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Biotin-Thiamine-Responsive Basal Ganglia Disease: Clinical Features, Treatment Response and Predictive Factors in a Cohort in a Tertiary Hospital

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Abstract

Introduction: Biotin-thiamine-responsive basal ganglia disease (BTBGD) is a neuroregressive disorder associated with subacute encephalopathy, confusion, dysarthria, and dysphagia, as well as occasional external ophthalmoplegia or supranuclear facial nerve palsy. It may progress to severe rigidity, dystonia, and quadriparesis. Combination therapy of high-dose thiamine and biotin helps to control the symptoms and prevent progression of the disease. **Methods:** This retrospective, cross-sectional study was conducted at King Fahad Medical City in Riyadh, Saudi Arabia, to investigate the demographic, clinical features, treatment response, outcomes, and predictive factors of BTBGD in the pediatric population. **Results:** Twenty-five records of pediatric patients diagnosed with BTBGD were included in the study. The most common symptoms observed at presentation were ataxia in 13 patients (52%), followed by developmental regression in 11 patients (44%), and seizures in 7 patients (28%). Statistically significant associations were found between patient's age of presentation, seizures at presentation, lactate level and their health outcomes. Multivariate logistic regression analysis revealed significant differences in patient outcomes (prognosis) based on their age at presentation, seizures, and lactate levels ($p < 0.001$); with lactate levels found to be 0.211 times likely to predict patient outcomes. Furthermore, age at first presentation and the presence of seizures were associated with negative health outcomes, with regression coefficients of $B = -0.009$ and $B = -0.561$, respectively. **Conclusion:** This study reported BTBGD in 25 pediatric patients in Saudi Arabia. Age at presentation, seizures, and lactate levels were found to be significantly associated with patient health outcomes. Increasing public awareness of the condition, particularly

among parents and pediatricians, is imperative. Early diagnosis, along with timely management using biotin and thiamine supplementation, promotes improved health outcomes and prevents progressive neurodegeneration and death.

Keywords

Biotin-Thiamin-Responsive Basal Ganglia Disease, Neuroregression, Neurometabolic, Biotin, Thiamine

1. Introduction

Biotin-thiamine-responsive basal ganglia disease (BTBGD), also known as thiamine metabolism dysfunction syndrome-2 (THMD2) (OMIM: 607483), is an autosomal recessive inherited neurometabolic disorder [1] [2]. It was first described by Ozand *et al.* in 10 patients and renamed biotin thiamine-responsive basal ganglia disease by Alfadhel *et al.* in 2013 [2]. A vague history of a febrile illness and neuroregression with sub-acute encephalopathy, confusion, dysarthria, and dysphagia, as well as an occasional external ophthalmoplegia or supranuclear facial nerve palsy that progresses to severe cogwheel rigidity, dystonia, and quadriparesis, are the disease's characteristics [1] [2]. The disease was discovered to be caused by a mutation in the SLC19A3 gene, which codes for hTHTR2, a second thiamine-transporter, in 2005, and was mapped to chromosome 2q36.3 [1]-[3].

Three stages are defined in BTBGD: stage 1, a sub-acute encephalopathy frequently brought on by a febrile illness; stage 2, an acute encephalopathy accompanied by seizures, loss of motor function, developmental regression, dystonia, external ophthalmoplegia, dysphagia, and dysarthria; and stage 3, a chronic or slowly progressing encephalopathy [4]. Depending on the age of onset, pathogenic variants in SLC19A3 gene mutations cause 4 different clinical pictures, including: Leigh syndrome-like phenotype characterized by acute encephalopathy and lactic acidosis in the neonatal period [5], a severe disease occurring in early infancy characterized by epileptic spasms, severe psychomotor retardation, progressive brain atrophy and bilateral thalamus and basal ganglia lesions [6]; Biotin-thiamine-responsive basal ganglia disease in childhood [7]; Wernicke's encephalopathy-like condition in the second decade of life [5]-[7].

