East African Scholars Journal of Medical Sciences
*Abbreviated Key Title: East African Scholars J Med Sci*
ISSN 2617-4421 (Print) | ISSN 2617-7188 (Online) |
Published By East African Scholars Publisher, Kenya

OPEN ACCESS

DOI: 10.36349/easms.2019.v02i06.006 Volume-2 | Issue-6| Jun -2019 |

**Review Article**

# Map of some inborn errors of metabolism in Upper Egypt: Metabolic and Genetic Disorders' unit, ten years' experience

Tahia H. Saleem[1] and Mohammed H. Hassan[2]

[1]Medical Biochemistry Department, Faculty of Medicine, Assiut University, Assiut, Egypt
[2]Medical Biochemistry Department, Faculty of Medicine, South Valley University, Qena, Egypt

*Corresponding Author
Mohammed H. Hassan, E-mail: mohammedhosnyhassaan@yahoo.com

**Abstract:** Metabolic diseases develop when the metabolic processes are abnormally functioning primarily due to the deficiency or accumulation of bio-chemical substances that might interfere with various normal physiological functions in the human body. Early diagnosis can lead to early medical and therapeutic interventions. Inborn errors of metabolism are usually referred to as congenital metabolic diseases. The offspring of consanguineous relationships are at a greater risk of having congenital metabolic diseases. Inherited disorders accompanied the human race since its earliest existence. Metabolic and Genetic Disorders' unit (MGD) is a major tertiary referral, if not the only, centre in Upper Egypt for diagnosis of various metabolic and genetic disorders with its actual work has been stated since 2010. The aim of this review article is to give spotlight on various metabolic disorders that have been diagnosed by MGD in Upper Egypt mainly Aswan, Qena, Sohag, and Assiut, and their relative frequencies, main clinical presentations, and helpful diagnostic and prognostic markers, so that increase the awareness of the pediatricians, neonatologists, neurologists, and general practitioners about the magnitude and frequency of metabolic disorders and their common clinical manifestations, in Upper Egypt, using our data from previously published researches in international journals.
**Keywords:** Upper Egypt; Metabolic and Genetic Disorders' unit; metabolic disorders.

## INTRODUCTION

Inborn errors of metabolism (IEM) are disorders of single gene and implicated in the disturbances in the metabolism (anabolism or catabolism) of major dietary elements (carbohydrates, fats and proteins) via deficiency of certain enzymes or transport proteins with subsequent block in the metabolic pathway and metabolites accumulation in various tissues (Fateen *et al.*, 2014).

The field of metabolic diseases has changed from a limited group of rare, untreatable, often fatal disorders to an important cause of acutely life-threatening but increasingly treatable illness. Unchanged is the orphan nature of these disorders with mostly relatively nonspecific initial clinical manifestations. The patient does not come to the physician with the diagnosis; the patient comes with a history, symptoms, and signs. We will briefly explore some of the metabolic disorders which were diagnosed by Metabolic and Genetic Disorders' unit (MGD) in Upper Egypt, They include the followings:

### 1. Disorders related to carbohydrate metabolism

#### *A) Lactose intolerance*

Lactose, a disaccharide that comprises the monosaccharides glucose and galactose, is the primary carbohydrate found exclusively in mammalian milk. A β-galactosidase termed "lactase-phlorizin hydrolase" (lactase) accounts for most of the lactase activity in the intestinal mucosa (Semenza, 1986). Lactose intolerance is a clinical syndrome of 1 or more of the following: abdominal pain, diarrhea, nausea, flatulence, and/or bloating after the ingestion of lactose or lactose-containing food substances. The amount of lactose that will cause symptoms varies from individual to individual, depending on the amount of lactose consumed, the degree of lactase deficiency, and the form of food substance in which the lactose is ingested (Heyman, 2006).

