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Autism: An overview

Lakkana Rerksuppaphol*✉, Sanguansak Rerkguppaphol**

*Department of Preventive Medicine, Faculty of Medicine, Srinakharinwirot University

**Department of Pediatrics Faculty of Medicine, Srinakharinwirot University

Abstract

Autism is a type of pervasive developmental disorder characterized as an abnormality in the brain development. The present review focuses on the causes, diagnosis, pathophysiology theories and treatment interventions for autism. Up to the present the causes of autism are inconclusive, however, from available data, genes and chromosome may involve in the pathogenesis. Other factors are prenatal and postnatal environment such as food allergy, exposure to metals such as mercury and dysfunction in amygdala. Various diagnostic methods are used such as the national autism plan for children (NAPC), the checklist for autism in toddlers (CHAT) and multiagency assessment (MAA). Various interventions such as biologically based interventions, phychodynamic interventions, behavioral therapy, family-based interventions and complementary and alternative medications (CAM) are also presented.

Keywords: Autism, etiology, causes, interventions, pathophysiology, pervasive developmental disorder, theory

Lakkana Rerksuppaphol✉
Department of Preventive Medicine,
Faculty of Medicine, Srinakharinwirot University
62 Moo 7, Rangsit-Nakhon Nayok Rd, Nakhon Nayok 26120, Thailand.

ภาพรวมของโรคออทิสซึม

ลัคนา ฤกษ์ศุภผล*, สงวนศักดิ์ ฤกษ์ศุภผล**
*ภาควิชาเวชศาสตร์ป้องกันและสังคม คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ
**ภาควิชากุมารเวชศาสตร์ คณะแพทยศาสตร์ มหาวิทยาลัยศรีนครินทรวิโรฒ

บทคัดย่อ

ออทิสซึมจัดอยู่ในกลุ่มความบกพร่องของพัฒนาการแบบรอบด้าน (Pervasive developmental disorder) ที่เป็นผลจากการพัฒนาการของสมองที่ผิดปกติ บททบทวนวรรณกรรมนี้ได้รวบรวมสาเหตุ การวินิจฉัย ทฤษฎีพยาธิสรีรวิทยา และการรักษาโรคออทิสซึม จนถึงปัจจุบันยังไม่สามารถสรุปสิ่งที่เป็นสาเหตุของออทิสติกได้ แต่ความผิดปกติของยีนและโครโมโซมอาจเกี่ยวข้องกับในการเกิดโรค สาเหตุของโรคออทิสซึมมีหลากหลายและปัจจุบันสามารถตรวจพบความผิดปกติของยีนและพันธุกรรมซึ่งเชื่อว่าเป็นต้นเหตุสำคัญของการเกิดโรค ปัจจัยอื่นที่เชื่อว่าเป็นสาเหตุให้เกิดอาการออทิสซึม เช่น ผลกระทบจากสิ่งแวดล้อมทั้งระหว่างอยู่ในครรภ์หรือหลังเกิด เช่น การแพ้อาหาร การได้รับสารโลหะหนัก เช่น ตะกั่ว และความผิดปกติของสมองส่วน amygdala เป็นต้น

การวินิจฉัยออทิสซึมสามารถใช้แบบประเมินต่างๆ เช่น National Autism Plan for Children (NAPC) The checklist for autism in toddlers (CHAT) และ Multiagency assessment (MAA) เป็นต้น การทบทวนนี้ยังได้นำเสนอหลักการการรักษาด้วยวิธีต่างๆ เช่น ชีวบำบัด พฤติกรรมบำบัด การรักษาโดยอิงครอบครัว การแพทย์ทางเลือกและการรักษาเสริม

Definition

Autism is a type of pervasive developmental disorder characterized as an abnormality in brain development in children before the age of three years. The manifestations of autism include reciprocal social interaction, impaired communication, and restricted, stereotyped, repetitive behavior. Also the autistic patients show symptoms of phobia, sleeping and eating disturbances, temper tantrums, and aggression[1]. The pervasive developmental disorder is also known as an autistic spectrum disorder. It includes autistic disorder, classic or Kanner's autism, high functioning autism (HFA), Asperger's syndrome, Rett's syndrome, childhood disintegrative disorder (CDD) and pervasive developmental disorders not otherwise specified (PDD-NOS), known as an atypical autism[1, 2].

Causes of Autism

Genetics

Autism has been linked with diseases such as fragile X syndrome and tuberous sclerosis complex[3]. In a mouse model, the deletion of fragile X mental retardation 1 (Fmr1) gene was found to associate with autism. It was found that glycogen synthase kinase-3 (GSK3) activity was increased in brains of Fmr1 gene knockout mice. Chronic lithium administration inhibited GSK3 and ameliorated anxiety-related behaviors such as grooming, rearing, and digging[4]. Tuberous sclerosis also associated with autism. The incidence of tuberous sclerosis complex (TSC) in the autism spectrum disorder is 1 to 4%, whereas the incidence of autism spectrum disorder is present in 16 to 50% of individuals with tuberous sclerosis complex[5, 6]. The mechanism underlying for this association is as yet unclear but an abnormal TSC gene may influence the development of autism spectrum disorder[5, 6]. Cytogenetic assays are used to determine chromosomal abnormalities. Various genes have been identified to be associated with autism[3, 7, 8] (Table 1). The comparative study for cognitive and language skills between 39 siblings with autism (SIBS-A) and siblings with typically developing children (SIBS-TD) at ages 4, 14, 24, 36, and 54 months using the Bayley Scales of Infant Development—2nd Edition (BSID-II), Reynell Developmental Language Scales (RDLS), Kaufman Assessment Battery for Children (K-ABC), Clinical Evaluation of Language Fundamentals- Preschool (CELF-Preschool) and Survey of Clinical and/or Educational Services revealed that higher percentage of SIBS-A showed a delay in cognition and language compared to SIBS-TD (30.8 % vs. 5.1%)[9]. The deletion on chromosome 4q leading to hemizygosity for genes encoding for glutamine and glycine neurotransmitter receptor sub-units (AMPA 2, GLRA3, GLRB) and neuropeptide