The diagnosis requires a high index of suspicion and is supported by the patient's medical history, neurologic clinical features, and abnormal signal hyperintensities in the caudate and putamen on magnetic resonance imaging (MRI), as well as widespread cortical and subcortical white matter involvement throughout the brain and infratentorial regions, with less frequent involvement of the thalamus, brain stem, cerebellum, and cervical spine [1] [2]. Due to the similarities in clinical, biochemical, and MRI findings, BTBGD can be mistakenly diagnosed as a mitochondrial disease. These MRI findings do resemble those of Leigh disease

or Gayet-Wernicke encephalopathy [8]. To help with early diagnosis and prompt therapeutic intervention, biochemical markers are required [9]. Measurement of the free thiamine level in cerebrospinal fluid (CSF) and fibroblasts may be a useful biomarker for both diagnosis and treatment [1] [2] [10]-[12]. About 5 to 10 mg/kg/d of biotin and 40 mg/kg/d of thiamin should be started as soon as the diagnosis is suspected and continued for life [13]. This combination of therapy maintains a good prognosis and minimizes the risk of crisis [13]. The timing of the diagnosis and the start of treatment affects the overall neurological and psychological outcome [2] [13] [14].

Despite this condition being almost universally known and being misdiagnosed, there is insufficient research on its clinical features and prognosis, particularly in populations with high consanguinity, like Saudi Arabia. Region-specific studies would provide a foundation for a more targeted and effective intervention. Therefore, this retrospective study aimed to assess the clinical features, treatment response, and predictive factors of BTBGD in the pediatric population of Riyadh, Saudi Arabia.

2. Methodology

2.1. Study Design

This retrospective study included pediatric patients under 14 years of age who were diagnosed with BTBGD between January 2000 and January 2023 at King Fahad Medical City, Riyadh, Saudi Arabia. The study aimed to assess the clinical features, treatment response, and predictive factors of BTBGD in this population.

2.2. Inclusion and Exclusion Criteria

The inclusion criteria for this study included available and complete medical records of all patients aged under 14 years with positive genetic confirmation of BTBGD. Conversely, the exclusion criteria encompassed medical records of patients older than 14 years, incomplete records and the cases where BTBGD was not the final diagnosis during the study period.

2.3. Sampling Technique

This study used a non-probability purposive sampling technique, including patient records with a final diagnosis of BTBGD during the study period to minimize selection bias.

2.4. Sample Size

The study included 25 complete medical records of pediatric patients under 14 years old who were diagnosed with BTBGD over the past 23 years.

2.5. Data Collection Tools and Procedures

A pre-designed checklist was used to collect: patients' demographic and clinical

characteristics such as gender, age of presentation, symptoms at presentation, genetic testing, consanguinity, serum lactate level (if high or normal), MRI, treatment and outcome.

2.6. Data Analysis

After completion of data collection, data was first entered into an Excel database for the initial cleaning process, which included identifying and removing outliers, duplicates, and typos in entries. After cleaning, the data was coded and transferred to SPSS version 23 for analysis. Qualitative data was presented as frequency and percentages, while quantitative data was expressed as minimum, maximum, means, standard deviations (SD), median and interquartile range. Fisher's Exact test was used to test for the presence of association between categorical variables. The non-parametric test Mann-Whitney U test was utilized to assess the presence of association between age and prognosis due to the non-normal distribution of age variable. Univariate logistic regression was used to determine the risk factors for having a poor outcome. Based on the significant results, a multivariate regression analysis was subsequently performed to determine the significant independent factor of poor outcome, with corresponding odds ratios and 95% confidence intervals. Statistical significance was identified at $p < 0.05$.

2.7. Ethical Considerations

Ethical clearance was obtained from King Fahad Medical City, Riyadh ethics committee before data collection. The researcher adhered to privacy and confidentiality by excluding the patients' personally identifiable information and preventing any linkage between the patients' identities and study outcomes. The researcher ensured that the data was securely stored with restricted access to only authorized persons.

3. Results

Of the 25 patients included in the study, a considerable proportion 15 (60%) of them were females while about 10 (40%) of them were males. The ages at the time of presentation ranged from a minimum of 1 month to a maximum of 120 months. The mean age was 34.88 ± 27.98 months, the median was 36 months, and the interquartile range was 36 months (**Table 1**).

