Autism – A Neurological Disorder in Children

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Summary

Autistic disorder are the group of related conditions defined as chronic neurodevelopmental disorders that typically affects a person's ability to communicate, form relationships with others and respond appropriately to the environment starting in early childhood and affecting a significant number of children and families. These disorders mainly affect the children at the age of 3 years. Although various causes have been postulated the exact cause of the disease is still unknown. In this review we will discuss about the various causes, diagnosis, clinical features, pathophysiology and treatment approach of this disorders.

Key words: - Autism, autistic spectrum disorders.

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Introduction

Autistic disorder and the group of related conditions defined as chronic neurodevelopmental disorders that typically affects a person's ability to communicate, form relationships with others, and respond appropriately to the environment starting in early childhood and affecting a significant number of children and families. It is part of a group of conditions, defined as pervasive development disorder, and often referred to also as "autistic spectrum" disorders [1]. By *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria, autism represents an extreme form of pervasive developmental disorder [2]. Most children have passed several predictable milestones before 3 years of age, on the path to learning language. It has been found that about half of the children diagnosed with autism remain mute throughout their lives. Some may speak only single words and seem unable to combine words into meaningful sentences.

Autism causes impaired social interaction, communication difficulties, and restricted or repetitive activities and interests. People with autism often exhibit abnormal responses to sensory stimulation like touch, sound, light usually have moderate mental retardation, and have a higher risk for developing epilepsy. Some autistic patients exhibit aggression and self-injurious behavior like head banging, biting themselves. Children and adults with autism typically have deficiencies in verbal and non-verbal communication, social interactions and leisure or play activities. The disorder makes it hard for them to communicate with others and relate to the outside world [3], demonstrating a high rate of uneven cognitive development in children with autism spectrum disorders. Indications of dissociation between verbal and visual-perceptual skills among the older children, and the specific association of discrepantly high nonverbal skills with increased social symptoms suggest that the nonverbal greater than verbal profile may index an etiologically significant subtype of autism [4].

Executive dysfunction in autism is not directly related to language impairment but rather involves an executive failure to use of language for self-regulation [5]. Autism, also called infantile autism or autistic disorder, is a lifelong disorder that causes abnormal neurological development. It is one of five pervasive development disorders that also include Asperger disorder, Childhood disintegrative disorder, Rett's disorder, and Pervasive development disorder.

Specialists may also consider other conditions that produce many of the same behaviors and symptoms as autism, such as Rett's disorder or Asperger's disorder [6]. Rett's disorder is a progressive brain disease that affects only girls but like autism, it produces repetitive hand movements which lead to loss of language and social skills. Children with Asperger's disorder are high-functioning like children with autism.

Autism is also caused by abnormalities in brain structures or functions. However, number of problems may interfere with normal brain development. A problem with the communication network may interfere with the overall task of coordinating sensory information, thoughts, feelings, and actions. Magnetic Resonance Imaging and Positron Emission Tomography scans shows abnormalities in the structure of the brain, with significant differences within the cerebellum [7]. The pathophysiology of brain enlargement in autism is unclear, and several developmental processes are to be considered. Several distinct mechanisms have been suggested [8]. About one-third of patients with autism have normal or nearly normal intelligence quotients (IQs). Many are able to display emotion, affection and respond to their environment. Terms used to describe patients with the disorder include autistic-like, autistic tendencies, autism spectrum, and high-functioning or low-functioning autism.

Developmental profile may help in distinguishing young children with autistic disorder from non-autistic children with comparable development delays [9]. With early intervention and appropriate treatment, some autistic patients are able to learn and function productively. There is no cure for the disorder and most patients require lifelong care. Autism is a chronic and lifelong pervasive developmental disorder for which there is no effective treatment and medical management remains a major challenge for clinicians [10].

Medications used to treat anxiety and depressions are being explored as a way to relieve certain symptoms of autism. Scientists believe that like anxiety and depressions, autism also associated with problem in the functioning of the neurotransmitter serotonin, hence the drugs like fluoxetine, fluvoxamine, sertraline and clomipramine are often used to treat autism. As we get closer to understanding the brain, we approach a day when we may be able to diagnose very young children and provide effective treatment earlier in the child's development.

As data accumulate on the brain chemicals involved in autism, we get closer to developing medications that reduce or reverse imbalances. We may even have the ability to prevent the disorder. Lastly, if different features of autism are caused by different genes, associated with different brain regions and related to different core cognitive impairments, it seems likely they will respond to different types of treatment. Abandoning the search for a single cause for a single entity of autism may also mean abandoning the search for a single 'cure' or intervention [11].

EPIDEMIOLOGY

Neuropathological as well as epidemiological studies suggest that autism is best viewed as a convergent behavioral manifestation of various brain dysfunctions with different causes [12]. There is no clear-cut ratio of incidence between boys and girls. Studies have found that higher prevalence in boys at the high-functioning end of the spectrum, while the ratios appear to be closer to 1:1 at the low-functioning end. In addition, it is found that men over 40 are more likely to father a child with autism than younger men and the ratio of autism incidence in boys and girls is closer to 1:1 with older fathers [13].