Table 1 Genes involved and manifestations for autism[3, 7, 8]

Genes involved	Manifestations
17q11.2 region, SERT (SLC6A4) locus	Serotonin is important for brain development and hyperserotonemia is observed in autism leading to brain abnormalities.
$GABA_A$ receptors on 15q11-q13 locus	Excessive glutaminergic activity is involved in epilepsy associated autism disorder.
Inotropic glutamate receptor GluR6 gene on chromosome 6q21 Metabotropic glutamate receptor GRM8 in the chromosome 7q31-q33	Upregulated glutamate transporter gene in autism
Oxytocin (OT) receptor gene on chromosome 3p25-p26 locus	Oxytocin involved in parturition and lactation shows lower plasma levels in autism.
Engrailed 2 (EN2) gene	Engrailed 2 gene misexpression is involved in abnormal cerebellar development.
Homeobox HOX genes, HOXA1 on chromosome 7p15, HOXB1 on chromosome 17q	HOX involved in hindbrain development, appendicular skeletal growth and differentiation of the urogenital system.
Dopamine β hydroxylase (DBH) gene on chromosome 9q34	DBH involved in conversion of dopamine to nor-epinephrine. Reduced DBH activity in autism.
Shank3/ProSAP2, 22q13 and Neuroligins	SHANK3 (also designated ProSAP2) involved in structural organization of neurotranmsitter receptors in post-synaptic dendritic spines. Neuroligins organizes and matures postsynaptic membranes.

receptors NPY1R, NPY5R was showed to be associated with autism[10].

Prenatal environment

Teratogenic agents are responsible environmental agents causing birth deformities. Exposure to the teratogenic agents such as thalidomide, valproic acid, misoprostol, or to rubella infection to the mother, in the first eight weeks of conceptional age prone to develop autism was considered to be involved. High level of amniotic testosterone, taking folic acid during pregnancy and exposure to ultrasound waves during pregnancy may cause autism[11, 12]. Beard et al reported[12] that the correlation between the percentage of prescription prenatal vitamins containing 1 mg folic acid and research-identified autism incidence was 0.87 [95% confidence interval (CI)=0.19–0.99]. They also found that there was a weak association between pediatric vitamins containing folic acid and autism incidence (r=0.62, 95% CI=—0.38–0.95). In conclusion, it seem possible that the high dose (1mg) folic acid may result in nervous tissue damage associated with autism and further study is required to prove this association.

Postnatal environment

Amygdala dysfunction

Bilateral amygdala damage in human due to Urbach-Wiethe disease was reported causing of impaired recognition of emotion, theory-of-mind abilities and social distance in autism[13].

Food allergy associated gastrointestinal (GI) symptoms

Gastrointestinal intestinal epithelial barrier dysfunction known as leaky gut hypothesis contributes to autism. It was observed that children with autism spectrum disorder (ASD) frequently revealed various gastrointestinal (GI) symptoms which may resolve with an diet elimination along with apparent improvement of some of the behavioral symptoms[14]. Evidence suggests that gastrointestinal symptoms in children with ASDs may be partly associated with aberrant (inflammatory) innate immune responses. This may predispose ASD children to sensitization to common dietary proteins, leading to GI inflammation and aggravation of some behavioral symptoms[15]. Non-IgE mediated food allergy was found a higher incidence compared to IgE mediated food allergy in children with autism spectrum disorders (ASDs)[15].

Mercury (Hg)

Mercury containing products such as eye, ear, nose drugs, bleaching creams, antiseptics, fungicides, herbicides, dental fillings and thermometers, thimerosal-containing vaccines to infants and consumption of Hg containing fish, can precipitate autism by decrease in excretion or exposure to mercury. Elemental Hg

and inorganic Hg, after releasing into the air or water, are methylated and rapidly accumulate in animal tissues[16]. $HgCl_2$ stimulated vascular endothelial growth factor (VEGF) and IL-6 release from human mast cells was reported to cause the disruption of the blood-brain-barrier and brain inflammation in autism.[17].

Prevalence of Autism

The prevalence of autism had increased from 0.4 to 6 per 1000 children in the past decade particularly in male population with a ratio of 4:1. The higher prevalence may caused by increasing awareness of pediatrician, and improving in autistic screening methods[18].