The most common symptoms observed at presentation were ataxia in 13 patients (52%), followed by developmental regression in 11 patients (44%), seizures in 7 patients (28%), and asymptomatic cases in 4 patients (16%) (**Figure 1**). It was observed that most of the children (22, 88%) had normal development prior to presentation, while 3 (12%) had their developmental affected (**Figure 2**). The consanguinity status among the parents showed that the majority of patients (23, 92%) had consanguineous parents, while about 2 (8%) had non-consanguineous parents (**Figure 3**). All 25 (100%) patients had positive result for SLC19A3 gene mutation.

Table 1. Socio-demographic profile of the patients (n = 25).

Question	n	%
Gender		
Male	10	40
Female	15	60
Age (in months) at Time of Presentation		
Minimum	1	
Maximum	120	
Mean	34.88	
Standard Deviation	27.98	
Median	36	
Interquartile Range	36	

Socio-demographic information is presented in frequencies (n) and proportion (%).

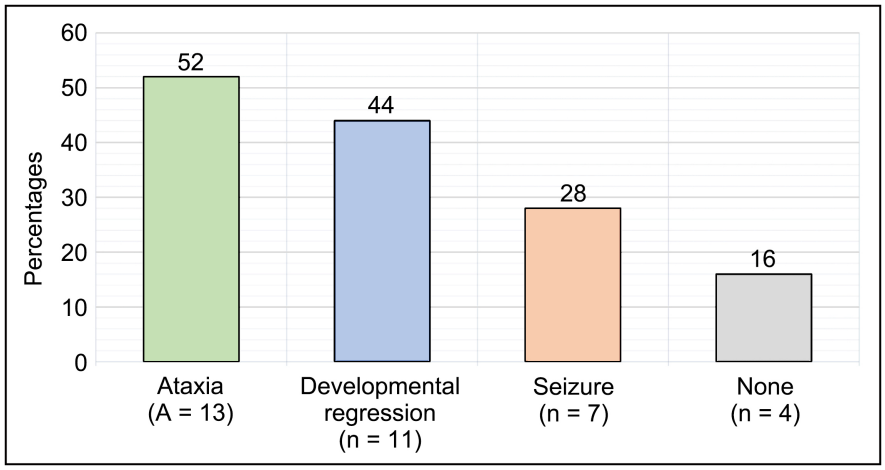

Figure 1. Patients' symptoms at presentation.

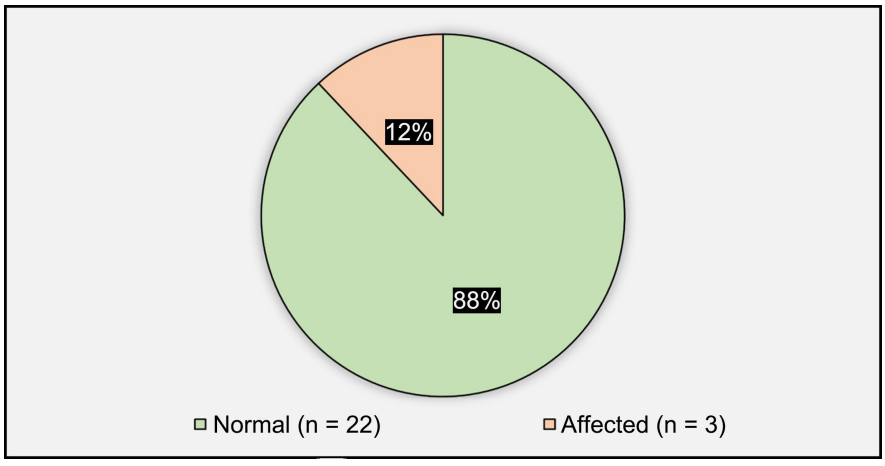

Figure 2. Development status prior to presentation.

