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Adult bile acid amino transferase deficiency

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Patient: Female, 70
Final Diagnosis: Bile acid amino transferase deficiency
Symptoms: Headache • indigestion • itching skin • nausea • vomiting
Medication: —
Clinical Procedure: —
Specialty: Gastroenterology and Hepatology

Objective: Challenging differential diagnosis
Background: Bile acid synthesis impairments are difficult to diagnose due to non-specific manifestations related to progressive failure to absorb essential fatty acids and fat soluble vitamins and failure to maintain normal intestinal microbiota.
Case Report: A 70-year-old female presented with long-standing history of recurrent headaches, indigestion, dry, scaly, itching skin, and fluid around knee joints. Quantitative Electroencephalography (QEEG) revealed widespread excess theta maximum in the temporal regions. A rare pattern of elevated plasma glycine and taurine led to suspicion of BAATD. A stool profile employing molecular probes for commensal bacteria revealed elevation of *Fusobacteria spp.* Implementation of bile acid replacement therapy (BART) produced rapid remission of headache and other symptoms and a three-month follow up stool profile revealed normalization of fecal *Fusobacteria* populations that remained normal after one year of BART. QEEG analyses 4 weeks following BART showed evidence of significant improvement in CNS functioning.
Conclusions: This case illustrates the potential for diagnosis of latent, adult BAATD by finding a unique pattern of plasma amino acids and monitoring of therapy by observing normalization of fecal commensal bacteria and functional brain assessments.

Keywords: bile acid amino transferase • plasma taurine • plasma glycine • chronic intractable headache • indigestion • dry, scaly skin • intestinal dysbiosis • fecal microbes • bile acid replacement therapy • quantitative electroencephalography

Full-text PDF: <http://www.amjcaserep.com/download/index/idArt/889906>

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Background

Adults excrete 20 to 30 grams of bile acids daily into the intestines. Over 90% of this flow may be derived from intestinal reabsorption of primary and secondary bile salts. The reabsorbed bile acids are largely deconjugated by bacteria in the ileum and must be re-conjugated in the liver. Resupply of the bile acids lost with feces constitutes about half of hepatic cholesterol production, where rates of bile acid synthesis are regulated by the farnesoid X nuclear receptor [1]. Bile acid amino-transferase (BAAT, EC: 2.3.1.65) catalyzes the final reaction in the formation of the primary conjugated bile acids, taurocholic, taurochenodeoxycholic, glycocholic and glycochenodeoxycholic acids. About 500 mg of these compounds are secreted from hepatocytes as bile salts that pass into the duodenum to aid digestion and regulate intestinal microbe populations [2]. Glycine and taurine represent 16% and 23% of the molar composition of their respective bile acids, so the total daily requirement for glycine and taurine utilization in re-conjugation and formation of newly synthesized conjugated bile acids can be a significant percentage of their daily turnover.

The ratio of glycine- to taurine-conjugated bile acids is usually about 4:1 [3]. For an average adult consuming 75 g protein daily that contains 8% glycine, about 30% can be required for conjugated bile acid synthesis. Thus, genetic impairment of glycine conjugation to bile acids could produce significant increases in circulating glycine levels. A similar argument applies for taurine, although peripheral blood level elevations are more affected by variations in sulfur amino acid intake. Substrate limitation of taurine conjugation is indicated by finding that administration of oral taurine at 3.2 g/day for 2 weeks to healthy humans can effectively raise taurine-conjugated bile acids [3].

Enteric absorption of fats and of fat-soluble substances, including several vitamins is facilitated by the detergent action of conjugated bile acids. A concurrent effect of bile salts in the small intestine is suppression of bacterial populations and growth rates to achieve the normal balance of bacteria throughout the small and large intestines [4]. Hepatic BAAT catalyzes the final step in formation of bile acid amides, including the glycine and taurine conjugates of cholic and chenodeoxycholic acids.