Diagnosis of Autism

According to the American Psychiatric Association's Diagnostic and Statistical Manual-IV, Text Revision (DSM-IV-TR)[2], the diagnostic criteria for autistic disorder is depicted in Table 2. Parental awareness and pediatrician's knowledge for diagnostic methods (Table 3), are useful for early detection of autism in young children[19, 20]. Even diagnosis of autism is confirmed by medical professional, the best and the earliest of autistic screening is mostly contributed by the parents[19]. It has been found that early detection and immediate implementation of interventions are useful for autism. The checklist for autism in toddlers (CHAT) is a simple screening tool for identification of autistic children for 18 months of age in the United Kingdom. Modified checklist for autism in toddlers (M-CHAT), created in the United States, consists of 23 questions, 9 questions from the original CHAT and 14 questions addressing core symptoms present among young autistic children. Using the screening questions from the M-CHAT combines with the observational section B from the original CHAT yields higher sensitivity and specificity of autistic screening tools[21]. A study of biometric device based on the gas discharge visualization (GDV) technique to assess psycho-emotional and physiological functional state discovered that the sympathetic autonomic nervous system activity was significantly altered in autistic children. However, the biometric method should have more investigating and breakthrough for future endeavors[22].

Pathophysiology of Autism

Copious theories had been hypothesized for pathophysiology of autism including 1) mirror neuron system theory, 2) underconnectivity theory, 3) neurophysiological therories e.g. mind-blindness theory, empathizing-systemizing theory, and executive dysfunction theory[23, 24].

Mirror neuron system (MNS) theory

causes interference in imitation and impairment of social behavior and communication. MNS is the network of pars opercularis, the inferior frontal gyrus and its ventral area 6, the

Table 2 Diagnostic criteria for 299.00 autistic disorder[2]

A. Six or more items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
   1. qualitative impairment in social interaction, as manifested by at least two of the following:
      a. marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
      b. failure to develop peer relationships appropriate to developmental level
      c. a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
      d. lack of social or emotional reciprocity

   2. qualitative impairments in communication as manifested by at least one of the following:
      a. delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
      b. in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
      c. stereotyped and repetitive use of language or idiosyncratic language
      d. lack of varied, spontaneous make-believe play or social imitative play appropriate to developmental level

   3. restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
      a. encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
      b. apparently inflexible adherence to specific, nonfunctional routines or rituals
      c. stereotyped and repetitive motor manners (e.g., hand or finger flapping or twisting, or complex whole-body movements)
      d. persistent preoccupation with parts of objects

B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.

C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder.

Table 3 Diagnostic tools used and methodology for autism[19, 20]

Type of diagnosis	Age group of children	Diagnostic methodology
National Autism Plan for Children (NAPC)	Pre-school and Primary school aged children	Qualitative abnormalities in communication such as delay in spoken language learning, lack of babbling and expression in interest, odd speech patterns. Qualitative abnormalities in social interaction such as poor eye contact, poor use of gestures, limited social smiling and playing. Restricted and repetitive interests and behaviors such as stereotyped behavior such as hand flapping, oversensitivity to household noises.
Multiagency Assessment (MAA)	Pre-school and Primary school aged children	Autism is diagnosed by an experienced member of the team. Observational assessments such as focused observations taken at home or nursery, Cognitive assessment such as unique profile of skills/ difficulties of an individual. Tools used for assessment are Bayley Scales of Infant Development, Mullen Scales of Early Learning, Differential Abilities Scales, Stanford-Binet IV, Merrill-Palmer Scale etc.Communication, speech and language, behaviour and mental health assessment.Family assessment using the Framework for the Assessment of Children in Need and their Families. Other assessments such as physiotherapy and occupational therapy, physical examination and medical investigations.
Standardized Autism Diagnostic Tools	Use with caution in children < 24 months	The Autism Diagnostic Interview Revised The Diagnostic Interview for Social and Communication Disorders The Autism Diagnostic Observation Schedule The Checklist for Autism in Toddlers (CHAT) The Social Communication Questionnaire

inferior parietal lobule and the superior temporal sulcus. The MNS area is activated during imitation of action, social cognition, emotion and understanding of other's intention. Various techniques such as magneto-encephalogram (MEG), transcranial magnetic stimulation (TMS), electroencephalogram (EEG), functional magnetic resonance imaging (fMRI), and electromyogram (EMG) are used for assessment of MNS defects and demonstrated that autistic children have smaller cortical thickness than normal children[25].

The underconnectivity theory

states that there is abnormal development of the cerebral white matter leading to inappropriate connection within the brain. The synchronization and coordination among the key brain areas e.g. amygdala, brainstem, cerebral cortex, cerebellum, corpus callosum is deteriorated. The various parts of the corpus callosum which responsible for communication between both cerebral hemispheres become smaller as well as the connectivity at the fronto–parietal region is affected[26].

Neuropsychological theories

There were 4 cognitive theories that had been proposed to explain behavioral pattern of autism.

Mind–blindness theory

Delay in the development of theory of mind (ToM) leads to a state of mind-blindness. For this reason, autistic children have difficulty in understanding, always being in a confusional state and get frightened easily by other people. For example, normal children are able to perform pretending play, whilst autistic children show less pretending tendency[27].