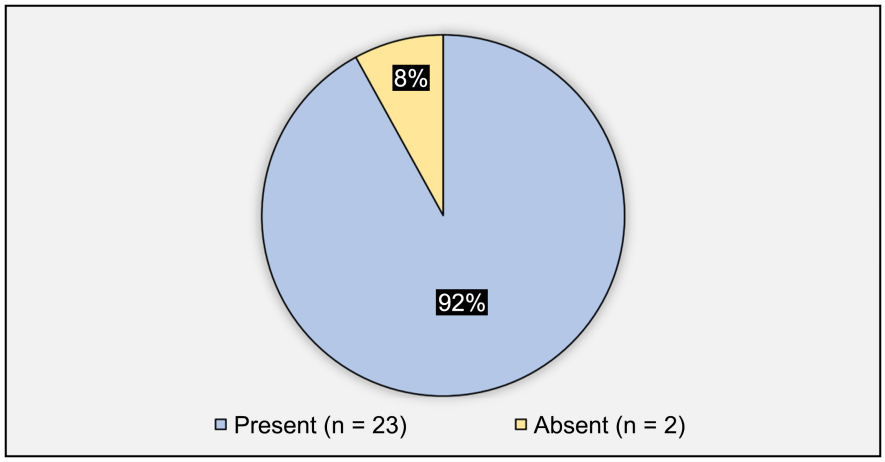

Figure 3. Consanguinity status among the patients' parents.

Table 2. Investigation profile (n = 25).

Question	n	%
Genetic Testing		
Positive Testing for SLC19A3 Gene Mutation	25	100
Lactate		
Not Done	12	48
Normal	8	32
High	5	20
MRI		
Not Done	4	16
Basal Ganglia Involvement	18	72
Other	2	8
Unremarkable	1	4

Investigation profile of patients is presented in frequencies (n) and proportion (%).

Lactate was not done for 12 (48%) patients, was normal for 8 (32%), and was elevated for 5 (20%). MRI brain was not done for 4 (16%), showed basal ganglia involvement in 18 patients (72%), other findings in 2 (8%), and was unremarkable in 1 (4%) (**Table 2**). About 23 (92%) patients received the specific treatment, 1 (4%) did not receive specific treatment (passed away before starting the treatment), and 1(4%) had the treatment stopped (parents' decision) (**Figure 4**). About 17 (68%) of the patients improved (full recovery, no residual disability), 6 (24%) were affected (improved with residual disability), and 2 (8%) passed away (**Figure 5**). Age of presentation (in months) was significantly associated with outcome ($p = 0.001$), where it was observed that those who improved had higher age at the time of presentation, compared to those who did not improve (median = 36 and

interquartile range = 23 for those who improved, and median = 6, and interquartile range of 27 for those who did not improve). Seizures at presentation were significantly associated with poor outcome as well (p = 0.017), where it was observed that those with seizure at time of presentation had lower rate of improvement compared to those who did not (28.6% vs 83.6%). Lactate level was also significantly associated with outcome (p = 0.032), as those with high level of lactate had lower rate of improvement compared to those with normal level of lactate (20% vs 87.5%) (Table 3). Gender, ataxia at the time of presentation, developmental regression at time of presentation, developmental status or consanguinity was not significantly associated with outcome (Table 4). The ANOVA results from the multiple regression analysis of patient outcomes, based on their age at presentation, seizures and lactate. The results indicate that the differences between these groups were statistically significant (p < 0.001). This suggests that the three attributes explain the variation in patients' outcomes (Table 5).

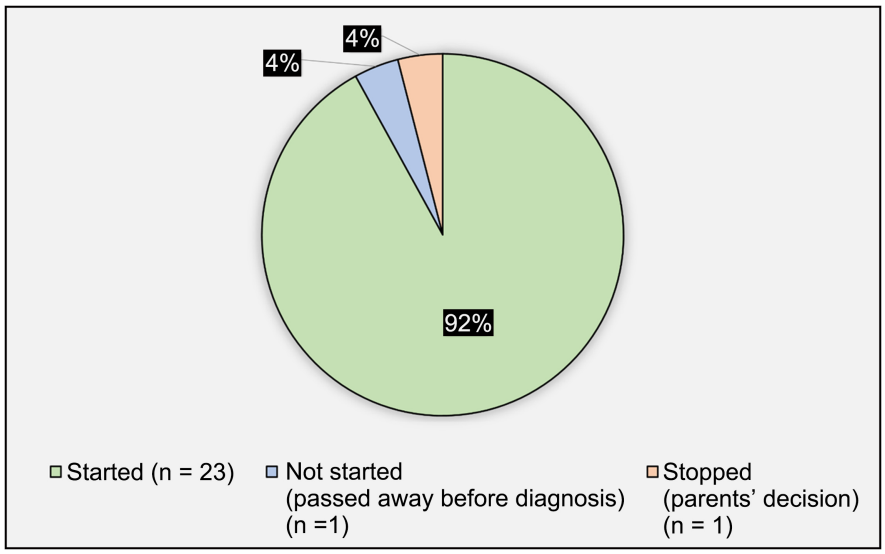

Figure 4. Treatment.

