Etiological Factors in Children with Autism

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Introduction: - Autism is a neuro – developmental pathology with multiple etiologies. The diagnosis of Autism is accomplished by DSM IV criteria and various rating scales e.g. Allan's play rating scale, Wing's social interaction scale, Childhood Autism Rating Scale etc. etc. There are many medical disorders known to be associated with Autism (1). Various metabolic and genetic disorders are already known to be strongly associated with Autism (1): -

1. Adenylosuccinate lyase deficiency
2. Addison's disease
3. Adreno – leuko – dystrophy
4. Coeliac disease
5. Histidinemia
6. Hurlers syndrome
7. Hypo / Hyper thyroidism
8. Hyper – uricosuria
9. Lipidosis
10. Phenylketonuria
11. Lactic Acidosis

Other Genetic disorders: -

1. Cornelia De Lang syndrome
2. Dandy Walker syndrome
3. Goldenhar syndrome
4. Hydrocephalus
5. Hypomelanosis of Ito
6. Oculocutaneous albinism
7. Tuberous sclerosis
8. Neurofibromatosis
9. Duchenne Muscular Dystrophy
10. Trisomy 21
11. 18q – XYY, XXX
12. Fragile X Syndrome

Recently it has been shown that milder varieties of Creatine Synthesis Defects (3) and Succinic Semialdehyde Dehydrogenase deficiency are also known to have Autism (4).

Objectives:- The awareness for diagnosis and management of Autism has increased dramatically, however in most of the cases the exact etiology is not known. Thus the treatment also remains experimental. We decided to study children with autism, who attended our clinic from Jan. 2002 till Dec 31st 2008. The main aim was to determine inborn errors of metabolism or fragile X syndrome as acusative factors for Autism.

Methods: - We selected 45 children with Autism who attended our clinic for genetic and metabolic evaluation. All the children were examined by pediatrician and psychologist. Clinically children were examined and following features were noted down – Microcephaly, Macrocephaly, dysmorphic features, suggestive of Down's syndrome, Tuberous sclerosis, Neurofibromatosis, DMD, Cornellia De Lang Syndrome etc. etc. None of these 44 children had any feature suggestive of the above clinical diagnosis. A clinical psychologist examined all the children and Autism was diagnosed if they fulfilled DSM IV criteria. "CARS" rating was performed in all of them and children with CARS score of more than 32 were entered in this study group. The main aim was to identify Inborn Error of Metabolism, as there is always a potential for some treatment. A battery of tests was performed in all these children, including Ammonia, Lactate, Blood Sugar level, Sr. Uric Acid, Urinary Uric Acid / Creatinine ratio, Amino-acidogram by HPLC, Acyl carnitine profile, Gas Chromatography with Mass Spectrometry, Antigliadin Antibodies Ig G, Ig A and Tissue trans – glutaminase IgA. Fragile X Chromosome was analyzed by PCR technique.

Results: of 45 children with autism 36 were males and 9 were females. Youngest person was 1.1 yr and eldest in this cohort was 15 yrs.

	Etiological Factors – Autism	**N = 46**
A	**Aminoacidopathy**	
1	Phenylkenoturia	2
2	Histidinemia	1
3	Hyper-Homocysteinemia	2
4	Hyperleucinemia	1
5	Hypervalinemia	1
B	**Carbohydrate Metabolism Defect**	
	Fructose Intolerance	1
C	**Urea Cycle Defect**	
1	Argininemia	3
D	**Mitochondrial Defect**	
1	Respiratory Chain Defect	2
2	Non-specific Mitochondrial Defect	1
E	**Fatty Acid Oxidation Defect**	
1	Carnitine Transport Defect	1
F	**Organic Acidemia**	
1	Partial Biotinidase Deficiency	4
2	Biotinidase Deficiency	1
G	**Neurotransmitter Metabolism Defect**	
1	Succinyl Semialdehyde Dehydrogenase Deficiency	1
H	**Miscellaneous**	
1	Gluten Sensitivity	8
	Gluten Sensitivity with elevated Hcy	2
2	Fragile X Syndrome	1
3	Incontinentia Pigmentii	1
4	Tuberous sclerosis	0
5	Rett's Syndrome	1
6	Idiopathic Autism	9
7	Gross Chromosomal Anomalies	1
8	Intrauterine Rubella Infection	0
9	Intrauterine CMV Infection	2
	Total	**46**

Conclusion: - Of the 46 children studied we found CMV Infection (2/46), Gluten Sensitivity (8/46), Gluten Sensitivity with Hyper-homocysteinemia (2/46) Partial Biotinidase deficiency (4/46), Biotinidase deficiency (1/46), Phenylketonuria (2/46),

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Histidinemia (1/46), Hyper-Homocysteinemia (2/46), Hyperleucinemia (1/46), Hypervalinemia (1/46),, Argininemia (3/46), Respiratory Chain Defect (2/46), Succinyl Semialdehyde dehydrogenase deficiency (1/46), Fragile X Syndrome (1/46), Rett's Syndrome (1/46), and Incontinentia Pigmentii (1/46). In 9 patients there was no apparent etiological factor and were labelled as Idiopathic (9/46). One child had one extra large chromosome of unidentified type.

Prenatal diagnosis:- Since there is no specific etiology for all the Autism children, it is important to identify a specific etiology with known inheritance pattern. Many of the above listed conditions can be diagnosed prenatally and that is very important for the family. Amino – acidopathies, disorder of Urea Cycle defects, Mitochondriopathies, Creatinine Synthesis defect, Succinic Semialdehyde dehydrogenase deficiency, Fragile X Syndrome, Down syndrome, can be diagnosed prenatally with full confidence. We strongly recommend that the index case should be investigated in detail to rule out Inborn Error of Metabolism, Gluten Sensitivity, and fragile X etc. Recently a DNA child has been made available to detect many gene defects which otherwise could not be identified by routine and extended Karyotype. This may be useful in the identification of genetic defect and also for the prenatal diagnosis.

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