Empathizing–systemizing theory

Systemizing refers to the collection and analyzing the things e.g. numerical systems, syntax of language etc. This theory explains that the autistic patients show social and communication difficulty due to a delay and defect in the empathy and systemizing system. This theory provides social and non-social features which help in characterizing the unique profile of an autistic patient. Based on this theory, the novel interventions such as DVD Mind Reading and computer software for learning of facial expressions are invented as the tools for treatment of autism[27].

Weak central coherence theory

Children suffering from autism may lost details and hardly understand the system as a whole. Autistic children may perceive subjects as mathematic and engineer but may have trouble in understanding language skills[27].

Executive dysfunction theory

The fact is that dysfunction of the prefrontal cortex affects the executive capability.

Autistic children are not able to administrate even the simplest functions e.g. planning, working memory, impulsion, control, inhibition, mental flexibility, shifting set and monitoring of action[28].

Managements of autism

Biologically based interventions

Up to the present time, there are no pharmacologic interventions that specifically target the core deficits of autism. However, there are some progressions in pharmacotherapy for control the behavioral symptoms associated with autism. Pharmacological interventions which have role in treatment of targeted symptoms in autism can be classified as:

1. **Typical Anti–psychotics**

This medical class was originally developed to treat psychiatric disorders like schizophrenia. The samples of this medical class are haloperidol, fluphenazine, and thioridazine. Previous studies showed the modest improved control of behavioral symptoms of children with autism however there were significant side effects on the extrapyramidal motor system including stiffness (dystonia), restlessness (akathisia) and involuntary movements (dyskinesias)[29].

2. **Atypical Anti–psychotics**

This medical group has been developed in the last 20 years to minimize the effects on the extrapyramidal system of the typical antipsychotics. The samples of this medical class are clozapine, risperidone, olanzapine, ziprasidone, quetiapine. A numbers of studies using Risperidone, an antagonist of both dopamine (D_2) and serotonin ($5HT_{2A}$ and others) receptors, showed a well tolerated and efficacious in treating behavioral symptoms associated with PDD in children[30-33]. Recently, the combination therapy of risperidone and topiramate, a GABA-ergic agents, showed more advantages than using risperidone alone by reducing in irritability, stereotypic behavior and hyperactivity/noncompliance[34]. The recent studies also reported the efficacy of other medications such as for olanzapine, quetiapine, aripiprazole and ziprasodone for the treatment of behavioral symptoms in children with autism[35-37].

3. **Stimulants e.g. Methylphenidate (Ritalin TM)**

The classic sample for this class is methylphenidate (Ritalin). It has a primary target in treatment of inattention and hyperactivity and has been used increasingly for children with an autism spectrum disorder. However, the response to stimulants can be idiosyncratic with up to 1/3 experiencing increased hyperactivity, stereotypies, dysphoria or motor tics[38].

4. **Specific Serotonin Reuptake Inhibitors**

This medical class was developed and

was used in the management of obsessive-compulsive disorder and anxiety disorders. The samples for this class are the tricyclic antidepressant clomipramine, the mixed antidepressant venlaflaxine and all selective serotonin reuptake inhibitors, fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram. The mechanism of action of this drug group is believed to link with serotonergic abnormalities in autistic patients. However, this medical group should be used with precaution due to an adverse reaction such as lowering seizure thresholds by clomipramine[39], behavioural activation by fluvoxamine[40]. Extrapyramidal side effects have also been reported in autistic patients treated with this drug group[41].

5. GABA–ergic agents

The sample for this class is topiramate. The previous studies showed that topiramate had significant improvements with regards to hyperactivity, inattention and conduct symptoms in autism. However, an adverse event of cognitive dulling had observed in some treated patients. Further study is required to clarify the long term use and risk-benefit[42].

6. Glutamatergic Agents

The samples of this class are lamotrigine, D-cycloserine and amantadine. There are a limit numbers of studies regarding autism management, moreover, their efficacy had still inconclusive. Lamotrigine which modulated glutamate release had no significant effects for clinical improvement for autism compared with placebo[43]. D-cycloserine showed a significant improvement of social withdrawal and responsiveness in a small-sample size, single blind study[44]. Memantine, an adjuctive therapy, is an antagonist of the N-methyl D-aspartic acid (NMDA) glutamate receptor affecting production of glutamate. Decrease in amount of glutamate not only alleviates the induction of neuroinflammation but also improves learning behavior, social behavior, self-stimulatory behavior, and language ability[45]. Open label study showed the efficacy in improvement language, social behavior and self-stimulatory behaviors. There was no serious side effect observed in chronic use so far[45]. Further study of a well-designed, large sample size, long term duration is required to explore the benefits and risks of this medical group.

7. Nor Adrenergic Agents

Clonidine had been reported to improve hyperactivity, aggression and irritability in autism. However, it should be used with precaution due to the adverse events include drowsiness, development of tolerance and risk of hypertensive crisis on withdrawal[46].

8. Cholinergic Agents

There are a limit numbers of studies of this drug class. Rivastigmine was reported

in improvement of speech and overall behavior over a short-term study in autism[35]. Donepezil, a cholinesterase inhibitor, was reported to improve irritability and hyperactivity, but had no benefits for speech repetitive behavior or lethargy[47]. Further study to clarify the beneficially is required.