A widely-cited pilot study conducted in California by the UC Davis MIND Institute, reported the incidences of increase in autism, even after accounting for changes to diagnostic criteria. It is four times more prevalent in boys than girls. Its prevalence rate now places it as the third most common developmental disorder. Out of every 10,000 people 15 individuals are affected from Autism. This is a kind of inborn disorder that begins right from fetal development and may go on to whole life. Autism interferes with the normal development of the brain in the areas of reasoning, social interaction and communication skills [14].

CAUSES

The etiology of autism is an area of debate and controversy. Till now there is no consensus and researchers are studying a wide range of possible causes. Since people with autism are different from one another there are probably multiple 'causes' that interact with each other in subtle and complex ways and thus give slightly differing outcomes in each individual. Autism involves primary impairments in both language and communication [14].

Autism is characterized by impairments in reciprocal social interaction and in communication with others, and by a preference for repetitive, stereotyped behaviors. The clinical picture of autism has changed dramatically over the past decade the possible range of behaviors seen at different ages and degrees of functioning. Like autism there are several closely related disorders exist that share the same essential features but differ in specific symptoms, age of onset or natural history. These disorders include Asperger syndrome, atypical autism and disintegrative disorder; these are often conceptualized as lying on a spectrum with autism hence they are also called as autism spectrum disorders [6]. The prevalence rates of autism-spectrum disorders are uncertain and speculation that their incidence are increasing to cause concern prevalence of pervasive developmental disorders [15].

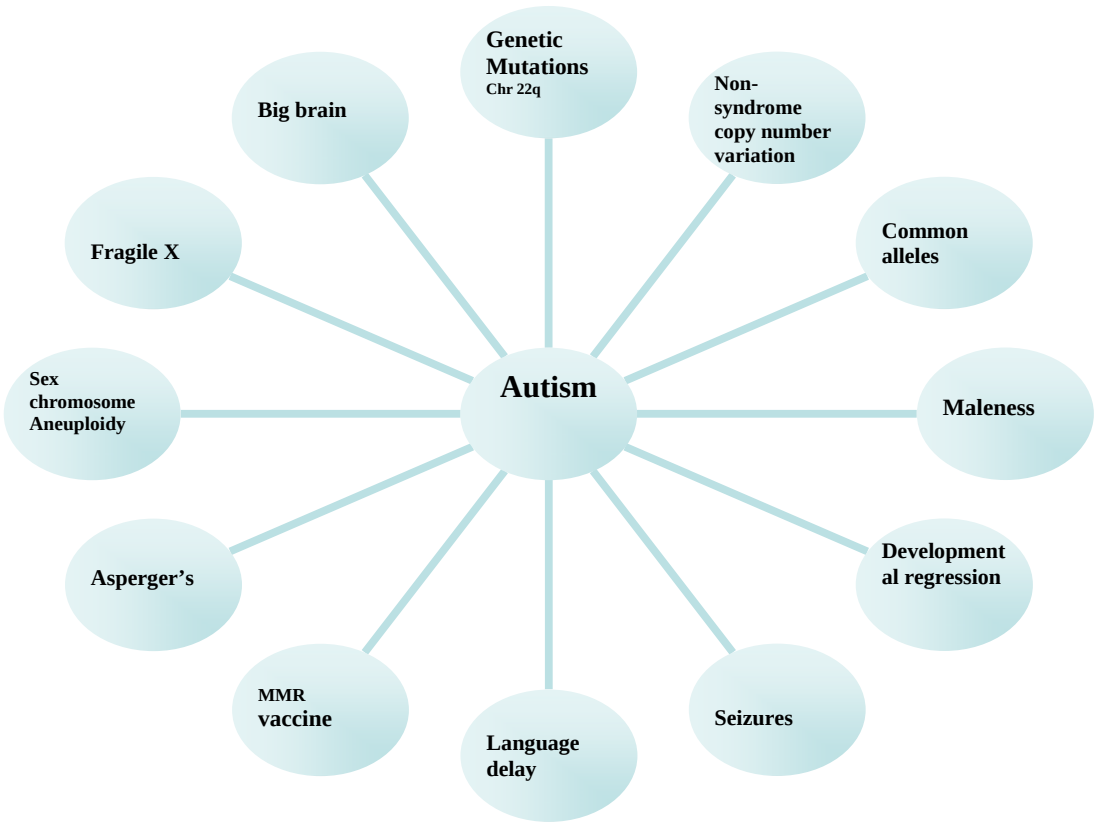


Fig: - The different types of causes responsible for producing autism.

In about 10-15 % of the cases; autism is due to associated medical conditions that affect normal brain functioning.

The post-mortem studies on small case series reported the cellular abnormalities in the limbic system and cerebellum. Between 10 - 20 % of subjects with autism have macrocephalia, which is in accordance with magnetic resonance imaging (MRI) findings of an increased total brain tissue volume and most prominent enlargement in the occipital and parietal lobes. The most robust and well-replicated neurobiological abnormality in autism is an elevation of whole blood serotonin found in over 30% of the patients [16].

Brain abnormalities may result from genetic defects, exposure to toxins, metabolic disorders like serotonin deficiency, viral infections like German measles or complications during pregnancy and delivery. Autism is caused by abnormalities in brain structures or functions. However, number of problems may interfere with normal brain development. A problem with the communication network may interfere with the overall task of coordinating sensory information, thoughts, feelings and actions. In some families they appear to be a pattern of autism or related disabilities, which suggests the genetic basis to the disorder.