Quick Response Code

Journal homepage:
http://www.easpublisher.com/easjms/

Article History
Received: 15.05.2019
Accepted: 02.06.2019
Published: 19.06.2019

Abuhamdah *et al.,* (2013) determined the prevalence of lactose intolerance, and its correlation with gastrointestinal symptoms, in primary school children aged 6-12 years in Qena Governorate, Egypt, using a cross-sectional study was carried out on 300 school children with clinical suspicion of lactose intolerance. Biological and clinical data were obtained from children's parents or guardians. The history of diarrheal attacks especially following ingestion of milk or dairy products, as well as the incidence of diabetes in the children or family history of such diseases was also obtained. The children were instructed to maintain a low fiber diet without lactose for 48 hours prior to the day of examination. After 12 hours of fasting lactose tolerance test was carried out. The data obtained revealed that 74% of the participants in the study were intolerant to lactose. However, only 56.8% of lactose-intolerant children had positive clinical history of abdominal pain, abdominal distension or diarrheal attacks following ingestion of milk or dairy products. Abuhamdah *et al.,* (2013) reported that the prevalence of lactose intolerance in the studied cohort increased with age. Such genetically determined intolerance was 58% at 6-7 years of age and increased to 90% by the age of 11-12.

***B) Glycogen storage diseases***

Glycogen is a branched polymer of glucose that contains a minor amount of phosphate and glucosamine. In the linear chains, the glucose residues are connected by α-1, 4-glycosidic linkages while α-1, 6-glycosidic bonds create the branch points (Chikwana *et al.,* 2013).

Glycogen storage diseases (GSDs) are a heterogeneous group of inherited disorders caused by defects in glycogen degradation and synthesis. GSDs are mainly observed in children and it mostly affects the liver, muscle and heart (Koshy *et al.,*. 2006). GSDs can be differentiated based on clinical, biochemical and enzymatic examination of the liver tissue. Based on enzyme deficiency, they are classified into 10 major types (Mundy and Leeb, 2004; Mahmoud *et al.,* 2017).

Saleem *et al.,* (2014) included 40 pediatric patients (25 male and 15 female) with age range 0.08-16 years who were selected from the pediatric outpatient clinics or inpatients pediatric departments of Assiut, Sohag and Qena university hospitals, Upper Egypt in their study, to identify the relative frequency of pediatric patients with Glycogen storage disease type-I (GSD-I) . Ten pediatric patients out of 40 were with the provisional and final diagnosis of glycogen storage disease type -I. The main presenting symptoms in GSD-I were failure to thrive and abdominal distension both have the highest frequency (90%) while convulsions have the lowest frequency (30%). Hepatomegaly was the main clinical sign in all patients (frequency = 100%) with or without splenomegaly (frequency =40%), with physical developmental delay (frequency= 90%).The main laboratory findings of GSD-I patients involved in their study were anemia, fasting hypoglycemia and raised aminotransferases have the highest frequency (100%) followed by hyperlipidemia (80%), hyperuricemia (70%), while hyperbilirubinemia has the lowest frequency (30%). In addition, there were statistically significant higher cholesterol and triglycerides among those patients. The definite diagnosis of GSD-I patients was by assay of G6Pase in the biopsied liver tissue homogenates. There was highly statistically significant lower G6Pase activity when measured in the biopsied liver tissue homogenates of the GSD patients (0.69±0.9 unit /mg liver tissue proteins) when compared with the control (9.5±2 unit / mg liver tissue proteins).The relative frequency of GSD-I in Upper Egypt was 5/100,000. They also reported elevated plasma biotinidase among GSD-I and was considered better positive than negative in prediction of GSD-I with higher sensitivity and low false negative rate.

Saleem *et al.,* (2017a) reported a four years old female patient with glycogen storage disease type-IV who exhibited an abdominal distension and failure to thrive since the age of 9 months. The patient showed hepatosplenomegaly and hypotonia of both upper and lower limbs proximally. The laboratory findings showed fasting hypoglycemia, raised liver enzymes, moderate hypochromic microcytic anemia, hyperlactatemia with raised total creatine phosphokinase & lactate dehydrogenase. The light microscopic findings of the liver biopsy specimen were consistent with GSD-IV.

**2. Disorders related to lipid metabolism**

***A) Gaucher's disease***

Gaucher's disease (GD) is an autosomal recessive genetic disorder that results from pathogenic mutations of the GBA gene encodingthe enzyme glucocerebrosidase (acid β-glucosidase), which islocated on chromosome 1q21.31. The absence or low activity of this enzyme leads to a progressive accumulation of its substrate (glucocerebroside) and hence causes the clinical manifestations of the disease. GD is one of the most common lysosomal storage diseases and one of the rare genetic diseases for which therapy is now available (Essabar *et al.,* 2015).