9. Beta Blockers

There is no well research for beta blockers treatment for autism. However, some of them had been used to reduce anxiety in autistic patients[48].

Psychodynamic interventions

These interventions are based on the hypothesis that autism is an emotional disorder caused by emotionally 'cold' parents, who subconsciously rejected their children (Jordan, 1999). There was some support evidence that severely traumatized children demonstrate autistic liked behaviors[49]. Psycho-dynamically oriented play therapies were keys in the psychodynamic therapeutic process[50]. The samples of phychodynamic interventions are:

1. Holding therapy is the technique that holds the children tightly to ensure eye contact, with the aim of deliberately provoking distress, until he or she needs and accepts comfort[51]. It is based on that autism is caused by an 'anxiety dominated emotional imbalance', which could be ameliorated by Holding Therapy. However, There is no a good designed study to support this method.

2. Pheraplay therapy is therapy in which children are provided stimulating the various experiences intense enough to overcome the sensory impairments rather than learning specific play skills. This method based on the hypothesis that autism was a failure of emotional attachment compounded by sensory impairments DesLauriers[52]. However, There is no a good designed study to support this method[53].

Developmental, Individual Difference, Relationship-based therapy (DIR), or "Floor time" approach, aims to assist children expressing their feeling and emotions by using interactive experiences and interactive play in a low stimulus environment[54]. Stanley Greenspan developed this theory that early developmentally-based intervention (as soon as the diagnosis done) will lead to the good outcome for children with autism[55].

Behavioral interventions

1. Applied Behavior Analysis (ABA) is applied by using principles of learning theory to increase and maintain the positive behaviors, to teach new skills, to transfer behavior from one situation to another, and to reduce the unfavorable or unacceptable behaviors (e.g. self-injury or stereotypes)[53].

2. Intensive Behavioral Intervention (IBI) and

Early Intensive Behavioral Intervention (EIBI) are based on the concept of that autistic children need special assistance for gaining skills as they show self-learning inability [53].

Family–based Interventions

The 'Hanen Program' is useful to improve the verbal skills when children are taught under naturalistic strategies. 'More than words' strategy encourages parents to use facilitative tools during teaching communication skill to their child. The Joint attention strategy emphasizes an early social development related to later cognitive competence. The People Games strategy e.g. peek-a-boo is very helpful for the pre-verbal child to learn about communication, initiation and respond to various emotions[53].

Complementary and Alternative Medications (CAM)

1. **Melatonin**

Autistic children usually have sleep disturbances caused by depletion of melatonin level with the evidence of high excretion of urinary 6-sulfatoxymelatonin (6-SM), a primary melatonin metabolite, detected in autistic children. Therefore, melatonin may ameliorate sleep problems of autistic children[56].

2. **Pyridoxine and magnesium**

Pyridoxine (vitamin B6) affects the formation of some neurotransmitters. The combination of pyridoxine with magnesium has been reported as the most effective, adjunctive treatment for autism as evidenced from the behavior rating scales, urinary excretion of homovanillic acid (HVA), and evoked potential (EP) recordings[57]. However, side effects such as sensory neuropathy, headache, depression, vomiting, and photosensitivity had been reported of the use of these medications in a large doses[51].

3. **Vitamin C**

Vitamin C, an antioxidative agent, regulates numerous metabolic pathways and acts as a cofactor for several neurotransmitter syntheses. In a 30-week double-blind, placebo-controlled trial, autistic children who received ascorbic acid at a dose of 8 grams per 70 kilograms per day for 10 weeks showed improvement in behavioral functions assessed by the Ritvo-Freeman scale[58].

4. **Vitamin B12**

Vitamin B12 is essential for methylation and its antioxidative effect is essential for vitamin B12 dependent methionine cycle. Deficiency of vitamin B12 causes optic neuropathy and visual loss in autistic children. Intramuscular vitamin B12 is a treatment to improve visual function of affected children[59].

5. **Dimethylglycine**

Dimethylglycine (DMG), also known as Dimethyl Glycine, Calcium Pangamate, Pangamatic

Acid, Pangamic Acid, and Vitamin B15, has been reported to be beneficial in children with autism and pervasive developmental disorder. In a double-blind, placebo-controlled study 37 children of age group 3 to 11 years were diagnosed for autism and/or pervasive developmental disorder. They were randomly assigned to receive either placebo or dimethylglycine for 4 weeks. The parameters assessed were the Vineland Maladaptive Behavior Domain and the Aberrant Behavior Checklist. The results were skeptical as some children gained outcomes whilst others did not[60].

6. Probiotics

Autistic children had significantly high levels of pathogenic organisms particularly Clostridium histolyticum. Thus probiotics may useful to balance the environment of endogenous gastrointestinal flora[61].

7. Omega-3 fatty acids

Three types of omega-3 fatty acids are mainly discovered in human diet: alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). Low level of omega-3 fatty acids was reported in autism. Moreover, in a therapeutic study of autistic children, omega-3 fatty acids can improve the autistic condition[62].

8. Secretin

Secretin is a peptide hormone secreted by the small intestine, which induces pancreatic secretions and suppresses gastric acid. Treatment with intravenous secretin may improve the behavioral outcome in some autistic cases and correlated to reduction of gastroesophageal reflux [63]. However, several randomized control trials failed to demonstrate its efficacy[64].