Genetic factors

Autism is known to be highly heritable; autism research at some institutions seeks methods for earlier and more accurate detection of autism, similar to specific tests for Rett syndrome. Instead of searching for one particular gene as the cause for autism, many studies currently underway are investigating complex interactions between multiple genes. A recent paper on the genetic basis of autism suggests that autism is not a single disorder [11].

There is neither a single biological or clinical marker to detect autism nor a single gene can be attributed for this disorder. The results of which have implicated the involvement of nearly every chromosome in the human genome. However, the most consistently replicated linkage findings have been on chromosome 7q, 2q and 15q [17]. But a group of unstable genes may trigger the disorder in some patients. The sexual dichotomy is an important factor in the genetics of autism [18].

Nutritional deficiencies factors

Children exhibiting behavioral and learning disorders may do so in part because of diets deficient in vital nutrients needed for their brains to function and develop normally. Some children with autism are said to have responded well to dietary intervention, such as eliminating gluten, a protein found in most grains like gluten-free diet and casein, a protein found in milk. Feingold diet program recommends the avoidance of phenyls and food coloring agents, for attention-deficit hyperactivity disorder (ADHD). Most data regarding the validity of these interventions have been criticized as the subjective observations of parents and caretakers. Critics allege that no scientific study with proper subject elimination has taken place. The effectiveness of dietary interventions may be affected by co-morbid conditions such as asthma, eczema, diarrhea and constipation, 'yeasty' diaper rash and difficulty of altering rigid eating habits. It is a common characteristic among people with autism.

Physical disorder factors

(A) Brain size:

Increased brain size has been observed in individuals with autism with a wide range of cognitive functioning. Mean cerebral and third ventricle volumes in the autistic subjects were significantly greater than in the controls when adjusted for intracranial volume [19].

(B) Preoperational-autism theory:

Studies of brain structure have implicated several aspects of brain development involved in neuronal organization including the elaboration of dendritic and axonal ramifications, the establishments of synaptic connections and cell death. These developmental neuronal disturbances may lead to a wide range of anatomic abnormalities including changes in brain volume. Several neuro imaging studies have reported an increase in brain size in autism. Increased brain size has been observed in individuals with autism with a wide range of cognitive functioning [20]. The pathophysiology of brain enlargement in autism is unclear and several developmental processes are to be considered. Several distinct mechanisms have been suggested [8]. Increased neurogenesis decreased neuronal death, increased production of non-neuronal brain tissues like glial cells and decreased synaptic pruning.

The limited neuropathologic data available in the literature is not been conclusive in support of either a derangement of neurogenesis or a failure of the programmed cell death [21], [22]. "There is not going to be rapid progress in autism research unless we subtype," Amaral says. He predicts that "brain differences in kids with a regressive form of autism will be different than those of kids with the more congenital type of autism" [23].

Study at the University of Washington in Seattle has reached the same conclusion. The majority of people with autism have slightly enlarged brain size, compared to the statistical average. "Although it is accepted that individuals with autism have an enlarged brain size, the nature of this abnormality remains unknown" [23]. It has been recorded an increase in brain volume in specific structure called amygdala in autistic brains, which is thought to be important for social behavior.

(C) Other brain differences factors:

(i) Amygdala neurons and fear theory

Scientists observed the development of monkeys whose amygdala was disrupted at birth indicating amygdala is known to regulate aspects of social and emotional behavior. High levels of the neurotransmitter serotonin have been found in a number of people with autism. Since neurotransmitters are responsible for passing nerve impulses in the brain and nervous system, it is possible that they are involved in the distortion of sensations that accompanies autism. Investigation of genetic causes , the role that heredity and genes play in passing the disorder from one generation to the next are going on. It has been postulated that; at early stages of development, when the blood-brain barrier is not yet fully developed, the high levels of serotonin in the blood enter the brain of a developing fetus and cause loss of serotonin terminals. This result in damaged neurocircuitry that persists throughout subsequent development and eventually the symptoms of autism appear.

Recent functional brain imaging studies, such as positron emission tomography, single photon emission computed tomography and functional magnetic resonance imaging studies indicate that autism may be caused by atypical functioning in the temporal lobes where the amygdala are present medially and an abnormal interaction between frontal and parietal brain areas. There is no one single unified theory that explains the etiology of autism.

Structural magnetic resonance imaging of brain have detected, increased total brain volume and abnormalities in the cerebellum, frontal lobe and limbic system containing amygdala and hippocampus in young children with autism [7].

It is also possible that etiologically distinct brain-based deficits in language and in the executive use of verbal working memory develop interactively and jointly contribute to the neurofunctional deficits in verbal self-regulation that have been identified. In contrast, executive performance was positively correlated with language ability in the comparison group. This pattern of findings suggest that executive dysfunction in autism is not directly related to language impairment but rather involves an executive failure to use of language for self-regulation [5].

(D) Underconnectivity theory:

Underconnectivity theory states that autism is a system wide brain disorder that limits the coordination and integration among brain areas. With the aid of Fourier Magnetic resonance imaging it was seen that white matter, which connects various areas of the brain like cables, has abnormalities in people with autism.

