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Case Report: Non-Responsive Biotin-Thiamine-Responsive Basal Ganglia Disease

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Abstract: **The following case study reviews an incident in which a three months old Saudi infant diagnosed with BTRBGD is admitted through the Emergency. The patient presented to the ER with lethargy and decreased activity. Despite the fact that extensive literature reviews the successful effects of early biotin and thiamine administration in treating Basal Ganglia Disease (a neurometabolic disorder characterized by confusion and seizures among other symptoms),[i] the case study reviewed below suggests that BTRBGD may in fact be unresponsive in cases in which the disease first develops during early infancy. This conclusion is primarily drawn from the fact that despite attempted treatment, the patient's case resulted in death.**

Keywords: **Biotin-Thiamine-Responsive Basal Ganglia Disease, BTBGD, Basal Ganglia Disease.**

I. INTRODUCTION

Biotin-Thiamine-Responsive Basal Ganglia Disease, otherwise known as BTRBGD describes a reversible neurometabolic disorder that is autosomal recessive. Characterizing symptoms include confusion, dysarthria, seizures, dystonia and, commonly, an individual history of febrile disease. Biotin-Thiamine is the most commonly used and effective treatment of Basal Ganglia Disease (BGD) thus the term "Biotin-Thiamine-Responsive BGD." BGD, when untreated can lead to quadriparesis and coma followed by fatality.[ii]

Clinically, BTRBGD is characterized by the symptoms described above in addition to encephalopathy, ataxia, external ophthalmoplegia and supranuclear facial palsy. BTRBGD generally develops during childhood, between two and 10 years of age. Early diagnosis and treatment is imperative to successful recovery. However, the following case study argues that BTRBGD may remain unresponsive if detected during early infancy. BTRBGD is tested for and diagnosed using MRI brain scans of the supratentorial cortex, brain cerebellum and stem. Additionally, chronic symptoms of the condition include atrophy, gliosis and necrosis in brain affected locations.

To be most successful, studies have revealed biotin and thiamine must be administered in doses of five to 10 mg/kg/day and 300 to 900 mg, respectively. Oral administration is most effective, and dosage is recommended to continue throughout one's life, however, symptoms generally subside within days after beginning biotin and thiamine treatment.[iii] Ongoing individual counseling and education may also be helpful in continuing to alleviate symptoms.[iv]

II. CASE PRESENTATION

This case study reviews, discusses and draws conclusions based upon the following 3-month-old male infant who presented to Emergency department with history of decrease activity and lethargy past 4 days, as well as history of spiking low grade fever 38 °C, but no history of diarrhea, vomiting or skin rash. There was no history of any drug intake or herbal medications. The patient was alert and awake but not following or fixating, with axial hypotonia and peripheral hypertonia in addition to Dysmorphic features in form of hypertolerism, wide anterior fontanelle, high arched palate, locked Jaw and full lips. In addition to right extropia, hyperreflexia with clonus and joint contractures. Other systemic examination was unremarkable.

The patient initially went to private hospital 10 days ago before presenting to our institution with query of abnormal movement based on that was admitted to PICU and started on anticonvulsant medication "Phenobarbital".

The chart below (figure 1) characterizes the patient's basic profile, symptoms and relevant care history:

Category	Description
Age / gender	3 month old, full term / male
Dysmorphic features	Hypertolerism, wide AF, high arched palate, locked Jaw and full lips. As well as right sided extropia, hyperreflexia with clonus and joint contractures
Medications / Feeding	Phenobarbital/NGT feeding tube
Presentation	ER
History	Lethargy, decreased activity for 4 days
Temperature / abnormal vitals	Fever: 38 degrees C
Skin / movement	No rash / normal movement
Potential allergies	Milk (choking afterwards)
Sensory function	Normal eye movement, no apnea
Elimination	Normal, no vomiting or diarrhea
Urine	Normal, no change frequency, color, no UTI
Respirations	Normal (no SOB or cough)
Contact with illness	No known history
Care history	Hospital discharge 10 days prior to our ER admission
Past surgery	Encephalopathy
Current diagnoses	BTRBGD
Known Allergies	None