Hassan *et al.,* (2017) reported significantly higher plasma chitotriosidase (ChT) levels and increased total acid phosphatase activity were observed in GD patients versus those suspected to have storage disorders. High plasma ChT and ferritin have higher sensitivity, while high plasma total acid phosphatase activity, and globulin and low A/G ratio have higher specificity in diagnosing GD concluding that plasma ChT and total acid phosphatase activity, both together are more valid than ferritin and globulin in screening for GD. Saleem *et al.,* (2017b) reported 76.9% of

included patients were of type 1 GD, while 23.1% were of type 3 GD and none of our patients was classified as type 2 GD. The main frequent clinical presentations of GD in this study were hepatosplenomegaly (88.5%); pallor (76.9%); abdominal distension (61.5%) and musculoskeletal involvement (37.1%). Neurological abnormalities of type 3 GD included in this study were squint, seizures and delayed mental development. Five different genotypes were detected, homozygous for the mutation L444P, homozygous for the mutation N370S, heterozygous for the mutations N370S and rec Ncil, heterozygous for IVS2 +1 and rec NciI, heterozygous for L444P and IVS2 +1, concluding that Non-neuropathic type 1 and type 3 GD were the only clinical types found in the present study. The most common mutant alleles found in this study were L444P and N370S.

Hassan *et al.,* (2016) also reported significant higher plasma levels of ChT, total acid phosphatase activity, ferritin and globulin among GD not receiving enzyme replacement therapy (ERT) versus both GD on ERT and Control group. Positive correlation between plasma ferritin and total acid phosphatase activity, concluding that plasma ChT, total acid phosphatase activity; ferritin and globulin are collectively helpful in evaluation and follow up the effect of ERT.

***B) Non-alcoholic fatty liver disease (NAFLD)***

NAFLD is a condition defined by significant lipid accumulation (5–10%) in hepatic tissue in the absence of significant chronic alcohol consumption. Most patients with NAFLD have increased liver fat content alone (simple steatosis), but others develop increasing hepatic inflammation known as nonalcoholic steatohepatitis (NASH), and up to 20% of patients reveal progressive hepatic fibrosis and may eventually develop cirrhosis or liver failure and even hepatocellular carcinoma .The hallmark feature of the pathogenesis of NAFLD, both histologically and metabolically, is the accumulation of triacylglycerol (TAG) in the liver (Ezzat *et al.,* 2012; Mohamed *et al.,* 2014).

Mahmoud *et al.,* (2015) concluded that anthropometric measures, lipogram and serum adiponectin are associated with progression of steatosis in nondiabetic patients with NAFLD. So their detection is important for evaluation and management, as they reported that cholesterol, triglyceride and Low density lipoprotein-cholesterol (LDL-C) were significantly higher in patients with steatosis. High density lipoprotein-cholesterol (HDL-C) and serum adiponectin were significantly lower in patients with steatosis. Patients with severe steatosis showed significantly higher values for BMI and WC, cholesterol, triglyceride, LDL-C and lower values for HDL-C and adiponectin than those with mild or moderate steatosis. Positive correlations were detected between the age, BMI and WC, cholesterol, triglyceride, LDL-C and the grade of steatosis and negative correlations with HDL-C and adiponectin.

**3. Disorders related to protein metabolism**

***A) Inherited hyperammonemia***

Inherited hyperammonemia is most frequently caused by urea cycle defects (UCD) and organic acidurias (OA). In UCD, partial or complete lack of activity of key enzymes of the urea cycle (carbamoyl phosphate synthetase 1 [CPS1], ornithine transcarbamylase [OTC], argininosuccinate synthetase [ASS], argininosuccinate lyase [ASL], arginase 1 [ARG1], N-acetyl glutamate [NAG], ornithine/citrulline antiporter [ORNT1]) induces primary accumulation of ammonium and a secondary increase in glutamine production, owing to the action of intracellular glutamine synthetase in the presence of hyperammonemia (Häberle *et al.,*. 2012).

