



Original Research Article

Inborn Errors of Metabolism and Autism Spectrum Disorders - Experience At a Tertiary Care Center

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ABSTRACT

Aims & Objectives: Recently the diagnosis and treatment of inborn errors of metabolism have improved substantially. Metabolic disorders are individually rare, together they constitute a significant percentage of autism children presenting with acute problems. The aim of our study was to perform diagnosis and assessment of inborn errors of metabolism for autism spectrum disorders.

Methods: One fifty two patients were referred for clinical and metabolic assessment. Ninety patients were subjected to a metabolic work up depending on the provisional diagnosis.

Results: A variety of metabolic disorders were diagnosed in patients presented with signs and symptoms. The diagnosis was confirmed in 15% of patients with age range between 3 years to 12 years.

Conclusion: This study addresses background information, and possible diagnostic tools of children with autism spectrum disorders, and the need for future research was aimed at understanding the relations among autism and neurometabolic disorders.

Key Words: Autism Spectrum Disorders, IEM, GC-MS.

INTRODUCTION

Autism Spectrum Disorder (ASD) is a complex, behaviorally defined developmental disorder characterized by social deficits, language impairments and repetitive behaviors with restricted interests. Leo Kanner first described autism in 1943.

^[1] The Diagnostic and Statistical Manual (DSM-IV-TR), Fourth edition and text revision of the American Psychiatric Association includes five different disorders under an umbrella term of Pervasive Developmental Disorders (PDDs). These include Autistic disorder, Asperger's disorder, Pervasive Development Disorder-Not Otherwise Specified (PDD-NOS), Rett syndrome, and Childhood Disintegrative

Disorder (CDD). ^[2] The overall prevalence of ASD is 10 cases per 1000. The overall sex ratio of males to females with autism has traditionally been reported at approximately 3:1 to 4:1. ^[3] In India, there are no reliable figures reported.

Epidemiologic studies indicate several prenatal and postnatal factors may contribute to apparent increase in incidence of ASD in the recent years. The prenatal factors are advanced paternal age, advanced maternal age, Genetic and environmental factors, maternal immigration, gestational diabetes, gestational bleeding, medication use during pregnancy, prenatal complications, and prenatal stress. ^[4]

Postnatal factors are food allergies, IEM, brain dysfunction, neuroinflammatory anomalies, Low Birth Weight (LBW), learning deficits, seizure disorders, and MMR immunization. [5]

Autism is an etiologic heterogeneous entity caused by many different diseases occurring in the central nervous system at an early stage in life. Recent surveys indicate that approximately 5% children with autism may have an IEM. [6] Metabolic disorders that present with an ASD phenotype are probably very rare. However, exact estimates are not available because there are few population-based studies. Most studies in the literature use metabolic testing as one part of a larger genetics evaluation and the results regarding positive yields are routinely low. [7] There are many metabolic disorders with an autistic phenotype. These include amino acids disorders (phenylketonuria), disorders of organic acids metabolism, disorders of fatty acids metabolism, disorders of carbohydrates metabolism, purine and pyrimidine metabolism, neuro metabolic syndrome and others. [8] Selective metabolic testing should be done in the presence of suggestive clinical findings, including lethargy, cyclic vomiting, early seizures, dysmorphic features, and mental retardation. [9]

IEM are typically inherited in an autosomal recessive fashion and are generally present within the first 3 years of life. The early onset of these symptoms can coincide with the emergence of the behavioral abnormalities seen in autism. [10] Similarly, accumulating clinical, genetic, and biochemical evidence suggests that mitochondrial dysfunction in ASD is more commonly seen than expected. Mitochondrial dysfunction with concomitant defects in neuronal oxidative phosphorylation within the central nervous system and frequent association of lactic acidosis and carnitine deficiency was seen in

autistic patients. [11,12] Some patients with ASD phenotypes clearly have genetic-based primary mitochondrial disease. [13] Recent study suggested children with Attention-Deficit/Hyperactivity Disorder (ADHD) have altered fatty acid metabolism. Omega-3 fatty acids are dietary essentials, and are critical to brain development and function. Increasing evidence suggests that a relative lack of omega-3 may contribute to many psychiatric and neurodevelopment disorders. Omega-3 has possible role in Attention-Deficit/Hyperactivity Disorder and related Childhood Developmental Disorders. [14] One study suggested Phenyl acetate may cause autistic like behavior. Although, it is clear that most of the cases of autism are not directly associated with identifiable metabolic disorders. [15]

MATERIALS AND METHODS

Patient's History

A comprehensive database containing all of the autistic patient's details was systematically updated in the Neonatal Screening Laboratory, Neopel Bioscience, Chennai. This database contains clinical history, diagnostic and treatment information for each patient. All information was collected at the time of initial patient contact and updated when the results of diagnostic investigations became available, or regularly at each subsequent patient visit.