Errors in synthesis of bile acids may lead to hepatic cholestasis that is usually diagnosed in children [5]. Diagnosis of a bile acid amidation defect in a child by immunohistochemistry has been reported [6]. An earlier report on a child with hypocalcemic convulsions, rickets, and epistaxis due to secondary vitamin K deficiency showed the difficulty with direct detection of bile acid abnormalities in serum and urine. Definitive diagnosis requires demonstration of undetectable cholic acid metabolites in duodenal contents [7].

Intestinal dysbiosis has been connected to impaired bile acid metabolism [8], and, in turn, dysbiosis modulates the capacity for bile acid modification in the gut microbiome [9]. Thus, the normal system for maintaining daily enterohepatic flow of primary and secondary bile acids is disrupted by impairment in BAAT. This flow is required not only for fat-soluble nutrient digestion and absorption, but also for regulating microbe populations throughout the small and large intestines. Some of the signs found in this case are readily explained by lack of normal bile acid flow. Skin abnormalities are classic signs of essential fatty acid deficiency, and digestive disturbances are generally associated with states of dysbiosis.

Case Report

A 70-year-old female presented with a lifelong history of headaches. Her headaches were usually frontal and one sided, sometimes of debilitating severity and often associated with nausea and vomiting, but with distinct absence of migraine character. Treatment with usual OTC analgesics was ineffective, and caffeine was sometimes helpful for mild occurrences but was ineffective for relief from more severe ones. She was using 60 mg Amour thyroid daily for hypothyroid diagnosis associated with dry, itchy skin that worsened in winter months. She had received a diagnosis of calcium pyrophosphate dihydrate disease (pseudogout) due to fluid accumulation around both knees and associated pain and swelling that was being treated with combinations of Celecoxib and Ibuprofen + colchicines. The fluid required periodic drainage and cortisone injection. Although she was meticulous about oral hygiene, she required frequent dental care for tooth decay and abscessed teeth and gums, and all dental amalgams had been removed. Various medical consultations for headaches, skin conditions and symptoms of indigestion over the past 15 years had resulted in courses of nystatin and dietary restrictions for yeasts plus multiple herbal medications, 10 mg BID dehydroepiandrosterone and multiple dietary supplements.

An initial Quantitative Electroencephalogram (qEEG) analysis was employed in advance of metabolic testing and treatment. Additionally, in order to identify specific brain structures that may be more susceptible to the metabolic problems identified in this case, Low Resolution Electromagnetic Tomographic Analysis (sLORETA) was employed as a method of source localization of the abnormalities noted in qEEG [10]. The sLORETA is an algorithm that identifies the mathematically most probable underlying sources of the scalp recorded EEG, color coded for voxel z-scores relative to normative data at the narrow frequency band indicated. Metabolic profiling of plasma amino acids and stool microbes and chemistries were then conducted at Genova Diagnostics laboratory, Atlanta, Georgia.