Saleem *et al.,* (2018) investigate the possibility of using some screening laboratory tests as rapid and conventional biochemical markers in blood for early pick up patients with high suspicion of urea cycle disorders. They found that 58% of the included pediatric patients proved to have urea cycle defects (UCDs). Consanguinity among the patients' parents (62.8 %) was significantly high compared with the controls. Blood ammonia was significantly higher in patient's groups suspected to have UCDs with normal arterial blood gases when compared with other patients involved in the study and the controls, concluding that UCDs are the most prevalent cause of inherited hyperammonemia in Upper Egypt. Arterial blood gases and blood ammonia can be aid in their diagnoses and help to differentiate from other causes of hyperammonemia.

***B) Phenylketonuria***

Phenylketonuria (PKU) is an autosomal recessive genetic disorder characterized by a deficiency in the enzyme phenylalanine hydroxylase. When this enzyme is deficient, phenylalanine accumulates and is converted to phenyl pyruvate, which is also known as phenylketone, which is detectable in the urine. Other unknown factors also interfere in determining the metabolic profile of PKU (Oh *et al.,* 2004; Blau *et al.,* 1996).

Oriquat *et al.,* (2013) reported two cases of PKU in Sohag Governorate, Upper Egypt. The first diagnosed case was a three year old girl of a consanguineous couple. The child presented with history of delayed growth milestones, repeated vomiting and hyperirritability since birth. She was treated for hypoxic ischemic encephalopathy with seizures. There was family history of mental retardation, but no sibling deaths, convulsions or albinism. The child had frequent myoclonic jerks with drooling of saliva. There was gross microcephaly with head circumference of 37 cm. Overall motor, language

and social developmental delays were noted. Brain CT scan was uneventful. Urine was tested for PKU by the ferric chloride method, and gave a positive result. The second diagnosed case was a three and half years old boy of a sanguineous couple. Family history revealed death of 2 siblings after 1-2 weeks of birth. Clinical examination revealed delayed developmental parameters like walking; speaking and head support (Table 3). CNS examination showed normal higher mental functions. There was generalized hypotonia with normal plantar reflex and lordosis of the lumbar spine. The urine sample which was taken was turbid and foul smelling. Screening for PKU by the ferric chloride method was positive.

Sadek *et al.,* (2018) reported 113 PKU patients, diagnosed during the period from 2012 to 2017, at the Pediatric Neurology Clinic of Sohag University Hospital, Upper Egypt. One hundred cases were diagnosed based on the clinical suspicion combined with laboratory confirmation by measuring their plasma phenylalanine levels, using amino acid analyzer (SYKAMS433, Germany, Catalog No: 1120001). This analyzer combines the classical method of ion exchange separation with derivrtization using ninhydin, with the modern technique of high liquid chromatography. While, three cases were detected during neonatal screening using dried blood spot analysis. Eighteen cases (15.9%) have hyperphenylalaninemia, 40 cases (35.4%) have mild to moderate PKU and the remaining 55 (48.7%) patients have classical PKU. This categorization was based on the blood phenylalanine level as follow: Plasma Phe level >3 mg/dl (>180 µmol/L) was considered elevated. Patients were classified as having classic PKU if their Phe levels were >1200 µmol/L, mild to moderate PKU if Phe levels fall within 600–1200 µmol/L, while, those with Phe level <600 µmol/L were categorized as having mild hyperphenylalaninemia (HPA) (Guldberg *et al.*,1994; Guldberg *et al.*,1998).

**C) Homocysteine amino acid and stroke**

Homocysteine (Hcy) is a toxic, sulfur-containing intermediate of methionine metabolism. Hyperhomocysteinemia (hHcy), as a consequence of impaired Hcy metabolism or defects in crucial co-factors that participate in its recycling, is assumed as an independent human stroke risk factor. Neural cells are sensitive to prolonged hHcy (Lehotský *et al.*, 2016)

Saleem *et al.,* (2016) measured plasma homocysteine levels and lipid profile (serum cholesterol, triglycerides, HDL and calculation of LDL) in pediatric patients with ischemic or hemorrhagic stroke and assessed the role of homocysteinemia as an associated risk factor in pediatric ischemic stroke, concluding that elevated plasma homocysteine can be considered as an associated risk factor among pediatric patients with ischemic stroke that could be explained by its atherogenic and thrombotic effects. This was associated with hyperlipidemia.