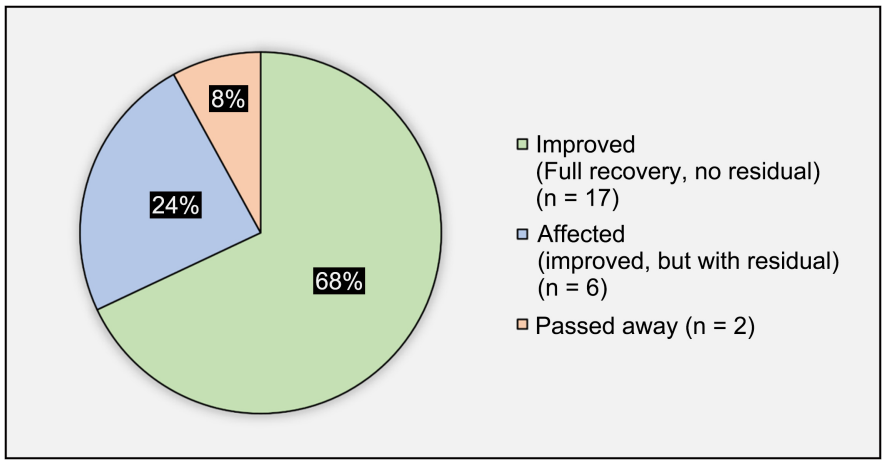

Figure 5. Outcome.

Table 3. Factors associated with outcome.

Factor	Outcome		P-value
	Improved	Not Improved (Affected/Died)	
Age in Months (Median, Interquartile Range)	36 + 23	6 + 27	0.001*
Gender (n, %)			
Male	7 (70%)	3 (30%)	0.861
Female	10 (66.7%)	5 (33.3%)	
Presence of Ataxia at Presentation (n, %)			
Yes	10 (76.9%)	3 (23.1%)	0.411
No	7 (58.3%)	5 (41.7%)	
Presence of Developmental Regression at Presentation (n, %)			
Yes	6 (54.5%)	5 (45.5%)	0.389
No	11 (78.6%)	3 (21.4%)	
Presence of Seizure at Presentation (n, %)			
Yes	2 (28.6%)	5 (71.4%)	0.017*
No	15 (83.3%)	3 (16.7%)	
Having No Symptom (n, %)			
Yes	4 (100%)	0 (0%)	0.269
No	13 (61.9%)	8 (38.1%)	
Development status prior to presentation (n, %)			
Normal	16 (72.7%)	6 (27.3%)	0.231
Affected	1 (33.3%)	2 (66.7%)	
Consanguinity (n, %)			
Present	17 (73.9%)	6 (26.1%)	0.093
Affected	0 (0%)	2 (100%)	
Lactate (n, %)			
Normal	7 (87.5%)	1 (12.5%)	0.032*
High	1 (20%)	4 (80%)	

Factors associated with outcome presented in frequencies (n) and proportion (%); *Significant at level 0.05.

Table 4. Univariate logistic regression (factors predicting poor outcome).

Factor	P-value	Odds Ratio	Confidence Interval	
Age	0.012*	0.91	0.84	0.98
Gender (Male vs Female)	0.861	0.86	0.15	4.82
Presence of Ataxia at Presentation (Yes vs No)	0.325	0.42	0.08	2.36
Presence of Developmental Regression at Presentation (Yes vs No)	0.209	3.06	0.54	17.46
Presence of Seizure at Presentation (Yes vs No)	0.016*	12.50	1.60	97.65
Development Status Prior to Presentation (Yes vs No)	0.203	0.19	0.01	2.47
Lactate (Yes vs No)	0.031*	28.00	1.35	580.59

*Significant at level 0.05.