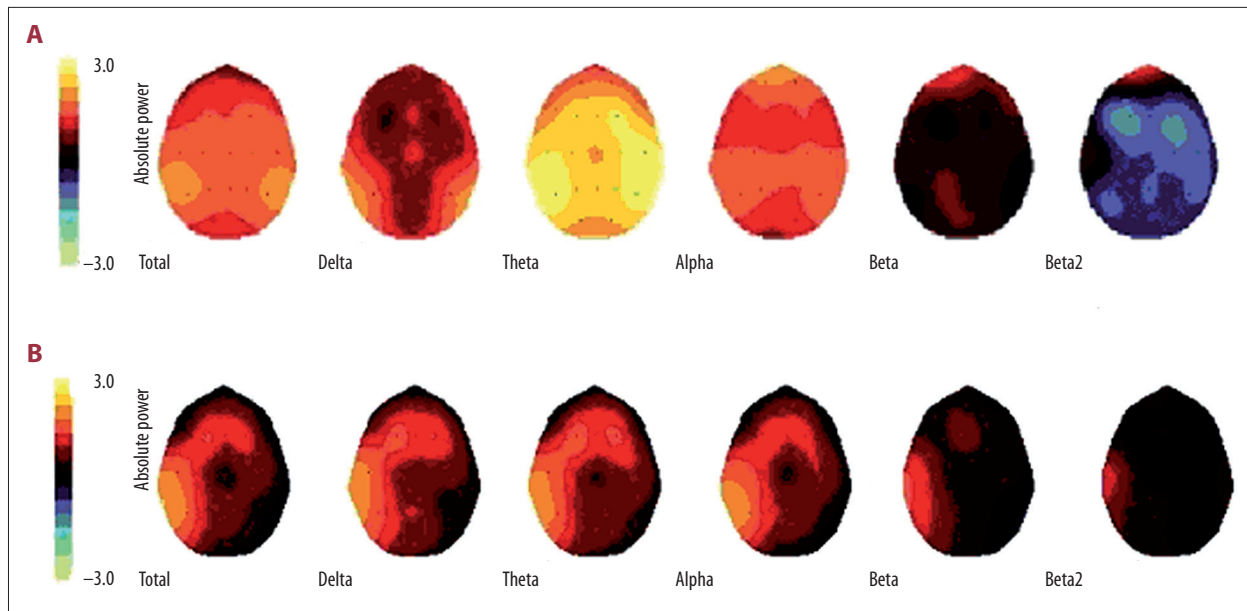


Figure 1. QEEG brainwave activity Z-scored for age and absolute power. Approximately 2 minutes of artifact free EEG was used to derive the absolute power for total power, delta (1–3.5 Hz), theta (3.6–7.5 Hz), alpha (7.6–12.5 Hz), beta (12.6–25 Hz), and beta2 (25.1–35 Hz). The –3.0 to 3.0 color scale indicates Z-scores (standard deviations) away from age-adjusted normal absolute power of the EEG brainwave activity. Areas of excessive brainwave power in each frequency band are colored yellow, orange and red, and blue and green areas indicate reduced activity. The color black indicates normal activity. (A) Brain map images 2 years before starting BART. (B) Brain map images 4 weeks after starting BART.

Bile acid amino transferase deficiency (BAATD) was initially indicated by finding a unique pattern on a profile of plasma amino acids. Except for glycine and taurine, all amino acids were within their central 80th percentile limits. Glycine was found at 460 mM (182–348) and taurine at 97 mM (31–73). This pattern is rarely found in plasma amino acids, and it suggests a specific failure in utilization of glycine and taurine. When only the two amino acids uniquely utilized in the final steps of bile acid synthesis are elevated, a potential focal impairment in bile acid aminotransferase (BAAT, EC: 2.3.1.65) is indicated. This indication was consistent with the skin and joint symptoms and difficulty with digestion of foods high in fat that are known associations with chronic, secondary essential fatty acid and vitamin deficiency. Thus, signs and symptoms prompted a clinical trial of bile acid replacement therapy. Since an inherited metabolic defect was indicated by the amino acid abnormalities, no changes were expected in the amino acid profile and no further testing of amino acid levels was done.

Bile acid replacement therapy (BART) was initiated with 2 tablets tid at mealtime of Cholocol, a product containing 115 mg of purified bovine bile salts and 230 mg of collinsonia root powder per capsule. After 3 weeks on this regimen additional stool specimens were collected, symptoms were assessed and, at 4 weeks, a follow-up quantitative EEG was performed.

Symptom improvements led to continuation of the BART for a year, after which additional laboratory fecal microbe metabolite testing was performed.

During the year following initiation of therapy, symptom improvements continued, and no further medical treatments for CPPD or other conditions were required. The patient was careful not to overstrain her knees, using only ice packs as necessary to reduce inflammation. Symptoms were reduced so that no anti-inflammatory medications were used. A self-assessment symptom inventory checklist was administered prior to the initial testing sequence, again after 19 days of BART, and after the additional 11 months during which the bile acid replacement was continued. Areas of most notable improvement were reduction of headaches and improvements in dry skin, digestion and joint pain.

