) of 23 residents in Group CL with a mean age of 41.1 (16–68) years. These residents had clinical symptoms of fever and an increased heart rate, but no abdominal tenderness, recurrent pain, general malaise, or visible jaundice. Cholecystitis and cholangitis were suspected based on elevated biliary enzymes and blood levels of inflammatory markers. The diagnosis was confirmed based on findings of ultrasonography and other imaging modalities. Cholecystitis in all six affected patients was severe enough to require cholecystectomy, and two of them also required preoperative endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic gallbladder drainage (PTGBD). The severity of cholecystitis was confirmed during surgery. Only 1 of the 61 patients in Group N developed biliary inflammatory disease, presenting with fever and tachycardia. This patient’s condition improved with conservative treatment, and cholecystectomy was avoided.

Multivariate analyses of the prevalence of cholelithiasis in residents with SPIMD

Results of multivariate logistic regression analysis demonstrated that the risk factors for the prevalence of cholelithiasis in patients with SPIMD were enteral nutrition (OR 10.4, 95% CI 1.98–54.7) and ventilator support (OR 20.0, 95% CI 1.99–201.0).

Tracheostomy/laryngotracheal separation was not significant after adjustment for ventilator support (OR 0.16, 95% CI 0.014–1.82) (Table 2).

Discussion

We investigated the prevalence of cholelithiasis and risk factors in a cohort of residents at a facility that specifically provides care for patients with SPIMD. We found a high prevalence of cholelithiasis and identified the key risk factors, i.e., enteral nutrition, and ventilator support. This emphasised the need for proactive screening and specialised care for this population and calls for more research to understand the underlying causes.

The prevalence of cholelithiasis in our cohort of SPIMD is 27%, which surpassed that of 4%–10% found in Japanese cohorts without SPIMD (Higashizono et al. 2022, Fujita et al. 2021, Index of Health 1993). The incidence of acute cholecystitis or cholangitis in patients with SPIMD accompanied by cholelithiasis is 25%, which is significantly higher than the general incidence of cholelithiasis in patients with acute cholecystitis or cholangitis (1%–2%) (Fujita et al. 2023, Littlefield and Lenahan 2019, Mayumi et al. 2018, Lammert et al. 2016). These results emphasise the need for increased vigilance in the management of patients with SPIMD for cholelithiasis and gallstone-related symptoms.

In this study, sex, age, weight, height, and GMFCS scores did not significantly differ between patients with and without cholelithiasis. The lack of an association between these factors and cholelithiasis in our SPIMD cohort contradicted findings of the general population, where age, sex, and obesity are established important risk factors (Fujita et al. 2023, Amorim-Cruz et al. 2023, Song et al. 2020, Littlefield and Lenahan 2019, Di Ciaula et al. 2019, Mayumi et al. 2018, Zhang et al. 2017, Pak and Lindseth 2016, Lammert et al. 2016, Wong and Ko 2013, Kitamura and Ogino 2011, Sanders and Kingsnorth 2007, Shaffer 2006, Halldestam et al. 2004). This discrepancy might be due to a specific pathophysiological mechanism in the SPIMD population or the result of the small sample size. Further studies with larger cohorts are required to clarify whether sex, age, weight, height, and GMFCS scores or age, sex, and obesity are risk factors that also apply to patients with SPIMD.