Patient's counseled location

Patients contained in this database have been seen in 4 different locations;

- (1) Neopel Bioscience-based outpatient department.
- (2) Neopel Bioscience -based outpatient clinics.
- (3) Private autism camps conducted by Autism Society, Bangalore and
- (4) Private autism schools arranged consultation visits.

Each patient was counseled then reviewed for eligibility in the study of diagnosis.

Patient's Clinical symptoms

Patients were clinically diagnosed of autism, according to the DSM-IV-TR criteria, established by the American Psychiatric Association and they had already been evaluated by a developmental pediatrician, a pediatric neurologist, and/or a licensed psychologist for developmental delay and their learning disabilities. Totally 152 patients were counseled. All the patients were in the age group of 3-12 years. Of these 62.25% were clinically evaluated with ASD, 20.53% for PDD-NOS and 17.22% for ADHD. The Male: Female ratio in this study was found to be 4:1. Amongst this study group, 67 % were seen to be having sleep related disorders. We found a higher prevalence of sleep disturbances and sudden irritability in children with autism disorders. 64 % of children's was seen developmental delay. 30% children in the study group were seen to be suffering from constipation. 12% mothers of patients in the study group had a history of Urinary Tract Infection (UTI) during pregnancy. In our study, 3% were born to consanguineous parents. In our studies 56% of children were predominantly non-vegetarian while only 44% of them were vegetarian.

Procedure used for examination of metabolic disorders

Of the 152 patients, 90 patients only had related clinical symptoms to do metabolic investigations and 62 patients were excluded. 5cc of urine samples from 90 subjects (82 males and 8 females) were collected. The quantitative determination of metabolic markers was performed by Gas Chromatography and Mass Spectrometry (GCMS).^[16] Precision, accuracy, sensitivity was measured. Controls worked satisfactorily. Exact determination of metabolic markers in body fluids is of paramount importance for a definitive diagnosis and therapeutic control of inborn errors of metabolism in Autism.

RESULTS

Autism is an etiologic heterogeneous entity caused by many different diseases occurring in the central nervous system at an early stage in life. Several metabolic defects have been associated with autistic symptoms with a rate higher than that found in the general population. The analysis of metabolic markers in human urine is necessary for diagnosis of comprehensive metabolic profile. Large number of metabolic components are present in body fluids, because of that its separation and quantization is very difficult. In the case of comprehensive metabolic investigations, a few metabolic disorders have been, diagnosed in autistic patients with abnormal levels. The etiopathogenesis of infantile autism is still unknown. Pediatricians and neurologist have an important role not only in early recognition and evaluation of autism spectrum disorders but also in chronic management of these disorders.

We investigated ninety cases, and thirteen cases found positive for IEM disorders. For age matched controls, urine samples were collected from healthy adult volunteers, normal children and infants. We have elaborated details of the disorders detected (Table 1). Dietary intervention was applied to all thirteen positives for autistic patients with help from dietary department. The primary goals of treatment were to reducing maladaptive behaviors, educating and supporting families. It was also aimed to assist pediatricians in educating families and guiding them toward empirically supported interventions for their children.^[17]

DISCUSSION

Research on IEM and autism has begun to clarify many aspects of this enigmatic and devastating neurodevelopment disorder. Studies are being conducted at all levels of analysis, and

we are beginning to see the interconnections between the underlying metabolic causes and the cognitive and behavioral manifestations of autistic disorder. The early onset of these metabolic symptoms can coincide with the emergence of the behavioral abnormalities seen in autism. Metabolic defects have also been associated with autism suggesting inborn errors of metabolism as a potential pathogenic factor. Deficits in cell adhesion molecules, second messenger systems and secreted molecules have also been implicated in autism's rather than complex pathophysiology. [18] Interest in studying these rare cases is increasing, not only because proper diagnosis is important

to a given patient but also because these cases may be able to provide clues to the underlying metabolic abnormalities in idiopathic autism. [19] The follow-up improvement in the child is promising in the case of many such affected children, who may go undiagnosed if not screened for an inborn error of metabolism. These study addresses background information and possible dietary managements of children with autism spectrum disorders. In our present view, patient recovery from autistic disorders is unexpected and unexplained. There is no specific treatment for autistic disorders. [20]