Table 5. ANOVA.

Model	Sum of Squares	df	Mean Square	F	Sig
Regression	3.734	3	1.245	15.324	<0.001
Residual	1.706	21	0.081		
Total	5.440	24			

Dependent variable: Prognosis; Predictors: (Costant), Lactate, Symptoms at presentation (seizure), Age at presentation (in months); *Significant at level 0.05.

Table 6 highlights key predictors of patient outcomes in Biotin-Thiamine-Responsive Basal Ganglia Disease (BTBGD). Age at presentation ($B = -0.009$, $p < 0.001$) and seizures at presentation ($B = -0.561$, $p < 0.001$) were significantly associated with worse prognosis, indicating that younger age and presence of seizures increased the likelihood of poor outcomes. Additionally, elevated lactate levels ($B = 0.211$, $p = 0.009$) were linked to a higher risk of residual disability or mortality.

Table 7 provides demographic and clinical characteristics of the 25 pediatric patients studied. The mean age at presentation was 34.88 months, with 60% female and 92% having consanguineous parents, emphasizing the genetic nature of the disease. Ataxia (52%) and developmental regression (44%) were the most common symptoms, while seizures (28%) were a significant predictor of poor prognosis. All patients tested positive for the SLC19A3 gene mutation. MRI findings showed basal ganglia involvement in 72% of cases, and elevated lactate levels were seen in

20%, further correlating with poor outcomes. Despite 92% receiving treatment, 8% of patients passed away, revealing the critical role of early diagnosis and intervention in improving prognosis.

Table 6. Model coefficients.

	B	Std. Error	t	Sig.	95% Confidence Interval for B	
					Lower Bound	Upper Bound
Constant	2.447	0.244	10.010	<0.001*	1.939	2.956
Age at Presentation (in Months)	−0.009	0.002	−4.319	<0.001*	−0.013	−0.005
Symptoms at Presentation	−0.561	0.127	−4.422	<0.001*	−0.826	−0.297
Lactate Level	0.211	0.074	2.871	0.009*	0.058	0.364

Dependent variable: Prognosis; *Significant at level 0.05.

Table 7. All (n = 25).

Question	n	%
Age (in Months)		
Minimum	1	
Maximum	120	
Mean	34.88	
Standard Deviation	27.98	
Median	36	
Interquartile Range	36	
Gender		
Male	10	40
Female	15	60
Patients' Symptoms at Presentation		
Ataxia	13	52
Developmental Regression	11	44
Seizure	7	28
None	4	16
Development Status Prior to Presentation		
Normal	22	88
Affected	3	12

Continued

Consanguinity Status among the Patients' Parents		
Present	23	92
Not Present	2	8
Genetic Testing		
Positive Testing For SLC19A3 Gene Mutation	25	100
Lactate		
Not Done	12	48
Normal	8	32
High	5	20
MRI		
Not Done	4	16
Basal Ganglia Involvement	18	72
Other	2	8
Unremarkable	1	4
Treatment		
Started	23	92
Not Started (Passed Away before Diagnosis)	1	4
Stopped (Parents' Decision)	1	4
Outcome		
Improved (Full Recovery, No Residual)	17	68
Affected (Improved, but with Residual)	6	24
Passed Away	2	8

Socio-demographic, genetic testing, treatment, and outcome information are presented in frequencies (n) and proportion (%).

4. Statistical Analysis

Data analysis was performed using Statistical Package for the Social Sciences, SPSS 23rd version. Frequency and percentages were used to display categorical variables. Minimum, maximum, mean, standard deviation, median, and interquartile range were used to present numerical variables. Fisher's Exact test was used to test for the presence of association between categorical variables. The non-parametric test Mann-Whitney U test was utilized to assess the presence of association between age and prognosis due to the non-normal distribution of age variable. Univariate logistic regression was used to determine the risk factors for having a poor outcome. The univariate logistic regression analysis included the following variables: gender, age, presence of ataxia at presentation, presence of developmental

regression at presentation, presence of seizure at presentation, developmental status prior to presentation, and lactate level. Level of significance was set at 0.05.