Figure 1: Patient presenting conditions, history and symptoms

Afterward the patient developed apnea requiring PICU admission. During the patient first PICU visit, invasive ventilation was used to treat the patient's apnea during a 17-day ICU stay. During the PICU stay, the BTRBGD diagnosis was given, biotin and thiamine treatment initiated immediately, concluding that the disease had first occurred during early infancy. This prognosis was determined based off of a molecular discovery of homozygous duplication in the patient's SLC19A3 gene [c.191dupT (p.Val65Glyfs*160)]. The patient was eventually weaned from ventilation and given non-invasive O_2 administration. However, 24 hours later, the patient failed to maintain SpO_2 readings above 80%, eventually presenting as bradycardic. Few days later the patient was announced as deceased. Despite biotin and thiamine treatments, this outcome suggests that in cases in which BTRBGD is developed during early infancy, BTRBGD may in fact be non-responsive.

III. DISCUSSION

Gaining a deeper understanding of the surrounding conditions, potential causes and outcome of such a case requires first reviewing the functions of basal ganglia (BG) along with BG disease. BG are responsible for participating in complex neural signalling affecting but not limited to emotional regulation, cognition, descending motor skills and eye movements. As a result, lesions in the BG (abnormalities resulting from disease) commonly lead to Huntington's disease (characterized by hyperkinetic movement), Parkinson's disease (the archetypal BG disease characterized by hypokinetic movement) and/or a combination of the above.[v]

The following figure 2 illustrates the basic structure of a healthy BG, while figure 3 demonstrates a diseased BG, such as in the case of Parkinson's disease:

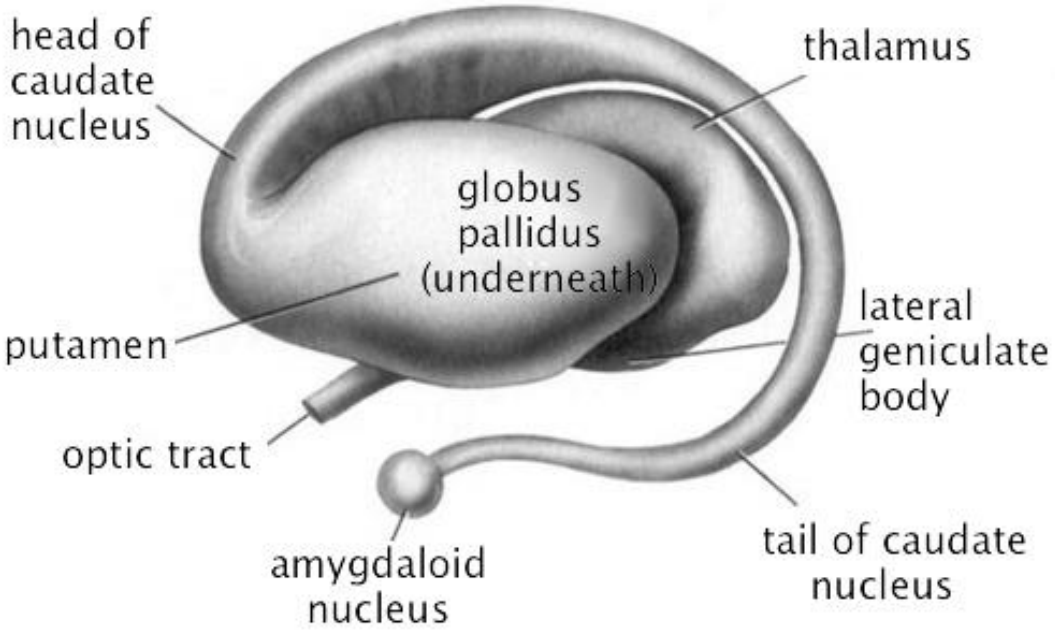

Figure 2: BG structure. Retrieved from: https://webspace.ship.edu/cgboer/basalganglia.html