(E) Psychogenic theories:

Psychogenic theories in general have become increasingly unpopular, particularly since twin studies have shown that autism is highly heritable. Nevertheless, some case reports have found that deep institutional privation can result in "quasi-autistic" symptoms without the neuroanatomical differences [24]. Other case reports have suggested that children predisposed genetically to autism can develop autistic disorders in response to traumatic events such as the birth of a sibling [25].

(F) Vaccine theory

The possibility that the mumps, measles, and rubella (MMR) vaccines may be causally related to the risk of autism is currently causing substantial concern. Viral infections like rubella (also called German measles) particularly in the first three months of pregnancy, may lead to a variety of problems, possibly including autism and retardation. Data provide evidence that no correlation exists between the prevalence of mumps, measles, and rubella vaccination and the rapid increase in the risk of autism over time [26].

A link has been postulated between measles-mumps-rubella vaccine and a form of autism that is a combination of developmental regression and gastrointestinal symptoms that occur shortly after immunization. This hypothesis has involved 3 separate claims: 1) that there is new phenotype of autism involving regression and gastrointestinal symptoms, 2) that this new variant is responsible for the alleged rise of autism rates and 3) that this phenotype is associated with biological findings suggestive of the persistence of measles infection. No evidence was found to support a distinct syndrome of mumps, measles, and rubella induced autism or of autistic enterocolitis. These results add to the recent accumulation of large-scale epidemiologic studies that all failed to support an association between mumps, measles, and rubella and autism at population level [27]. There is good epidemiological evidence that the measles, mumps, and rubella vaccine is not an environmental risk factor for autism [28]. The measles-mumps-rubella vaccine may contribute to autism in some cases. More research is necessary to evaluate this potential risk factor.

Intrauterine exposure to the teratogenic drugs thalidomide and valproate have been implicated as the cause of autism in a few affected children [29],[30].Cases of autism may occur in conjunction with chromosomal anomalies, such as duplications on the long arm of chromosome 15q11- 13, Rett syndrome (MIM 300005) and fragile-X syndrome (MIM 309550). However these recognized conditions explain only a small fraction of the observed prevalence of autism, currently estimated to be as high as 3 in 1,000. Linkage analyses of 109 autistic sibling pairs from 91 AGRE families in combination with analyses of those pairs from an independent sample of 345 families from the same cohort establish three points.

First, stratification of families with autism into only those with affected males reveals significant linkage to 17q11-21 in both samples, supporting the value of this approach. Second, linkage to 17q11-21 is replicated at the genome wide level of significance; this provides the first formal replication of a locus for idiopathic autism. Third, the multipoint linkage evidence in the combined sample localizes the peak to 17q21 [31]. Recent studies have shown some children with autism have abnormally low cholesterol levels (hypocholesterolemia) which may indicate cholesterol plays a role in some cases.

Pregnancy:

The brain testosterone theory proposes that high levels of testosterone in the amniotic fluid of mothers influence the development of the growing fetus. The high levels of testosterone is theorized to push brain development towards improved ability to see patterns and analyze complex systems while diminishing communication and empathy, emphasizing male traits over female [32]. In one set of studies, infants with higher exposure to testosterone in the womb had smaller vocabularies and less eye contact at one year, while at four years they were less socially developed and males demonstrated more restricted interests than females [33].

Blood type theory:

A study on secretin and Asperger's reported that children with Asperger's Syndrome or Autism and gastrointestinal problems had improved gastrointestinal function after secretin infusion and the children became more social and communicative. They also benefited with a low lectin and wheat diet. This suggests that there might be a gastrointestinal and diet cause of Asperger's or Autism [34].

Folic acid

Increased intake of folic acid by pregnant women roughly coincides with the reported increase in the prevalence of autism. The explanation offered is that folic acid allows more brain cells to survive than should.

Social construct theory

Results indicated that sensory sound processing; including pitch discrimination was largely intact in high-functioning children with autism regardless of the acoustic sound complexity or speechness quality. In contrast their attentional orientation to sound changes was impaired, exclusively for the speech sound (vowel). At present no evidence is found for abnormalities in the processing of the sensory sound features in high functioning children with autism. Therefore the first auditory orienting deficits in autism cannot be explained by sensory deficits and it is thought that orienting deficit in autism might be speech–sound specific [35].

Medical conditions associated with an increased risk for autism include the following:

(A) Fragile X syndrome more common in males may cause mental retardation

(B) Tuberous sclerosis syndrome that causes seizures, mental disorders, and tumors.

(C) Congenital rubella syndrome results from transmission of the rubella virus causes

German measles in utero.

(D) Untreated phenylketonuria PKU; hereditary disease caused by a defective enzyme.

TYPES OF AUTISM:

1. **Asperger's and Kanner's syndrome**

The most significant difference between Autistic Disorder (Kanner's) and Asperger's syndrome is that a diagnosis of the former includes the observation of 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; while a diagnosis of Asperger's syndrome observes "no clinically significant delay" in the latter two of these areas.

2. **Autism as a spectrum disorder** [11]

Autism spectrum disorder is an increasingly popular term that refers to a broad definition of autism including the classic form of the disorder as well as closely related conditions such as pervasive development disorder-not otherwise specified and Asperger's syndrome.