**4. Current and future metabolic research studies include**

***A) Metabolic myopathies.***

***B) Galactosemia.***

***C) Maple syrup urine.***

In the previously three mentioned metabolic disorders we aimed to assess the relative frequencies, clinical types and common genetic mutations of the affected enzymes.

## CONCLUSIONS

IEM are now recognizable to a much better degree in Upper Egypt which mainly attributed to the consanguineous marriage among the patients' parents noticed in all our previously published reports which reach up to 100% in some disorders. We hope to complete the map of such inherited disorders, and this is our main aim which runs in parallel to study the genetic and metabolic nature of various diseases including cancer.

***Acknowledgments***

Special thanks to the teamwork of MGD unit who do their best to validate all laboratory parameters so that an accurate diagnosis was achieved to our pediatric patients in our locality, Upper Egypt.

## REFERENCES

1. Fateen, E. M., Ibrahim, M. S., & Abdallah, Z. Y. (2014). Fifteen years experience: Egyptian metabolic lab. *Egyptian Journal of Medical Human Genetics*, *15*(4), 379-385.
2. Semenza, G. (1986). Anchoring and biosynthesis of stalked brush border membrane proteins: glycosidases and peptidases of enterocytes and renal tubuli. Annu Rev Cell Biol, 2, 255–313.
3. Heyman, M.B. (2006). Lactose intolerance in infants, children, and adolescents. Pediatrics. 118 (3), 1279-86.
4. Abuhamdah, S.M.A., Oriquat, G.A., Saleem, T.H., & Hassan, M.H. (2013). Prevalence of Lactose Intolerance in Primary School Children in Qena Governorate, Egypt. JJBS, (4), 334-336.
5. Chikwana, V. M., Khanna, M., Baskaran, S., Tagliabracci, V. S., Contreras, C. J., DePaoli-Roach, A., ... & Hurley, T. D. (2013). Structural basis for 2′-phosphate incorporation into glycogen by glycogen synthase. *Proceedings of the National Academy of Sciences*, *110*(52), 20976-20981.
6. Mahmoud, S. K., Khorrami, A., Rafeey, M., Ghergherehchi, R., & Sima, M. D. (2017). Molecular analysis of glycogen storage disease type Ia in Iranian Azeri Turks: identification of a novel mutation. Journal of genetics, 96(1), 19-23.
7. Mundy, H., & Leeb, P. J. (2004). The glycogen storage diseases. Curr. Pediatr. 14, 407–413