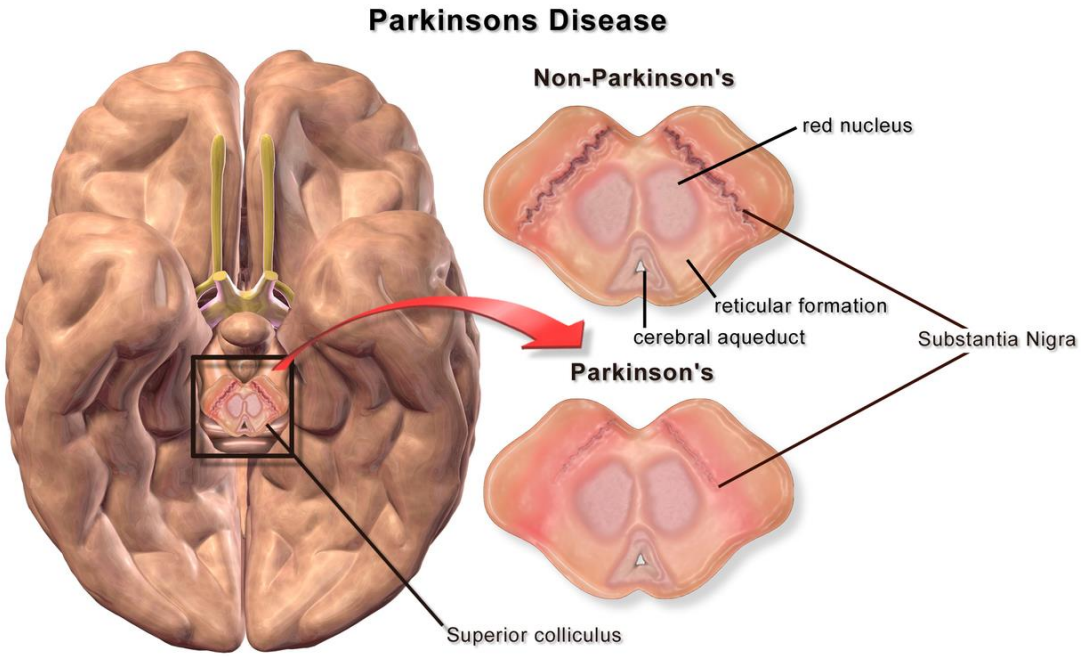

Figure 3: Diseased BG. Retrieved from https://commons.wikimedia.org/wiki/File:Blausen_0704_ParkinsonsDisease.png

As seen above in the case of Parkinson's disease, abnormal BG are characterized by rigidity and bradykinesia in addition to a resting tremor between 4 and 6 Hz. In progressed stages of such diseases, posture and gait are affected.[vi]

In our case, the patient was observed as demonstrating severe developmental delay, and was prescribed phenobarbital in response to abnormal movements, which seemed (according to observation) to effectively manage the symptom. An EEG report revealed low voltage activity with bursts (low voltage) following suppression periods, in combination with multifocal epileptic discharges in the right temporal region. The patient's CT report (completed in response to pupil abnormality) revealed remonstrations of bilateral diffuse cystic encephaomalacia. The patient's extra-axial collection had improved. As a result, neurosurgical teams were consulted, and it was concluded that no further intervention was needed. However, the patient exhibited extensive brain damage in combination with noted encephalomalacia, enlarged ventricles and cerebral volume loss.

No haemorrhaging was identified on the patient's imaging scans. Neurology team assessments concluded that he might have suffered from an ischemic injury, as mitochondrial causes of presenting symptoms were concluded to be a possibility. Furthermore, neurology teams suggested sulphite oxidase deficiency might have been a contributing factor. The patient's last recorded vital signs were as follows: HR 122, BP 99/57, RR 25 and T 36.3C. In further conclusion, the patient's encephalopathy was speculated to be due to BTRBGD rather than a potential infection, since he exhibited no other signs of infection. Hence, the patient was no prescribed antibiotics.

Recent advancements in CT and MRI imaging have advanced medical practitioners' abilities to see and understand the condition of patients' basal ganglia, further aiding the speculation and discovery of BGD's emergence and causes.[vii] Hence, in the case of our patient, it was speculated that BGD began during early infancy. Because of the exceptionally early development of BTRBGD development, biotin and thiamine treatment may have been ineffective.