A related continum, Sensory integration Dysfunction involves how well humans integrate the information they receive from their senses. Autism, Asperger's syndrome and Sensory Integration Dysfunction are all closely related and overlap. Some research has indicated a possible genetic and behavioral connection between ADHD and autism.

Recently a paper published in 2006 concerning the behavioral, cognitive, and genetic bases of autism argues that autism should perhaps not be seen as a single disorder, but rather as a set of distinct symptoms social difficulties, communicative difficulties and repetitive behaviors that have their own distinct causes. An implication of this would be to search for a cure for autism but it is unlikely to succeed if it is not examined as separate disorder [11].

Behaviorally certain characteristics identify the autism spectrum. The number of autistic traits present determines the severity of autism in the individual

(A) Social impairment

(B) Language impairment

(C) Imaginative impairment and repetitive adherence

(D) Sensory integration dysfunction

Autism involves primary impairments in both language and communication [14].Young people with specific language impairment have an increased risk of autism. The magnitude of this risk is considerable. In addition a larger proportion of individuals present with a number of behaviors consistent with autism spectrum disorder. The prevalence of autism spectrum disorders in young people with specific language impairment was found to be 3.9%, about 10 times what would be expected from the general population. In addition a much larger number of young people with a history of specific language impairment showed only some autism spectrum symptoms or showed them in a mild form [36]. Traditionally, autism and specific language impairment are regarded as distinct disorders with differential diagnosis hinging on two features.

First, in Specific language impairment one sees isolated language impairments in the context of otherwise normal development, whereas in autism a triad of impairments is seen, affecting communication, social interaction and behavioral repertoire.

Second, there are different communication problems in these two conditions. Children with Specific language impairment have particular difficulty with structural aspects of language like phonology and syntax. In contrast, abnormal use of language like pragmatics is the most striking feature of autism [37]. Primary language deficit in autism has been thought to be pragmatic and in specific language impairment it is structural, recent research suggests phenomenological and possibly genetic overlap between the two syndromes. Results suggest that impaired communication is part of the broader autism phenotype and a broader specific language impairment phenotype, especially among male family members [38].

SIGNS AND SYMPTOMS

Signs of autism may appear during infancy and the disorder is usually diagnosed at the age of 3 years. Sometimes the child's development appears normal until about 2 years old and then regresses rapidly. Symptoms of autism occur in various combinations from mild to severe. It is characterized by three main symptoms: impaired language, social and communicative deficits, repetitive and stereotyped behaviors; such as hand flapping, rocking and unusual responses to sensory stimuli. Infants with the disorder often display abnormal reactions to sensory stimuli like senses may be over or under active. Touches may be experienced as painful, smells may be overwhelmingly unpleasant and ordinary daily noises may be painful. Loud noises like motorcycle sound, vacuum cleaner and bright lights may cause inconsolable crying.

Other signs of the disorder in infants include the following: [1], [12]

a) Appears indifferent to surroundings
b) Appears content to be alone, happier to play alone
c) Displays lack of interest in toys
d) Displays lack of response to others
e) Does not point out objects of interest to others called proto declarative pointing
f) Marked reduction or increase in activity level
g) Resists cuddling
h) Avoids cuddling or touching
i) frequent behavioral outbursts, tantrums
j) Inappropriate attachments to objects
k) Maintains little or no eye contact
l) Over- or under sensitivity to pain, no fear of danger
m) Sustained abnormal play
n) Uneven motor skills
o) Unresponsiveness to normal teaching methods and verbal clues (may appear to be deaf despite normal hearing)

Young children with autism usually have impaired language development. They often have difficulty expressing needs like use gestures instead of words and may laugh, cry or show distress for unknown reasons. Some autistic patients develop rudimentary language skills that do not serve as an effective form of communication. They may develop abnormal patterns of speech that lack intonation and expression and may repeat words or phrases repetitively called echolalia. Some children with autism may learn to read, in general autistic children do not express interest in other people and often prefer to be alone. They may resist changes in their routine, repeated actions like turn in circles, flap their arms over and over and engage in self-injurious behavior like bite or scratch themselves and bang their head.

Several studies have showed that from age's two to four, autistic children have larger overall brain volumes and correspondingly larger head circumferences than normal children but that the difference had disappeared by about age six or seven [23].

Symptoms of autism may increase in severity when the child enters adolescence and often decrease in severity during adulthood.

GENETICS

Autism is considered by many to be the most strongly genetically influenced multi factorial childhood psychiatric disorder. The data clearly do not support twinning as a substantial risk factor in the etiology of autism [39]. Autism is a common neurodevelopmental disorder of complex genetic etiology [40]. These children lack some of the key social skills that normal toddlers pick up naturally looking to others for reassurance or cues, focusing on faces, and playing together. Social and communication impairment is a hallmark of autism and can show up as early as 12–18 months of age. But with an unknown cause, and genetic linkages still hazy, there is little consensus among researchers on how the disorder develops in children and how it causes a broad spectrum of social, language, and behavioral deficits [23]. Twin and family genetic studies provide evidence for strong genetic components. An international consortium using an affected sib pair strategy has found a promising linkage to a region on chromosome 7 [16].