The frequency of dietary supplement intake at least once a day significantly differed between the groups. This suggested that supplements play roles in gallstone formation. Enteral nutritional supplements, which often contain carbohydrates with a high glycaemic index, may contribute to gallstone formation *via* a hyperinsulinaemic mechanism (Wong and Ko 2013). Serum sphingolipids are potential biomarkers of cholelithiasis in children (Zdanowicz et al. 2022). This biomarker might be useful as an early diagnostic tool for SPIMD populations because nutritional supplements for patients with SPIMD contain ingredients derived from milk and soy that are rich in sphingolipids. Increased contents of specific sphingolipids might also elevate the risk of gallstone formation. Therefore, patients with SPIMD using nutritional supplements might be at a higher risk of developing gallstones (Zdanowicz et al. 2022). Regarding enteral nutrition, gastrostomy and fundoplication did not significantly correlate between the groups. However, vagal nerve damage due to fundoplication is involved in gallstone formation (Sallum et al. 2015, Stahlgren et al. 1980), and further investigation is warranted. No significant association was found between constipation and its management in the present study. Despite these findings, the exact underlying mechanism and relationship between enteral nutrition and gallstone formation remain unclear, and further studies are essential to validate and elucidate the potential mechanisms.

In patients with SPIMD, a history of tracheostomy or laryngotracheal separation and the need for respiratory assistance, especially mechanical ventilation, are associated with a higher risk of gallstone formation. This is consistent with previous findings of a higher incidence of cholelithiasis and cholecystitis in patients with SPIMD who are dependent on invasive ventilation through long-term tracheostomy (Kitamura and Ogino 2011). However, the close correlation between tracheostomy and respiratory assistance, such as laryngotracheal isolation and mechanical ventilation, and possible correlations with other risk factors, such as prolonged bed rest might be significant confounding factors. These factors interfered with our ability to identify precise mechanistic associations between respiratory support and gallstone formation.

In severe cases of acute cholecystitis, various therapeutic approaches, such as PTGBD, were necessary. The high degree of inflammation encountered during cholecystectomy increases the complexity of routine surgical procedures and prolongs the surgical duration. This highlights the complications and severity associated with gallbladder disease.

We evaluated 6 (25%) of 24 patients with acute cholecystitis that was treated by cholecystectomy. The age at the onset of acute cholecystitis was 41.1 years, which is younger than the average age at onset in the general population (50–60 years) (Fujita et al. 2023, Amorim-Cruz et al. 2023, Song et al. 2020, Littlefield and Lenahan 2019). The details of these patients could not be obtained from medical records. A 54-year-old female with detailed information was diagnosed late because of a lack of symptoms other than fever and required PTGBD before cholecystectomy and endoscopic retrograde cholangiopancreatography at a later date due to severe cholecystitis, requiring more than 2 months of hospitalisation.

The period between the onset of acute cholecystitis and the start of treatment is an important factor that influences patient outcomes. Considering the higher prevalence of cholelithiasis and acute cholecystitis in patients with SPIMD than in the general population, early detection and timely intervention are important to prevent the progression of acute cholecystitis to life-threatening sepsis (Fujita et al. 2023, Amorim-Cruz et al. 2023, Song et al. 2020, Littlefield and Lenahan 2019). Therefore, regular and proactive monitoring of these patients for early signs and symptoms is essential to enable timely intervention and optimise their clinical outcomes.

This study has some limitations. First, this was an observational study conducted at a single institution, which could introduce potential selection bias. Additionally, our conclusions were based on a small number of patients, underscoring the need for further investigations to establish definitive relationships between the diagnostic difficulty or severity of acute cholecystitis and the necessity for cholecystectomy. The retrospective nature of this study also warranted consideration, and the presence of missing data, such as information regarding the type of cholelithiasis and treatment specifics, could have influenced the outcomes. To gain a more comprehensive understanding of the risk and pivotal factors for cholelithiasis in SPIMD populations, future prospective and broad-ranging studies should provide clearer insights into the subject matter.

In conclusion, we found a higher prevalence of cholelithiasis and incidence of acute cholecystitis in persons with SPIMD than in the general population and that ventilator support and use of enteral nutrition were risk factors for cholelithiasis in patients with SPIMD. We believe that this comprehensive understanding of the prevalence and risk factors for cholelithiasis in patients with SPIMD may contribute to the development of prevention strategies and therapeutic interventions for cholelithiasis in such patients. These findings have clinical implications that may require further investigations in larger cohorts to advance our understanding of the pathophysiology of SPIMD.

