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AMMONIA HIGH BLOOD LEVEL IN CYSTIC FIBROSIS PATIENTS AND ITS POSSIBLE RELATIONSHIP TO PROBLEMATIC EATING BEHAVIOR IN THIS POPULATION

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Abstract

Children with Cystic Fibrosis (CF) very often experience problematic eating behaviour, anorexia, poor adherence to Daily Dietary Recommendations that in addition to being at increased risk for malnutrition and failure to thrive (FTT) may contribute to the hastening in decline of their pulmonary function because of poor growth and adversely affect health outcomes.

The objective of this study was to evaluate blood ammonia level in children with CF and its possible relationship to eating problems in this population.

Serum ammonia level was evaluated in CF patients attending University CF Clinic. Twenty patients aged from 4 months to 16 years were enrolled in study. Several parameters were taken into consideration: nutritional and clinical status, liver function studies (albumin, serum transaminases, bilirubin, prothrombin time, alkaline phosphatase, γ-glutamyl transpeptidase, glucose), liver ultrasound, and lung function tests in patients above 5 years. Liver function studies and lung function testing were performed on the same day of actual investigation. During the study parents were strictly advised to keep dietary and enzyme therapy recommendations in order to prevent catabolic state. The exclusion criterion was exacerbation of the disease.

Data suggest the possible correlation between problematic eating behaviour and blood ammonia level in CF patients. Multicenter studies should be encouraged to confirm these data.

Keywords: Cystic Fibrosis, eating behaviour, ammonia, hyperammonemia, liver

INTRODUCTION

Children with Cystic Fibrosis (CF) very often experience problematic eating behaviour, anorexia and poor adherence to Daily Dietary Recommendations. Parents of children with CF describe meal times as ‘’battling’’ with the child. The above mentioned in addition to being at increased risk for malnutrition and failure to thrive (FTT) may contribute to the hastening in the decline of their pulmonary function because of poor growth and adversely affect health outcome [*Powers S. et al., 2002; 2005; 2008; Stark L. et al., 2005; Piazza-Waggonner C. et al., 2008; Collins S., Stuhler R., 2009; Laing D. et al., 2010*].

Ammonia is a normal constituent of all body fluids. Ammonia metabolism involves primarily: the gut, liver, kidney and brain. It is the product of protein catabolism. Ammonia is produced mostly in the gut (bacterial hydrolysis), but also in the kidney and muscle. In kidneys ammonia is synthesized from glutamine in the proximal tubules.

In hyperammonemia setting the kidney decreases ammonia production and increases its excretion. Excess ammonia is excreted as urea in liver through the urea cycle, which comprises several enzymes acting in sequence. Both acute and chronic hyperammonemia result in alterations of the neurotransmitters.

Chronic hyperammonemia is associated with an increase in inhibitory neurotransmission as a consequence in downregulation of glutamate receptors secondary to excessive accumulation of glutamate and in addition changes in the glutamate – nitric oxide – cGMP pathway leading to alteration in cognition and learning.

Ammonia also increases transport of aromatic amino

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acids (e.g., tryptophan) across the blood-brain barrier. This leads to an increase in the level of serotonin, which is the basis for anorexia.

The causes of hyperammonemia are as follows: inborn errors of metabolism, certain drugs, renal conditions, chronic liver disease especially in CF. Modes of presentation of liver disease in CF are asymptomatic hepato-splenomegaly, alimentary bleeding and asymptomatic abnormalities of liver function revealed through appropriate tests, ultrasound. Chronic liver dysfunction even at mitochondrial and cytosolic levels can cause hyperammonemia in CF patients.

The objective of this study was to evaluate blood ammonia level in children with CF and its possible relationship to eating problems and decreased appetite in this population.

MATERIAL AND METHODS

Twenty CF patients aged from 4 months to 16 years were enrolled in this study. Patients studied were admitted to University CF Clinic for routine follow-up.

Blood was drawn into tubes for ammonia in the morning and ammonia level was measured on "Cobas Integra" (Rosche, France) with reference values <60 *mmol/L.*

Clinical status of patients was assessed by Shwachman-Kulczycki score. Height and weight measurements, BMI (according to CDC charts) were used as parameters for growth and nutritional status. Growth velocity was assessed as well.