In utero insults, brain function as well as neuro chemical and immunological factors. On the basis of family and twin studies, there appears to be a genetic basis for a wide "autistic syndrome." About a quarter of autism cases are associated with genetic disorders such as fragile X syndrome or with infectious diseases such as congenital rubella. Genetic studies have shown an association between autism markers of brain development such as 3 markers of the c-Harvey-ras, oncogene and the homeobox gene EN2. In some cases autism is associated with insults early in gestation, including thalidomide embryopathy. Autism may arise from abnormal central nervous system functioning, since most autistic patients have indications of brain dysfunction and about half of them have abnormal electroencephalograms. Similarly the pattern of evoked response potentials and conduction time is altered in autistic children. There is substantial evidence from neuro imaging studies that dysfunctions in the cerebellum and possibly the temporal lobe and association cortex occur in autistic symptoms. Neurochemical studies have investigated the role of serotonin, epinephrine and nor epinephrine, since levels of these neurotransmitters are altered in autism, although other hypotheses implicate overactive brain opioid systems and changes in oxytocin neurotransmission.

Autoimmunity may also play a role; antibodies against myelin basic protein are often found in children with autism who also have increased eosinophil and basophil response to IgE-mediated reactions. In summary, the prevailing view is that autism is caused by a pathophysiologic process arising from the interaction of an early environmental insult and a genetic predisposition [12].
Autism is a common complex genetic etiology. Rett syndrome, an X-linked dominant disorder caused by *MECP2* mutations and Angelman syndrome, an imprinted disorder caused by maternal 15q11–q13 or *UBE3A* deficiency have phenotypic and genetic overlap with autism. MECP2 encodes methyl-CpG-binding protein 2 that acts as a transcriptional repressor for methylated gene constructs but is surprisingly not required for maintaining imprinted gene expression. Multiple quantitative methods were used including automated quantitation of immunofluorescence and *in situ* hybridization by laser scanning cytometry on tissue microarrays, immunoblot and TaqMan Polymer chain reaction. These results suggest an overlapping pathway of gene dysregulation within 15q11–q13 in Rett, Angelman and autism and implicate *MECP2* in the regulation of *UBE3A* and *GABRB3* expressions in the postnatal mammalian brain [40].

There is little disagreement on the heritable component of autism. Identical twin studies put it in a range between 0.36 and 0.957 with concordance for a broader phenotype usually found at the higher end of the range. Most studies confirm the heritability of autism with estimates well above 0.6 although one researcher claims lower heritabilities. Autism concordance in siblings and fraternal twins is anywhere between 0% and 23.5%. This is more likely 2-4% for classic autism and 10-20% for a broader spectrum. Assuming a general-population prevalence of 0.1%, the risk of classic autism in siblings is 20 to 40 fold that of the general population. Researchers usually note that autism is among the most heritable of all neurological conditions. There is significant evidence that idiopathic autism is a heritable disorder [41].

The heritability of autism is debated by psychology researchers, parents of children diagnosed with autism and members of the autistic community. Many researchers suspect that autism results from genetically mediated vulnerabilities to environmental triggers and there is disagreement about the magnitude, nature, and mechanisms for such environmental factors. Researchers have found seven genes prevalent among many individuals diagnosed as autistic.

1) Genetic predisposition **[42], [43], [48], [49], [50], [51].**

a) Twin studies
b) Sibling studies
c) Other family studies
d) Twin risk
e) Phenocopies
f) Proposed models
   i) Mendelian models
   ii) Multigene models
   iii) Other models
g) Candidate gene loci

2) Proposed environmental triggers

a) Infectious disease
b) Heavy metal toxicity
c) Prenatal and prenatal factors
d) Stress
e) Parenting

Twin studies

Twin studies are a helpful tool in determining the heritability of disorders and low-prevalence human traits in general. They involve determining concordance of characteristics between identical monozygotic twins and between fraternal dizygotic twins.

Possible problems of twin studies are:

(1) Errors in diagnosis of monozygocity

(2) The assumption that social environment sharing by dizygotic twins is equivalent to that of monozygotic twins. A condition that is environmentally caused without genetic involvement would yield a concordance for monozygotic twins equal to the concordance found for dizygotic twins. In contrast a condition that is completely genetic in origin would theoretically yield a concordance of 100% for monozygotic pairs and usually much less for dizygotic pairs depending on factors such as the number of genes involved and assortative mating.

An example of a condition that appears to have very little if any genetic influence is irritable bowel syndrome, with a concordance of 28% vs. 27% for monozygotic and dizygotic pairs respectively [42]. An example of human characteristics that is extremely heritable is eye colour, with a concordance of 98% for monozygotic pairs and 7- 49% for dizygotic pairs depending on age [43]. This was a case report of a pair of identical twins concordant for autism. The twins developed similarly until the age of 4, when one of them spontaneously improved. The other twin, who had suffered infrequent seizures, remained autistic. The report noted that genetic factors were not important in the development of the twins [44].