9. Other Interventions

Music therapy

The purposes of music therapy are to express various feeling, to improve verbal and gestured communication skills by using music and its element. A study of 50 autistic children aged 3 to 5 years old treated with music therapy (containing 6 songs and 36 pictures of target words) and speech therapy (containing 6 stories and pictures) revealed that both therapies improved the speech production either high or low functioning participants compared to the non-treatment group. For low functioning participants, music therapy seemed to provide better outcome than speech therapy[65].

Acupuncture

In a study 12 sessions of acupuncture treatment for four weeks were given to autistic and sham group. The parameters for assessed were Functional Independence Measure for Children (WeeFIM), Pediatric Evaluation of Disability Inventory (PEDI), Leiter International Performance Scale-Revised (Leiter-R), and Clinical

Global Impression-Improvement (CGI-I) scale etc. Acupuncture treatment was found to be 70% successful in children with an improvement in language skills and self-caring[66]. Acupuncture stimulation causes sensations of deqi, deactivation of a limbic-paralimbic-neocortical network, which encompasses the limbic system and activation of somatosensory brain regions. Acupuncture causes mobilization of the anti-correlated networks of the brain mediating its actions. The effects are dependent on the psychophysical response and are thus useful in autism[67].

Massage

A randomized controlled trial study using the Conners' Rating Scales to assess the behavioral and emotional disturbances of autistic Thai children at 0 and 8 weeks after receiving Thai Traditional Massage (TTM) therapy revealed that there was therapeutic effect of TTM in improving the condition of autistic children[68].

Hyperbaric Oxygen Therapy (HBOT)

Hyperbaric Oxygen Therapy (HBOT) is an emerging treatment of autism. Either setting of 1.3 atmospheres (atm) with 24% oxygen, or 1.5 atm with 100% oxygen lasting 45 minutes duration, 4-6 times a week for a total of 9 weeks had been researched by an open label pilot study in 18 autistic children aged from 3 to 16 years old. The study concluded that HBOT was effective in improving the clinical outcome regardless of oxygen and pressure used. HBOT also decreased inflammatory markers responsible for the worsening of autism's symptoms[69].

Conclusion

Autism is influenced by multifactorial causes e.g. genetic defect, pre- and post-natal exposure to toxic environments, food allergy, and mercury. Copious theories have been proposed for pathophysiology of autism. Diagnostic confirmation of autism including NAPC, MAA, and Standardized Autism Diagnostic Tools are worldwide used. Until recently, there is no curative treatment for autism but various interventions under clinical trials have been well explored e.g. biologically based interventions, behavioral interventions, family based interventions and complementary and alternative medications (CAM). These should ameliorate symptoms of autism and optimize quality of life of children and their families.

References

1. World Health Organization. Mental and behavioural disorders. International Statistical Classification of Diseases and Related Health Problems, 10th ed. (ICD-10). [cited 2010 Oct 10]. Available from:http://apps.who.int/classifications/apps/icd/icd10online/?gf80.htm+f84.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., text revision). Washington DC: Author,2000. .
3. Muhle R, Trentacoste SV, Rapin I. The genetics of autism. Pediatrics 2004;113:e472-86.
4. Mines MA, Yuskaitis CJ, King MK, Beurel E, Jope RS. GSK3 influences social preference and anxiety-related behaviors during social interaction in a mouse model of fragile X syndrome and autism. PLoS One 2010;5:e9706.
5. Wiznitzer M. Autism and tuberous sclerosis. J Child Neurol 2004;19:675-9.
6. Wong V. Study of the relationship between tuberous sclerosis complex and autistic disorder. J Child Neurol 2006;21:199-204.
7. Benayed R, Gharani N, Rossman I, et al. Support for the homeobox transcription factor gene ENGRAILED 2 as an autism spectrum disorder susceptibility locus. Am J Hum Genet 2005;77:851-68.
8. Durand CM, Betancur C, Boeckers TM, et al. Mutations in the gene encoding the synaptic scaffolding protein SHANK3 are associated with autism spectrum disorders. Nat Genet 2007;39:25-7.
9. Gamliel I, Yirmiya N, Sigman M. The development of young siblings of children with autism from 4 to 54 months. J Autism Dev Disord 2007;37:171-83.
10. Ramanathan S, Woodroffe A, Flodman PL, et al. A case of autism with an interstitial deletion on 4q leading to hemizygosity for genes encoding for glutamine and glycine neurotransmitter receptor sub-units (AMPA 2, GLRA3, GLRB) and neuropeptide receptors NPY1R, NPY5R. BMC Med Genet 2004;5:10.
11. Williams EL, Casanova MF. Potential teratogenic effects of ultrasound on corticogenesis: implications for autism. Med Hypotheses 2010;75:53-8.
12. Beard CM, Panser LA, Katusic SK. Is excess folic acid supplementation a risk factor for autism? Med Hypotheses 2011;77:15-7.
13. Paul L, Corsello C, Tranel D, Adolphs R. Does bilateral damage to the human amygdala produce autistic symptoms? . J Neurodevelop Disord 2010;2:165-73.
14. Jyonouchi H, Sun S, Itokazu N. Innate immunity associated with inflammatory responses and cytokine production

against common dietary proteins in patients with autism spectrum disorder. Neuropsychobiology 2002;46:76-84.

