Screening of Autism Spectrum Disorder in Metabolic Disorders by Modified Checklist of Autism-Revised/Follow-up

Thesis

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List of Abbreviations

Abb.	Full term

5 - MTHF..... 5 - methyltetrahydrofolate
AAP.....The American Academy of Pediatrics
ADDM .....Autism and Developmental Disabilities Monitoring
ADSL ..... Adenylosuccinate lyase
AGAT.....Arginine: glycine amidinotransferase
ALDH..... Aldehyde dehydrogenase gene
ASD .....Autism Spectrum Disorder
ATP..... Adenosine triphosphate
BH4.....Tetrahydrobiopterin
BISCUIT..... Baby and Infant Screen for Children with Autism Traits
CARS .....Childhood Autism Rating Scale
CASD.....Checklist for Autism Spectrum Disorders
CDS.....Creatine deficiency syndromes
CFD..... Cerebral folate deficiency
CHAT .....Checklist for Autism in Toddlers
CNS ..... Central Nervous System
CNV ..... Copy-number variants
co-Q.....coenzyme Q10
CSF.....Cerebrospinal fluid
DLD .....delayed Language Development
DSM-III .....The third edition of Diagnostic and Statistical Manual
DSM-V .....5th edition of the Diagnostic and Statistical Manual
DTI .....Diffusion-tensor imaging
EEG .....Electroencephalography
ESAT .....Early Screening for Autistic Traits
FMR1..... Fragile X Mental Retardation gene

List of Abbreviations (Cont...)

Abb.	Full term
GABA	*Gamma aminobutyric acid*
GAMT	*Guanidinoacetate methyltransferase*
GFCF	*Gluten-free and/or casein-free*
GHB	*Gamma-hydroxybutyric*
KD	*Ketogenic Diet*
M-CHAT	*Modified Checklist for Autism in Toddlers*
M-CHAT-R/F	*Modified Checklist for Autism in Toddlers, Revised with Follow-up*
MMR	*Measles, mumps and rubella*
MRI	*Magnetic Resonance Imaging*
MRS	*Magnetic resonance spectroscopy*
mtDNA	*Mitochondrial DNA*
NADH	*Nicotinamide adenine dinucleotide*
P5P	*Pyridoxal-5-phosphate*
PDD-NOS	*Pervasive developmental disorder, not otherwise specified*
PDS	*Pyridoxine dependent seizures*
PET	*Positron Emission Tomography*
PKU	*Phenylketonuria*
pls-4	*Preschool language Scale, fourth edition*
PRS	*Pyridoxine responsive seizures*
ROS	*Reactive oxygen species*
SAM	*S-adenosylmethionine*
SAMe	*S-adenosyl methionine*
SCI	*The Social Communication and Interaction*
SCQ	*Social Communication Questionnaire*
SLOS	*Smith-Lemli-Opitz Syndrome*
SON	*Snijders Oomen Non-Verbal Scale for Deaf and Hearing*

List of Abbreviations (Cont...)

Abb.	Full term
SPECT	*Single-Photon Emission Computed Tomography*
SSADH	*Succinic semialdehyde dehydrogenase*
STAT	*Screening Tool for Autism in Toddlers and Young Children*
WHO	*World Health Organization*
α-AASA	*α-aminoadipic semialdehyde*

ABSTRACT

It was done through using the validated Arabic version of the screening test (Modified Checklist for Autism, Revised and Follow-up). The test was applied on 100 children diagnosed as having metabolic disorders with age range of (16-30) months excluding children with visual or hearing impairment from the study.

The results showed that 20 % of the studied cases were at low risk for ASD, 58% were at medium risk and 22% were at high risk. But only 16% were true ASD and 84% were non-ASD cases but may have any other developmental concern other than ASD. The mitochondrial disorder had the highest percentage of ASD cases.

We have to conclude that Children with various metabolic disorders are considered a high risk group for different developmental concerns; one of the most important is ASD. So, screening for ASD is of a great significance for this suspicious group for early detection of ASD cases and providing better prognosis through starting therapy as early as possible.