A twin study which found high heritability for autistic traits in a large group of 3,400 pairs of twins [45].This study looked at 16 monozygotic twins and found a concordance of 43.75% for strictly defined autism. Neuroanatomical differences like discordant cerebellar white and grey matter volumes between discordant twins were found. The abstract notes that in previous studies 75% of the non-autistic twins displayed the broader phenotype [46]. There is convincing evidence that idiopathic autism is a heritable disorder. Twin studies reported 60% concordance for classic autism in monozygotic twins versus 0% in dizygotic twins, the higher monozygotic concordance attesting to genetic inheritance as the predominant causative agent. This suggests that interactions between multiple genes cause "idiopathic" autism but that epigenetic factors and exposure to environmental modifiers may contribute to variable expression of autism-related traits. This study examined whether the characteristic symptoms of autism like impaired social interaction, communication deficits and repetitive behaviors show decreased variance of symptoms among monozygotic twins compared to siblings in a sample of 16 families. The study demonstrated significant aggregation of symptoms in twins. It also concluded that the levels of clinical features seen in autism may be a result of mainly independent genetic traits [47].

Sibling studies

The importance of sibling studies lies in contrasting their results to those of fraternal dizygotic twin studies, plus their sample sizes can be much larger. Environment sharing by siblings is pressumably different enough to that of dizygotic twins to shed some light on the magnitude of environmental influence. This should even be true to some extent regarding the prenatal environment. Unfortunately dizygotic twin study findings have yielded a very large range of variance and are error prone because of the apparent low concordance and the fact that they

typically look at a small number of dizygotic pairs. For example, in studies involving 10 dizygotic pairs, a concordance below 10% would be impossible to determine precisely.

This study looked at data from the Danish Psychiatric Central Register and the Danish Civil Registration System to study some risk factors of autism, including place of birth, parental place of birth, parental age, family history of psychiatric disorders, and paternal identity." It found an overall prevalence rate of roughly 0.08%. Prevalence of autism in siblings of autistic children was found to be 1.76%. Prevalence of autism among siblings of children with Asperger's syndrome or pervasive development disorder was found to be 1.04%. The risk was twice as high if the mother had been diagnosed with a psychiatric disorder. The study also found that "the risk of autism was associated with increasing degree of urbanisation of the child's place of birth and with increasing paternal, but not maternal, age **[48].**

Other family studies

This report examined the family psychiatric history of 58 subjects with Asperger's syndrome diagnosed according to DSM-IV criteria. Three (5%) had first-degree relatives with Asperger's syndrome, Nine (19%) had a family history of schizophrenia, Thirty five (60%) had a family history of depression. Out of 64 siblings and 4 (6.25%) were diagnosed with Asperger's syndrome **[49].** This new conclusion from two studies using a large normative twin sample fits with results from family studies of individuals with autism spectrum disorder. Family and twin studies have shown that it is not only autism itself that is heritable, but that relatives show increased rates of the broader autism phenotype, which refers to sub clinical manifestations of all or part of the triad of autistic features. Importantly, some relatives show only isolated traits, for example communication difficulties without social impairment or rigidity. This suggests that the genes that contribute to autism segregate among relatives and have distinct influences on the different parts of the phenotype **[11].**

Twin risk

Some studies have suggested that the twinning process itself is a risk factor in the development of autism, pressumably due to perinatal factors. At least one study shows no correlation between twinning and autism, however Higher risk among twins due to environmental factors would have significant implications on twin studies **[50].**

Phenocopies

Evidence has mounted indicating that clinical pictures that look like autism (phenocopies) may not be due to the same genetic liability. Examples are congenital blindness, profound institutional privation, and a number of conditions related to mental retardation. Fragile-X syndrome, Rett syndrome and tuberous sclerosis are well-known causes of autism-like symptoms [51].A number of alleles has been shown to have strong linkage to the autism phenotype. In many cases the findings are inconclusive, with some studies showing no linkage. Alleles linked so far strongly support the assertion that there are a large number of genotypes that are manifested as the autism phenotype. At least some of the alleles associated with autism are fairly prevalent in the general population, which indicates they are not rare pathogenic mutations. This also presents some challenges in identifying all the rare allele *combinations* involved in the etiology of autism.

Candidate gene loci

There are 3 main approaches to identifying genetic loci and chromosomal regions likely to contain relevant genes:

1) Whole genome screens, searching for linkage of autism to shared genetic markers in populations of multiplex families (families with grater than 1 affected family member).

2) Cytogenetic studies that may guide molecular studies by pointing to relevant inherited or de novo chromosomal abnormalities in affected individuals and their families.

3) Evaluation of candidate genes known to affect brain development in these significantly linked regions or alternatively the linkage of candidate genes selected a priori because of their presumptive contribution to the pathogenesis of autism.

Cytogenetic abnormalities at the 15q11-q13 locus are fairly frequent in people with autism and a "chromosome 15 phenotype" was described in individuals with chromosome 15 duplications.

Among other candidate genes the *FOXP2*, *RAY1/ST7*, *IMMP2L* and *RELN* genes on chromosome 7q22- q33 , *UBE3A* genes on chromosome 15q11-q13 of GABAA receptor subunit and Variant alleles of the serotonin transporter gene (*5-HTT*) on chromosome 17q11-q12 are more frequent in individuals with autism than in non autistic populations [41].

A) 17q11.2 region, SERT (SLC6A4) locus

This gene locus has been associated with rigid-compulsive behaviors. Notably, it has also been associated with depression but only as a result of social adversity, although other studies have

found no link [52]. Significant linkage in families with only affected males has been shown [53], [54]. Researchers have also suggested that the gene contributes to hyperserotonemia [55].