IV. CONCLUSION

In conclusion, it may be reasonably assumed that in cases in which BTRBGD develops during early infancy, BTRBGD is unresponsive. Such metabolic brain disorders[viii] are generally treatable with early management.[ix] However, in cases such as the above-described incident, such inflammatory diseases[x] are unresponsive to biotin-thiamine treatment due to early infancy instigation. The following figure 4 demonstrates the patient's concluded and summarized scenario:

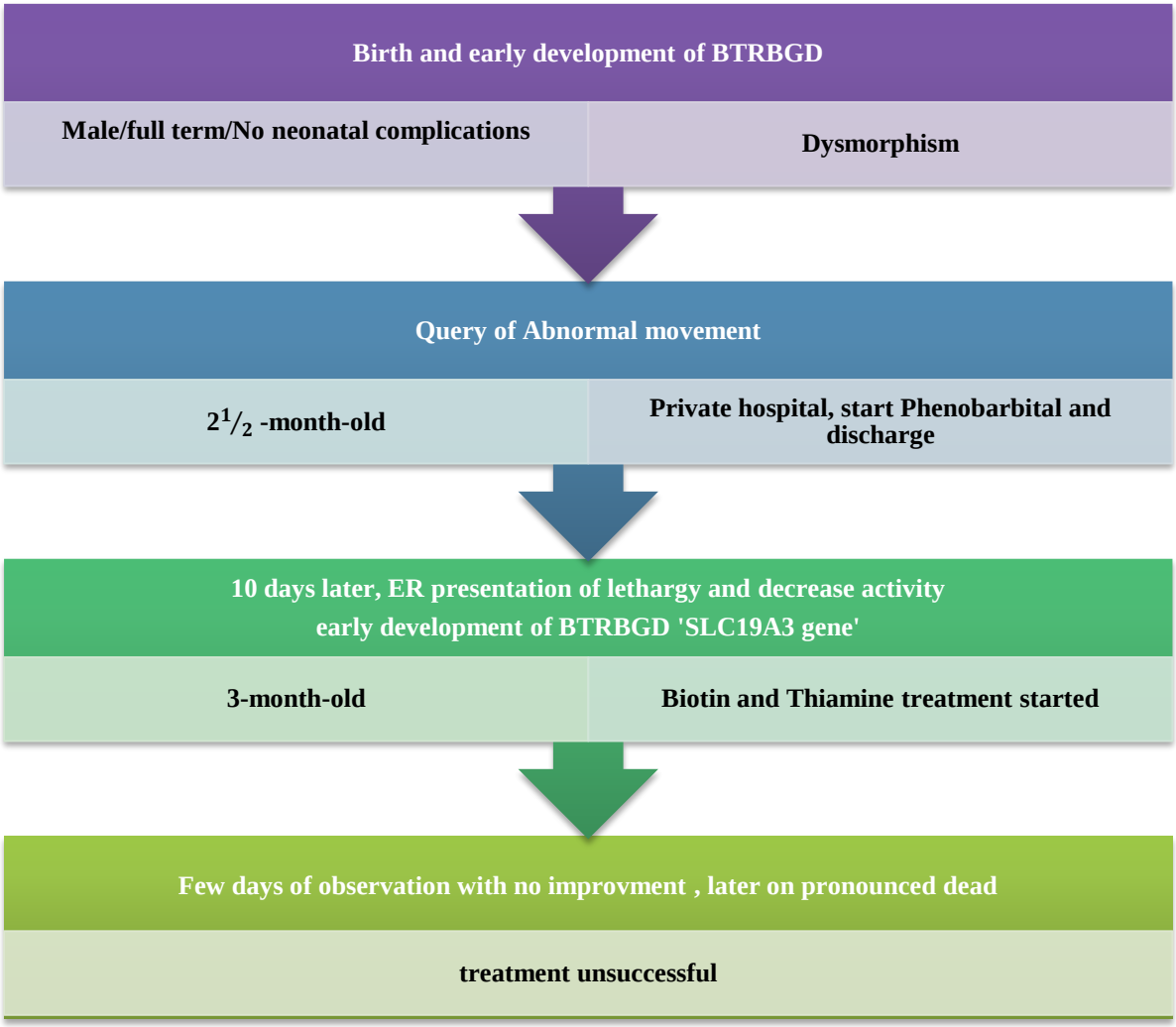

Figure 4: Case scenario summary

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Abbreviations:

BTRBGD = biotin–thiamine-responsive basal ganglia disease,

BGD = Basal Ganglia Disease

MRI = magnetic resonance imaging,

CT = Computed tomography,

PICU = Pediatric Intensive Care Unit,

ER = Emergency

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