15. Jyonouchi H. Food allergy and autism spectrum disorders: is there a link? Curr Allergy Asthma Rep 2009;9:194-201.
16. Geier DA, King PG, Sykes LK, Geier MR. A comprehensive review of mercury provoked autism. Indian J Med Res 2008;128:383-411.
17. Kempuraj D, Asadi S, Zhang B, et al. Mercury induces inflammatory mediator release from human mast cells. J Neuroinflammation 2010;7:20.
18. Faras H, Al Ateeqi N, Tidmarsh L. Autism spectrum disorders. Ann Saudi Med 2010;30:295-300.
19. Barbaresi WJ, Katusic SK, Voigt RG. Autism: a review of the state of the science for pediatric primary health care clinicians. Arch Pediatr Adolesc Med 2006;160:1167-75.
20. Dover CJ, Le Couteur A. How to diagnose autism. Arch Dis Child 2007;92:540-5.
21. Wong V, Hui LH, Lee WC, et al. A modified screening tool for autism (Checklist for Autism in Toddlers [CHAT-23]) for Chinese children. Pediatrics 2004;114:e166-76.
22. Kostyuk N, Rajnarayanan RV, Isokpehi RD, Cohly HH. Autism from a biometric perspective. Int J Environ Res Public Health 2010;7:1984-95.
23. Posey DJ, McDougle CJ. The pathophysiology and treatment of autism. Curr Psychiatry Rep 2001;3:101-8.
24. Penn HE. Neurobiological correlates of autism: a review of recent research. Child Neuropsychol 2006;12:57-79.
25. Hadjikhani N. Mirror neuron system and autism. . In: Carlisle P, ed. Progress in autism research. New York: Nova Science Publishers, Inc, 2007:151-66.
26. Just MA, Cherkassky VL, Keller TA, Kana RK, Minshew NJ. Functional and anatomical cortical underconnectivity in autism: evidence from an FMRI study of an executive function task and corpus callosum morphometry. Cereb Cortex 2007;17:951-61.
27. Baron-Cohen S. Autism: the empathizing-systemizing (E-S) theory. Ann N Y Acad Sci 2009;1156:68-80.
28. Hill E. Evaluating the theory of executive dysfunction in autism. Developmental Review 2004;24:189-233.
29. Posey DJ, McDougle CJ. The pharmacotherapy of target symptoms associated with autistic disorder and other pervasive developmental disorders. Harv Rev Psychiatry 2000;8:45-63.
30. Shea S, Turgay A, Carroll A, et al. Risperidone in the treatment of disruptive behavioral symptoms in children with autistic and other pervasive developmental disorders. Pediatrics 2004;114:e634-41.

31. Findling RL, Maxwell K, Wiznitzer M. An open clinical trial of risperidone monotherapy in young children with autistic disorder. Psychopharmacol Bull 1997;33:155-9.
32. Luby J, Mrakotsky C, Stalets MM, et al. Risperidone in preschool children with autistic spectrum disorders: an investigation of safety and efficacy. J Child Adolesc Psychopharmacol 2006;16:575-87.
33. Scott LJ, Dhillon S. Risperidone: a review of its use in the treatment of irritability associated with autistic disorder in children and adolescents. Paediatr Drugs 2007;9:343-54.
34. Rezaei V, Mohammadi MR, Ghanizadeh A, et al. Double-blind, placebo-controlled trial of risperidone plus topiramate in children with autistic disorder. Prog Neuropsychopharmacol Biol Psychiatry 2010;34:1269-72.
35. King BH, Bostic JQ. An update on pharmacologic treatments for autism spectrum disorders. Child Adolesc Psychiatr Clin N Am 2006;15:161-75.
36. Stigler KA, Posey DJ, McDougle CJ. Aripiprazole for maladaptive behavior in pervasive developmental disorders. J Child Adolesc Psychopharmacol 2004;14:455-63.
37. Huang SC, Tsai SJ, Yang HJ. Aripiprazole improves social interaction in Taiwanese children with pervasive developmental disorder. Chang Gung Med J 2010;33:211-5.
38. Di Martino A, Melis G, Cianchetti C, Zuddas A. Methylphenidate for pervasive developmental disorders: safety and efficacy of acute single dose test and ongoing therapy: an open-pilot study. J Child Adolesc Psychopharmacol 2004;14:207-18.
39. Brodkin ES, McDougle CJ, Naylor ST, Cohen DJ, Price LH. Clomipramine in adults with pervasive developmental disorders: a prospective open-label investigation. J Child Adolesc Psychopharmacol 1997;7:109-21.
40. Martin A, Koenig K, Anderson GM, Scahill L. Low-dose fluvoxamine treatment of children and adolescents with pervasive developmental disorders: a prospective, open-label study. J Autism Dev Disord 2003;33:77-85.
41. McDougle CJ, Kresch LE, Posey DJ. Repetitive thoughts and behavior in pervasive developmental disorders: treatment with serotonin reuptake inhibitors. J Autism Dev Disord 2000;30:427-35.
42. Hardan AY, Jou RJ, Handen BL. A retrospective assessment of topiramate in children and adolescents with pervasive developmental disorders. J Child Adolesc Psychopharmacol 2004;14:426-32.
43. Belsito KM, Law PA, Kirk KS, Landa RJ, Zimmerman AW. Lamotrigine therapy for autistic disorder: a randomized, double-blind, placebo-controlled trial. J Autism Dev Disord 2001;31:175-81.