8. Saleem, T. H., Eltalawy, H. N., Ahmed, A. E., Abu-faddan, N. H., Mohamed, N. A., Sayed, A. A., ... & Hassan, M. H. (2014). Glycogen storage disease type-I among pediatric patients in Upper Egypt. *Gl Adv Res J Med Sci*, *3*, 281-90.
9. Saleem, T.H., Eltalawy, H.N., Ahmed, A.E., Abu-faddan, N.H., Mohamed, N.A., Sayed, A.A., Gamal, Y., & Hassan, M.H. (2017a). Glycogen storage disease type-IV: A case report. The Pharmaceutical and Chemical Journal, 4(5), 8-12.
10. Essabar, L., Meskini, T., Lamalmi, N., Ettair, S., Erreimi, N., & Mouane, N. (2015). Gaucher's disease: Report of 11 cases with review of literature. Pan African Medical Journal; 20 (1).
11. Hassan, M. H., Sayed, A. A., Ahmed, A. E. A., & Saleem, T. H. (2017). Diagnostic Utility of Plasma Chitotriosidase, Total Acid Phosphatase Activity, Ferritin and Globulin Levels in Screening for Gaucher Disease. *International Journal of Biochemistry Research & Review*, 1-8.
12. Hassan, M. H., Sayed, A. A., Ahmed, A. E. A., Saleem, T. H., Elsayh, K. I., & Mohammed, N. B. (2016). Effect of enzyme replacement therapy on disease burden biomarkers in Gaucher's disease. *Studies*, *3*, 4.
13. Saleem, T. H., Hassan, M. H., Ahmed, A. E. A., Sayed, A. A., Mohamed, N. A., Elsayh, K. I., ... & Mohammed, N. B. (2017b). Clinical and genetic assessment of pediatric patients with Gaucher's disease in Upper Egypt. *Egyptian Journal of Medical Human Genetics*, *18*(3), 249-255.
14. Ezzat, W. M., Ragab, S., Ismail, N. A., Elhosary, Y. A., ElBaky, A. M. N. E. A., Farouk, H., & Rasheed, I. A. (2012). Frequency of non-alcoholic fatty liver disease in overweight/obese children and adults: Clinical, sonographic picture and biochemical assessment. *Journal of Genetic Engineering and Biotechnology*, *10*(2), 221-227.
15. Mohamed, A. A., Shousha, W. G., Shaker, O., Mahdy, M. E. S., Ibrahim, E. M., & Mohmoud, S. (2014). Role of Serum Adiponectin, IL-6 and Hs CRP in Nonalcoholic Fatty Liver Egyptian Patients. *International Journal of Biochemistry Research & Review*, *4*(6), 493.
16. Mahmoud, H. S., Helal, M. M., Hassan, M. H., & Sherif, M. F. (2015). Correlation between anthropometric measures, lipid profile and serum adiponectin and steatosis in nondiabetic nonalcoholic fatty liver disease. *British Journal of Medicine and Medical Research*, *7*(9), 771-8.
17. Saleem, T.H., Ahmed, A.E., Hassan, M.H., Rashwan, N.I., & Salama, D.A. (2018). Arterial blood gases and blood ammonia as primary screening tests for pediatric patients suspected to have urea cycle disorders. Archives of Pediatrics.2018. (3), 1-10.
18. Häberle, J., Boddaert, N., Burlina, A., Chakrapani, A., Dixon, M., Huemer, M., Karall, D., Martinelli, D., Sanjurjo, Crespo, P., Santer, R., Servais, A., Valayannopoulos, V., Lindner, M., Rubio, V., & DionisiVici, C. (2012). Suggested guidelines for the diagnosis and management of urea cycle disorders. Orphanet Journal of Rare Diseases, 7, 32.
19. Blau, N., Barnesand, I., & Dhondt, J.L. (1996). International database of tetrahydrobiopterin deficiencies. J Inherited Metabolic Dis., 19, 1 8-14.
20. Oh, H. J., Park, E. S., Kang, S., Jo, I., & Jung, S. C. (2004). Long-term enzymatic and phenotypic correction in the phenylketonuria mouse model by adeno-associated virus vector-mediated gene transfer. Pediatric research, 56(2), 278.
21. Oriquat, G.A., Saleem, T.H., Ahmed, N.S., Abuhamdah, & S.M.A. (2013). Phenylketonuria in Sohag: A Preliminary Study. Jordan Journal of Biological Sciences. All rights reserved, 6 (3), 243 – 245.
22. Sadek, A.A., Hassan, M.H., & Mohammed, N.A. (2018). Clinical and neuropsychological outcomes for children with phenylketonuria in Upper Egypt; a single-center study over 5 years. Neuropsychiatr Dis Treat. 2018 Oct 5 (14), 2551-2561.
23. Guldberg, P., & Güttler, F. (1994). Mutations in the phenylalanine hydroxylase gene: methods for their characterization, ActaPaediatr. 407, 27–33.
24. Guldberg, P., Rey, F., Zschocke, J., Romano, V., François, B., Michiels, L., ... & Meli, C. (1998). A European multicenter study of phenylalanine hydroxylase deficiency: classification of 105 mutations and a general system for genotype-based prediction of metabolic phenotype. *The American Journal of Human Genetics*, *63*(1), 71-79.
25. Saleem, T. H., Hassan, M. H., El Deen, Z. M. M., Ahmed, A. E. A., El-Ebidi, A. M., Qubaisy, H. M., & Hasan, O. A. (2016). Biochemical assessment of homocysteine and lipid profile in pediatric stroke: an egyptian study. *Int J Cur Res Rev| Vol*, *8*(6), 22.
26. Lehotský, J., Tothová, B., Kovalská, M., Dobrota, D., Beňová, A., Kalenská, D., & Kaplán, P. (2016). Role of homocysteine in the ischemic stroke and development of ischemic tolerance. *Frontiers in neuroscience*, *10*, 538.