Keywords: Single-Photon Emission Computed Tomography - Gamma aminobutyric acid

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by language delay, deficits in social interaction and communication, both verbal and non-verbal and restricted repetitive behaviors, interests or activities which are manifested by stereotyped, repetitive speech, motor movement or use of objects, inflexible adherence to routines, restricted interests, and hyper- and/or hypo-sensitivity to sensory input ***(American Speech-Language-Hearing Association, 1995).***

Recently the 5th edition of the Diagnostic and Statistical Manual (DSM-V) identified just two criteria for diagnosis of ASD which are social interaction domain (including language and social communication deficits) and repetitive or restricted behaviors ***(American Psychiatric Association, 2013).***

The prevalence of ASD has increased in the recent years. The previous epidemiological studies reported that the median rate of ASD is 5 cases per 10,000 individuals. In Egypt, the median rate is 62 cases per 10,000 individuals with average rate 4.3: 1 male to female ratio ***(El-Sabbagh et al., 2012).*** Also an Egyptian study was done with aim of screening for ASD in egyptian children in various health care units flagged a considerable result which was 1320 of the enrolled 5546 Egyptian toddlers (23.8%) are suspected to have ASD ***(Mohamed et al., 2016).***

ASD 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. In some patients, early diagnosis of the metabolic disorders and proper therapeutic interventions may significantly improve the long-term cognitive and behavioral outcome.

The main neurometabolic conditions that may start during the first 3 years of life e.g. phenylketonuria, creatine deficiency syndromes, adenylosuccinate lyase deficiency, inborn errors of cholesterol biosynthesis, histidinemia, succinic deficiency show autistic features as one of its clinical presentations and they are potentially treatable ***(Curatolo et al., 2008).***

Also, the recent studies have proved that the mitochondrial disorders may be central to the etiology of many neurologic diseases e.g. ASD. The brain has the highest mitochondrial energy demand of any organ. Therefore, subtle changes in mitochondrial energy production will preferentially affect the brain. Considerable biochemical evidence has accumulated revealing mitochondrial defects associated with neuropsychiatric disorders. Moreover, the mitochondrial genome encompasses over a thousand nuclear DNA genes plus hundreds to thousands of copies of the maternally inherited mitochondrial DNA (mtDNA). Therefore, partial defects in either the nuclear DNA or mtDNA genes or combinations of the two can be sufficient to cause neuropsychiatric disorders.

Inherited and acquired mtDNA mutations have recently been associated with autism spectrum disorder, which parallels previous evidence of mtDNA variation in other neurological diseases ***(Liming et al., 2017).***

So, the American academy of pediatrics advised early screening for ASD by Modified Checklist for Autism in Toddlers, Revised with Follow-up (M-CHAT-R/F) as the symptoms start to manifest at 1.5 years, however, it is often diagnosed after the child`s 3rd birthday.

M-CHAT-R/F is a two stage parent- report screening tool to assess risk for ASD ***(Robins et al., 2009).***The primary goal of M-CHAT-R is to maximize the sensitivity, meaning to detect as many cases of ASD as possible. But; it has a high false positive rate so it was developed with the follow-up scoring sheet to be M-CHAT-R/F which has a higher sensitivity and less false positive results.

The scoring algorism:

The scoring sheet of M-CHAT-R is composed of 20 questions, for all items except (2, 5 & 12) the response "NO" indicates ASD risk.

For items (2, 5 & 12) the response "YES" indicates ASD risk.

- Low risk scores (0-2) → if the child is less than 24 months, screen again after reaching 24 months. No further actions are required.

- Medium risk score (3-7) → Administer the second stage of M-CHAT-R/F to get additional information about at risk response. If M-CHAT score remains at 2 or higher, the child screened positive (Action needed: refer for diagnostic evaluation and early intervention). If M-CHAT score on follow up is (0-1) no further action is needed. Unless rescreening on the future visits.

- High risk score (8-20) → it is acceptable to by-bass the follow up stage and refer immediately for diagnostic evaluation and early intervention.