44. Posey DJ, Kem DL, Swiezy NB, Sweeten TL, Wiegand RE, McDougle CJ. A pilot study of D-cycloserine in subjects with autistic disorder. Am J Psychiatry 2004;161:2115-7.
45. Chez MG, Burton Q, Dowling T, Chang M, Khanna P, Kramer C. Memantine as adjunctive therapy in children diagnosed with autistic spectrum disorders: an observation of initial clinical response and maintenance tolerability. J Child Neurol 2007;22:574-9.
46. Fankhauser MP, Karumanchi VC, German ML, Yates A, Karumanchi SD. A double-blind, placebo-controlled study of the efficacy of transdermal clonidine in autism. J Clin Psychiatry 1992;53:77-82.
47. Hardan AY, Handen BL. A retrospective open trial of adjunctive donepezil in children and adolescents with autistic disorder. J Child Adolesc Psychopharmacol 2002;12:237-41.
48. Haspel T. Beta-blockers and the treatment of aggression. Harv Rev Psychiatry 1995;2:274-81.
49. Rutter M. Autism research: prospects and priorities. J Autism Dev Disord 1996;26:257-75.
50. Haag G, Tordjman S, Duprat A, et al. Psychodynamic assessment of changes in children with autism under psychoanalytic treatment. Int J Psychoanal 2005;86:335-52.
51. Howlin P. Prognosis in autism: do specialist treatments affect long-term outcome? Eur Child Adolesc Psychiatry 1997;6:55-72.
52. Lopez MI, Leon NA. [Structural therapy. Global therapeutic model of the psychotic child]. Neurol Neurocir Psiquiatr 1976;17:181-6.
53. Roberts J, Prior M. A review of the research to identify the most effective models of practice in early intervention of children with autism spectrum disorders. Australian Government Department of Health and Ageing, Australia 2006
54. Wieder S, Greenspan SI. Climbing the symbolic ladder in the DIR model through floor time/interactive play. Autism 2003;7:425-35.
55. Greenspan SI, Brazelton TB, Cordero J, et al. Guidelines for early identification, screening, and clinical management of children with autism spectrum disorders. Pediatrics 2008;121:828-30.
56. Leu R, Beyderman L, Botzolakis E, Surdyka K, Wang L, Malow B. Relation of melatonin to sleep architecture in children with autism. J Autism Dev Disord. 2010 Aug 4. [Epub ahead of print] PMID: 20683768. 2010.
57. Martineau J, Barthelemy C, Garreau B, Lelord G. Vitamin B6, magnesium, and combined B6-Mg: therapeutic effects in childhood autism. Biol Psychiatry 1985;20:467-78.

58. Dolske MC, Spollen J, McKay S, Lancashire E, Tolbert L. A preliminary trial of ascorbic acid as supplemental therapy for autism. Prog Neuropsychopharmacol Biol Psychiatry 1993;17:765-74.
59. Pineles SL, Avery RA, Liu GT. Vitamin B12 optic neuropathy in autism. Pediatrics 2010;126:e967-70.
60. Kern JK, Miller VS, Cauller PL, Kendall PR, Mehta PJ, Dodd M. Effectiveness of N,N-dimethylglycine in autism and pervasive developmental disorder. J Child Neurol 2001;16:169-73.
61. Kaur IP, Kuhad A, Garg A, Chopra K. Probiotics: delineation of prophylactic and therapeutic benefits. J Med Food 2009;12:219-35.
62. Meguid NA, Atta HM, Gouda AS, Khalil RO. Role of polyunsaturated fatty acids in the management of Egyptian children with autism. Clin Biochem 2008;41:1044-8.
63. Pallanti S, Lassi S, La Malfa G, et al. Short report: Autistic gastrointestinal and eating symptoms treated with secretin: a subtype of autism. Clin Pract Epidemiol Ment Health 2005;1:24.
64. Williams KW, Wray JJ, Wheeler DM. Intravenous secretin for autism spectrum disorder. Cochrane Database Syst Rev 2005:CD003495.
65. Lim HA. Effect of "developmental speech and language training through music" on speech production in children with autism spectrum disorders. J Music Ther 2010;47:2-26.
66. Wong VC, Chen WX. Randomized controlled trial of electro-acupuncture for autism spectrum disorder. Altern Med Rev 2010;15:136-46.
67. Hui KK, Marina O, Liu J, Rosen BR, Kwong KK. Acupuncture, the limbic system, and the anticorrelated networks of the brain. Auton Neurosci 2010.
68. Piravej K, Tangtrongchitr P, Chandarasiri P, Paothong L, Sukprasong S. Effects of Thai traditional massage on autistic children's behavior. J Altern Complement Med 2009;15:1355-61.
69. Rossignol DA, Rossignol LW, James SJ, Melnyk S, Mumper E. The effects of hyperbaric oxygen therapy on oxidative stress, inflammation, and symptoms in children with autism: an open-label pilot study. BMC Pediatr 2007;7:36.