Several parameters were taken into consideration: liver function studies (albumin, serum transaminases, bilirubin, prothrombin time, alkaline phosphatase, γ-glutamyl transpeptidase, glucose, ornithine carbamoyl transferase), liver ultrasound, lung function tests (FEV1, FVC, MEF25-75%) in patients above 5 years [*Kapranov N., Kashirskaya N., 2005*]. Liver function studies and lung function testing were performed on the same day. Liver ultrasound data were assessed by the Williams ultrasound scoring system [*Clinical Guidelines, 2007*]. During the study parents were strictly advised despite prolonged mealtime to keep dietary and enzyme therapy recommendations in order to prevent catabolic state, as well as stay on routine treatment (ursodeoxycholic acid, inhalation therapy and physiotherapy). The exclusion criterion was exacerbation of the disease. Parents' records of meal duration, mealtime behaviour, refusal of any food were also noted.

Results and Discussion

Overall, patients enrolled in this study had a good clinical status with a mean Shwachman score of 80. Only 3 (15%) patients were pancreatic sufficient.

Liver functions tests, besides alkaline phosphatase were normal in all patients during the time of investigation. Three (15%) patients showed high serum alkaline phosphatase. Ten patients were taking ursodeoxycholic acid. Liver ultrasound scores were "3" in 20 patients that are considered as normal. Twelve (60%) patients showed low serum albumin levels. Lung function test in two patients/FVC, FEV1/ (10%) were 71%, 68%, and 89%, 78% from predicted, respectively.

Serum ammonia levels were high in all patients with reference values <60 mmol/L. There was no correlation between alkaline phosphatase and ammonia levels [*Puls I. et al., 1983*].

According to ammonia levels patients were divided into 3 groups: below 80 *mmol/L*, 80-100 *mmol/L*, above 100 *mmol/L* (Figure).

There was correlation between problematic eating behaviour, anorexia and blood ammonia levels.

Patients with mild and moderate elevation of blood ammonia (65-95 *mmol/L*) showed moderate problematic eating behaviour, whereas in patients with blood ammonia advanced elevation the severe problematic eating behaviour was recorded by parents and family members and described as "battling" during meal time and complete refusal from any food.

Conclusion

In the present study it was shown that the problematic eating behaviour in children with CF may be related to high blood ammonia level and further studies are needed to find out a background of hyperammonemia in CF patients.

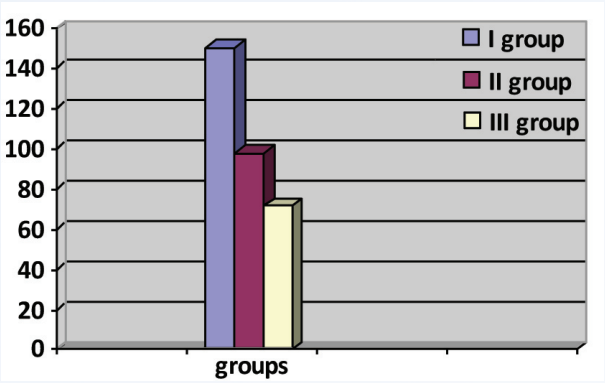

Figure. *CF patients grouped by blood ammonia levels.*

Liver dysfunction, either genetically determined or drug induced, might be an important cause for hyperammonemia.

The obtained data also suggest that liver routine tests or liver ultrasound screening have low sensitivity to diagnose CF liver dysfunction at early stage, and the most sensitive and specific diagnostic tools are required for early detection of CF liver disease as it is one of independent risk factors for survival in adults with CF [*Fagundes E. et al., 2004*].

The other source for ammonia hyperproduction in CF may be gut and bacterial overgrowth that is frequent in CF [*Lisowska A. et al., 2009*]. In this case the use of probiotics in the treatment protocols of CF should be discussed.

According to these data hyperammonemia in CF patients needs to be corrected and beside ursodesoxicholic acid and probiotics other interventions should be implemented in treatment protocols.

Multicenter studies should be encouraged to confirm these data.

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