QEEG [11] and sLORETA [12], analytic techniques were used to assess the impact of BART on brain function. To produce the maps shown in Figure 1, digital raw EEG information was used to derive measures of deviation from age matched normal using BrainDx¹ software. Significant Z-score deviations from age expected normal values with widespread excess theta maximum in the temporal regions are shown in Figure 1A. Changes toward normal (black) as compared with the baseline state of

¹ Information on this software can be attained from www.braindx.net

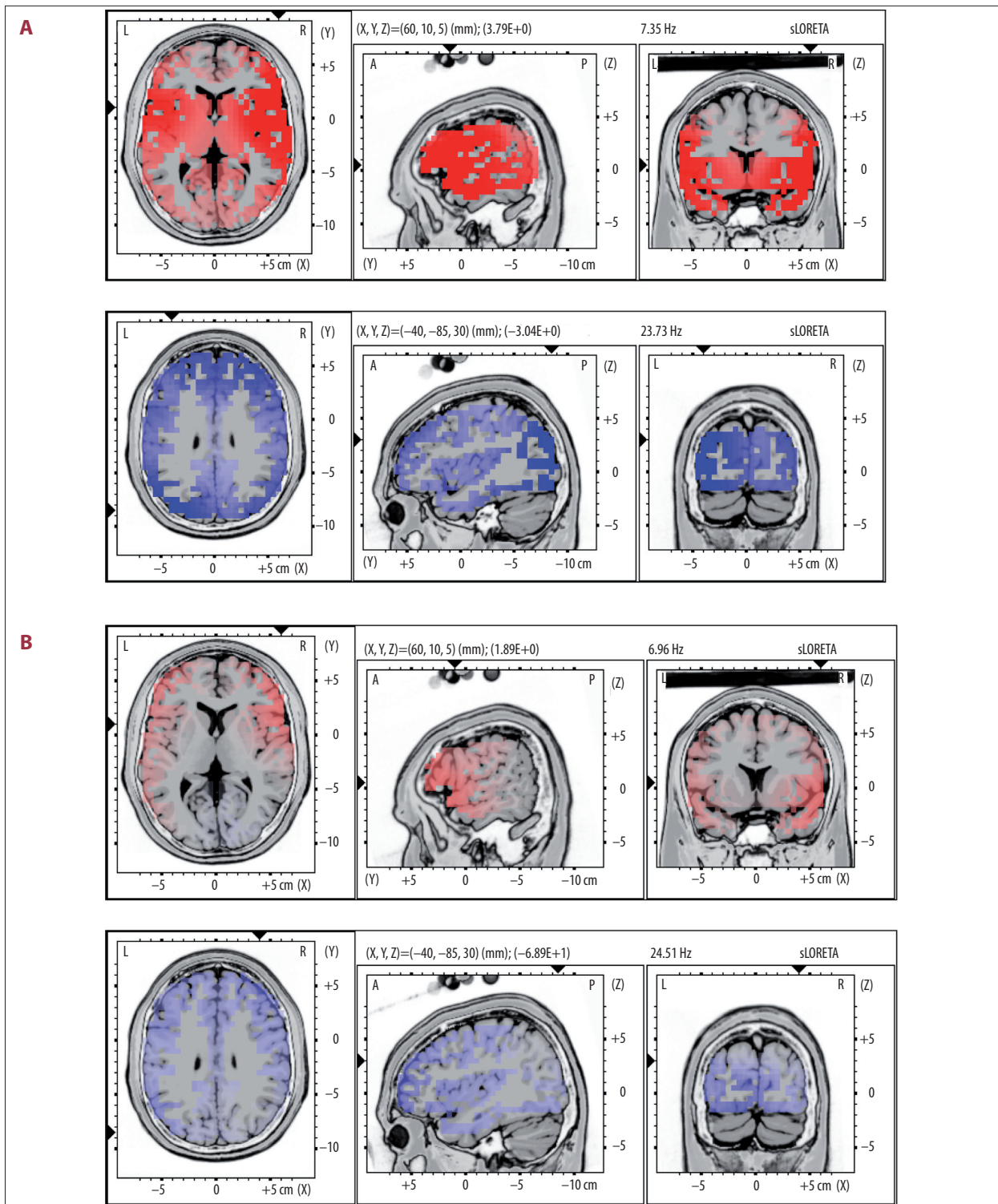


Figure 2. sLORETA maps of maximum and minimum activity (corrected for age). Two minutes of artifact free EEG was used to calculate Z-scores for the over 6,000 voxels of current density in the sLORETA calculations. Colors indicate brain regions showing significant increased (red) or decreased (blue) activity for age. **(A)** Images prior to starting BART showing probable sources for the maximum excess abnormality in the (7.35 Hz) theta band (top panel) and deficit activity in the (23.7 Hz) beta band (bottom panel). **(B)** Images 4 weeks after starting BART showing probable sources for the maximum excess activation in the (6.96 Hz) theta band (top panel) and maximum deactivation in the (24.51 Hz) beta band (bottom panel).