Table 1- Metabolic parameters in thirteen patients with IEM & Autism spectrum disorders. The investigation reveals that maximum numbers seen were amino acids disorders, seen in six cases. Organic acids and Fatty acids disorders were found in four and two cases respectively. Carbohydrate metabolism related disorder was seen in one individual.

S.No	Age/Sex	Presenting symptoms	Specimen	Metabolites Name	Control value	Patient Value	Disease Disorder
Case 1	4.5Y/M	Development delay, behavior problems, speech difficulty, metabolic crises, poor appetite, low muscle tone, vomiting, metabolic acidosis.	Urine	Methylmalonate	0.002	4.89	Methylmalonic acidemia
Case 2	4Y/M	Vomiting, delayed speech/language, development, and Infant seizures	Urine	2Keto glutarate, Malate	0.001 1.139	2.891 5.670	TCA cycle disorders
Case 3	5Y/M	Respiratory and gastrointestinal infections, mental retardation, metabolic acidosis, and speech difficulty.	Urine	Methylmalonate	0.002	3.75	Methylmalonic acidemia
Case 4	4Y/M	Consanguinities parents and developmental delay.	Urine	Phenyl acetate	0.019	1.439	Elevated level of Phenyl acetate
Case 5	9Y/M	Talkativeness, decreased sleep, disinhibited behavior, demanding attitude, and metabolic acidosis.	Urine	Lactate	45.408	103.781	Lactic acidosis
Case 6	3.8Y/M	Dysmorphic features	Urine	Phenyl acetate	0.019	2.143	Elevated level of Phenyl acetate
Case 7	5Y/M	Developmental delay, and metabolic crises	Urine	Propionate	0.001	4.89	Propionic acidemia
Case 8	4.6Y/M	Global Developmental delay (GDD)	Urine	Phenyl acetate	0.019	1.985	Elevated level of Phenyl acetate
Case 9	6Y/M	Poor Eye Contact, hypertonic, microcephaly, mousy body odor, onset, pigmentation, skin and sclera, seborrheic skin rash and muscle tone.	Urine	Suberate	0.016	2.980	Elevated Suberate
Case 10	3.5Y/M	Development delay, behavior problems, poor appetite, dysarthria, seizure attacks, metabolic crises and mental retardation.	Urine	Methylmalonate	0.002	6.74	Methylmalonic acidemia
Case 11	2.6Y/M	Seizures	Urine	2Keto glutarate, Malate	0.001 1.139	1.258 2.875	TCA cycle disorders
Case 12	3Y/M	GI track infection, ketosis and Developmental delay	Urine	Isovalerate	0.025	2.679	Isovaleric acidemia
Case 13	3Y/M	Neurologic symptoms	Urine	4-hydroxy phenyl acetate	0.647	3.502	Elevated levels of 4-hydroxy phenyl acetate

Early investigation and dietary treatments for metabolic disorders has allowed vast improvements in the IQ, psychological, sleep related disorders, constipation problem and behavioral outcomes. Parents reported improvement of autistic children's behavior on Protein restricted diets. [21] Where no improvement in his/her behavior was noted in such cases, parents need to concentrate on special educations. It is important for clinicians to be aware of ASDs being related to metabolic disorders.

CONCLUSION

These studies provide information, an algorithm to help the pediatrician to develop a strategy for early identification of children with autism spectrum disorders. [22] The early treatment of these disorders could greatly reduce the prevalence of certain symptoms in autistic children and may also improve the autistic phenotype in this population and need for future comprehensive research aimed at understanding the relations among autism and neurometabolic disorders. It is hoped that new knowledge about the IEM and cognitive deficits in autism will encourage more research on how to treat children and adults with autism, which is the ultimate goal of these endeavors.

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