5. Discussion

Biotin-thiamine-responsive basal ganglia disease (BTBGD) is a rare condition with a global prevalence estimated to be between 1 in 215,000 and 1,000,000 live births [15]. In Saudi Arabia, the condition is an important public health concern due to high rate of consanguinity in the region [16]. Given the limited research on the clinical features and prognosis of BTBGD in this area, this study aimed at assessing the clinical features, treatment response, and predictive factors of BTBGD in the pediatric population of a tertiary hospital in Riyadh, Saudi Arabia.

In our cohort, all 25 patients (100%) tested positive for the SLC19A3 gene mutation. The most common symptoms observed at presentation were ataxia in 13 patients (52%), followed by developmental regression in 11 patients (44%), and seizures in 7 patients (28%). Our study found a higher frequency of ataxia and fewer occurrences of seizures compared to a study by Tabarki *et al.*, which reported ataxia in 30% of patients and seizures in 37% of patients [17]. Other studies have reported common symptoms such as cogwheel rigidity, confusion, and dystonia [18] [19]. These findings highlight the need for further research with larger sample sizes to gain deeper insights.

The study observed developmental delay in 3 patients (12%), while the majority of patients (22, 88%) had normal development prior to presentation. Additionally, consanguinity was present in a significant majority of patients (23, 92%) with only 2 patients (8%) having non-consanguineous parents. Similarly, Algahtani *et al.* reported a considerably high level of consanguinity in more than three-quarters of patients with BTBGD [20]. This high rate of consanguinity underscores the importance of keeping a high level of suspicion for BTBGD in patients presenting with acute or subacute encephalitis and other associated symptoms, particularly those with a family history of autosomal recessive disorders and/or consanguinity.

The study noted that approximately one-fifth of the patients (5, 20%) had elevated lactate levels, which aligns with other studies that reported biochemical abnormalities, including elevated lactate levels in blood and increased concentrations of isoleucine in patients with BTBGD [21] [22]. Molecular genetic testing and the measurement of thiamine concentration in cerebrospinal fluid are established methods for diagnosing and treating BTBGD.

The outcome of therapeutic doses of biotin and thiamine revealed that a notable proportion of patients (17, 68%) made a full recovery with no residual disability. This is consistent with the findings of Owen *et al.*, who observed that timely treatment with biotin and thiamine is highly effective in treating, preventing recurrence, and even resolving clinical symptoms [23].

In this cohort, the age at the time of presentation, the presence of seizures, and lactate levels were significantly associated with patients' health outcomes. Younger age at presentation, the presence of seizures, and elevated lactate levels were found

to predict poorer outcomes, including residual disability or death. The regression analysis results indicate that differences in patient outcomes (prognosis) based on their age at presentation, seizures, and lactate levels were statistically significant ($p < 0.001$). The study found that lactate levels were 0.211 times as likely to predict patient outcomes. Age at first presentation and the presence of seizures were associated with negative health outcomes, with regression coefficients of $B = -0.009$ and $B = -0.561$, respectively.

A major limitation of this study is that data on BTBGD in the pediatric population were extracted from patients' medical records. The lack of detailed and accurate information on the age of symptom presentation and timing of diagnosis pose significant constraints on achieving the study's objectives. Additionally, although the sample size of 25 patients is relatively large for such a rare disease, it remains small and may potentially affect the strength of the associations and regression analysis, possibly leading to underestimation or overestimation of results.

6. Conclusion

This study reported BTBGD in 25 pediatric patients in a tertiary hospital in Riyadh, Saudi Arabia. Age at presentation, seizures, and lactate levels were found to be significantly associated with patient health outcomes. Increasing public awareness of the condition, particularly among parents and pediatricians, is imperative. Early diagnosis, along with timely management using biotin and thiamine supplementation, promotes improved health outcomes and prevents progressive neurodegeneration and death.

Abbreviations

BTBGD and BTRBGD: Biotin-Thiamin-Responsive Basal Ganglia Disease; MRI: Magnetic Resonance Imaging; THMD2: Thiamine Metabolism Dysfunction Syndrome-2; CSF: Cerebrospinal Fluid; Mg: Milligram; Kg: Kilogram; d: day; PDHC: Pyruvate Dehydrogenase Complex.

Conflicts of Interest

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

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