Figure 1A are shown in the Z-scores for absolute power measures following BART intervention of Figure 1B.

Brain mapping was done approximately 2 years before starting BART (Figure 1A) showing levels of delta, theta, alpha, beta, and high beta (beta2) activity over the surface of the scalp reflecting underlying brain activity.

The subject's symptoms had not changed in the 2 years prior to supplementation nor had any traumatic incidents occurred that would possibly account for changes in the age adjusted Z-score measures of the EEG. The brainwave Z-scored activity 4 months after BART (Figure 1B) indicates a normalization of all scores across all bandwidths for absolute power.

The changes in qEEG analysis add further confirmation that this subject's changes in symptoms occurred at a systemic neurophysiological level. It should be noted that the patient also stopped consuming foods that scored positive on the IG₄ test during the time of BART. Although only mild abnormalities were present in the initial testing, this intervention may have contributed to the changes in body metabolic status and improved CNS functioning as indexed by measures noted in the qEEG. The lack of significant improvement when a similar food restriction was done 12 years prior to the reported BART suggests that dietary changes had little influence on the current outcome.

The sLORETA 3-D images of Figure 2 show maximum Z-score for excess activation was found to be located at Brodman Area 44, Precentral Gyrus, and Frontal Lobe. The maximum Z-score for deficit or deactivation, was found to be located at Brodman Area 7, Superior Parietal Lobule, and Parietal Lobe. Comparing Figure 2A and 2B, a clear change toward more normal activity of the sources can be seen after starting BART.

Discussion

One of the puzzling aspects of this case is the relationship of chronic headaches and abnormal qEEG patterns to BAATD. Since normal bile acid flow is required for maintenance of the intestinal microbiome, we may hypothesize that intestinal dysbiosis lead to accumulation of neurotoxic microbial products, similar to effects reported in patients with irritable bowel syndrome [13].

An estimate of the incidence of BAATD was made by inspection of a set of 2970 plasma amino acid records from Genova

Diagnostics clinical laboratory for occurrences of the pattern described. An overall incidence of 0.54% was found. Thus, the incidence of BAATD could approach 500/100K in the US population, and the relatively low physiological impact of impaired bile acid conjugation may allow for such a high incidence. The main effects are likely to be mediated via alterations in essential fatty acid status and in farnesoid-X receptor functions [14]. The presence of such defects at birth can lead to progressive deterioration in essential fatty acid status that may affect myelination and neuronal plasticity in childhood brain development [15]. The qEEG and sLORETA profiles found in this case indicate a diffuse effect of many brain regions as might be expected with an associated metabolic disorder. Such high incidence values and degrees of impairment indicated by this case suggest potential large population morbidity and productivity effects.

Conclusions

This case illustrates the potential for diagnosis of BAATD and its remediation by a simple, safe BART. The long history of headaches, dry skin and indigestion suggest an adult onset syndrome that might be associated with inherited BAATD. The unique pattern of elevated taurine and glycine in plasma indicates a diagnostic test for the condition. The relatively high frequency of cases found in the laboratory database indicates a high penetration of this type of genetic BAATD. Extrapolation to the general population indicates that many patients may be helped by proper diagnosis and therapy. Low toxicity potential and low cost of the therapy facilitate clinical management of such patients. Undetected BAATD can confound diagnosis and thwart attempts to remediate chronic, debilitating symptoms and CNS dysfunction.

Compliance with ethics guidelines

Richard Lord is employed by Genova Diagnostics. Dan Tuttle declares that he has no conflict of interest. David Cantor is an owning partner of BrainDx, LLC.

Informed consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all patients for being included in the study.

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