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Table 1. Patient demographics and clinical characteristics.

Parameter	Group CL	Group N	p
Number of patients	23	61	-
Male sex	19 (82.6%)	37 (60.7%/)	.07
Age (years, mean ± SD)	43.6 ± 15.6	42.6 ± 15.8	.8
Weight (kg, mean ± SD)	39.5 ± 8.0	36.8 ± 9.4	.2
Height (cm, mean ± SD)	153.8 ± 12.5	149.6 ± 15.5	.25
Body mass index (kg/m^2 mean ± SD)	16.7 ± 2.7	16.41 ± 3.8	.75
Diagnosed causes of SPIMD			
Neuromuscular diseases	13 (48.1%)	20 (32.8%)	.078
Infection	1 (4.3%)	6 (9.8%)	.668
Hypoxia encephalopathy	6 (22.2%)	8 (13.1%)	.19
Cerebral palsy	6 (22.2%)	17 (28.9%)	1.0
Chromosomal abnormality	0 (0%)	7 (11.5%)	.18
GMFCS scores			.231
Level 1	0 (0%)	0 (0%)	
Level 2	0 (0%)	1 (1.6%)	
Level 3	1 (4.3%)	11 (18.0%)	
Level 4	4 (17.4%)	15 (24.6%)	
Level 5	18 (78.3%)	34 (55.7%)	
Epilepsy	20 (87.0%)	52 (85.3%)	1.0
Minimal communication skills	13 (56.5%)	44 (72.1%)	.2
Cardiac disease	0 (0%)	1 (1.6 %)	1.0
Diabetes	1 (9.1%)	1 (6.7%)	1.0
Bladder stones	2 (8.7%)	3 (4.9%)	.6
Urinary stones	5 (21.7%)	11 (18%)	.758
Tracheostomy/LTS	10(43.5%)	11(18%)	.024
Ventilator support	10 (43.5%)	9 (14.3%)	<.001
Constipation	18 (78.3%)	49 (80.3%)	1.0
Gastrostomy	13(56.5%)	27(44.3%)	.34
Fundoplication	5 (21.7%)	15 (24.6%)	1.0
Oral intake	11 (47.8%)	41 (67.2%)	.13
Enteral nutrition	9 (39.1%)	4 (6.5%)	<.001
TCI/W (mean ± SD)	28.8 ± 7.59	33.0 ± 10.9	.096
TWI/W (mean ± SD)	33.4 ± 15.7	31.1 ± 13.3	.49

LTS, history of laryngotracheal separation; SPIMD, severe or profound motor and intellectual disabilities; TCI/W, total calorie intake/weight; TWI/W, total water intake/weight.

Table 2. Logistic regression of cholelithiasis prevalence in patients with SPMID.

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Male sex	3.08 (0.93–10.2)	.06		
Age (>40 years)	0.75 (0.25–2.13)	.64		
GMFCS (4–5)	0.19 (0.004–1.42)	.10		
Epilepsy	1.15 (0.25–7.23)	1.00		
Minimal communication skill	0.51 (0.17–1.55)	.20		
Oral intake	0.45 (0.17–1.19)	.11		
Gastrostomy	1.64 (0.62–4.31)	.32		
Tracheostomy/LTS	3.50 (1.22–10.0)	.02*	0.16 (0.014–1.82)	.14
Enteral nutrition	12.4 (2.97–52.0)	<.01†	10.4 (1.98–54.7)	<.01†
Bladder stones	1.26 (0.39–4.14)	.70		
Urinary stones	1.60 (0.37–6.19)	.52		
Ventilator support	7.51 (2.53–22.3)	<.01†	20.0 (1.99–201.0)	.011*
Constipation	0.93 (0.26–3.84)	1.00		

*$P < .05$, †$P < .01$. GMFCS, Gross Motor Function Classification System; LTS, laryngotracheal separation; SPMID: severe or profound motor and intellectual disabilities.