B) GABA receptor subunit genes

GABA is the primary inhibitory neurotransmitter of the human brain. Ma et al (2005) concluded that GABRA4 is involved in the etiology of autism and that it potentially increases autism risk through interaction with GABRB1 [56]. The GABRB3 gene has been associated with savant skills [57].

C) Engrailed 2 (EN2)

Engrailed 2 is believed to be associated with cerebellar development. Estimate that this gene contributes to as many as 40% of autism spectrum disorder cases, about twice the prevalence of the general population [58].

D) 3q25-27 region

A number of studies have shown a significant linkage of autism and Asperger's syndrome with this locus [59]. The most prominent markers are in the vicinity of D3S3715 and D3S3037 [60].

E) 7q21-q36 region, REELIN (RELN)

In adults the Reelin glycoprotein is believed to be involved in memory formation, neurotransmission and synaptic plasticity. A number of studies have shown an association between the REELIN gene and autism [61], [62].

F) SLC25A12

This gene, located on chromosome 2q31, encodes the mitochondrial aspertate/glutamate carrier (AGCI). It has been found to have a significant linkage to autism in some studies [63].

G) HOXA1 and HOXB1

It was found an association of HOXA1 with increased head circumference and a number of studies have found no association with autism [64]. Transgenic mouse studies indicate that there is redundancy spread across HOX genes that complicate the issue and that complex interaction between these genes could play a role in determining whether or not a person inheriting the requisite combinations manifests an autistic spectum condition [65].

H) PRKCB1

Recently it is found that a strong association between this gene and autism. This is a recent finding that needs to be replicated [66].

I) FOXP2

The FOXP2 gene is of interest because it is known to be associated with developmental language and speech deficits. An association to autism appears to be elusive, nonetheless [67]. There are a large number of other candidate loci which either should be looked at or have been shown to be promising. Several genome-wide scans have been performed identifying markers across many chromosomes [68].

A few examples of loci that have been studied are the 17q21 region, the 3p24-26 locus, PTEN and 15q11-q13 [69]. Autism is not a disease but a syndrome with multiple non genetic and genetic causes except for Rett syndrome - attributable in most affected individuals to mutations of the methyl-CpG-binding protein 2 (*MeCP2*) gene - the other pervasive developmental disorder subtypes (autistic disorder, Asperger disorder, disintegrative disorder, and pervasive development disorder-not otherwise specified [PDD-NOS] are not linked to any particular genetic or non genetic cause.

Environmental triggers:

Review of 2 major textbooks on autism and of papers published between 1961 and 2003 yields convincing evidence for multiple interacting genetic factors as the main causative determinants of autism. Epilepsy, the medical condition most highly associated with autism, has equally complex genetic/non genetic (but mostly unknown) causes. Autism is frequent in tuberous sclerosis complex and fragile X syndrome, but these 2 disorders account for but a small minority of cases [70]. Genetic mutations that give rise to a number of additional diagnosable diseases may also be associated with autism. Neurofibromatosis, a common autosomal dominant disorder with neurologic and cutaneous manifestations, is much less frequently associated with autism than is TSC or FXS [71].

Finally, autism may also occur in the context of abnormal cellular metabolism such as mitochondrial disease or dysfunction [72], [73]. FXS is an X-linked genetic disorder that is significantly associated with autism and that is denoted by unusual facial features, macro-orchidism in adulthood and cognitive impairment of variable severity.

It is caused by an increased number of trinucleotide (CGG) repeats in the gene coding for the fragile X mental retardation protein. Approximately 30% of individuals with FXS are on the autistic spectrum [74], [75]. Research clearly shows that both nature and nurture play important roles in the genesis of psychopathology.

The interactions in psychiatric disorders using twin, adoption and association designs. They consider gene-environment interactions in selected neuro developmental disorders (autism and schizophrenia). Finally gene-environment interactions are evident both in a broad variety of mental disorders [76].

Evidence from twin, family and genetic studies supports a role for an inherited predisposition to the development of autism. Nonetheless, clinical, neuroanatomic, neurophysiologic and epidemiologic studies suggest that gene penetrance and expression may be influenced in some cases strongly by the prenatal and early postnatal environmental milieu. The CHARGE (Childhood Autism Risks from Genetics and Environment) study will address a wide spectrum of chemical and biologic exposures, susceptibility factors and their interactions. Phenotypic variation among children with autism will be explored as will similarities and differences with developmental delay. The CHARGE study infrastructure includes detailed developmental assessments, medical information, questionnaire data and biologic specimens [77].

Despite the profusion of investigations into the genetics of autism, few significant genetic linkages to autism have been identified. Even when strong genetic linkage is suggested, its significance remains undetermined until the functions of the gene product have been defined and its influence on brain development and physiology have been elucidated.

DISORDERS ACCOMPANIED WITH AUTISM

A] Mental Retardation

Mental retardation is the most widespread problems that can occur with autism.75 to 80 percent of people with autism are mentally retarded to some extent. 15 to 20 percent are considered severely retarded with intelligence quotients below 35. People with autism do not perceive or relate to their environment in typical ways. A child with autism may do extremely well on the parts of the test that measure visual skills but earn low scores on the language subtests.

B] Seizures

About one-third of the children with autism develop seizures, starting either in early childhood or adolescence. An electroencephalogram can help confirm their presence. Fortunately, in most cases, seizures can be controlled with medication.

C] Tuberous-Sclerosis

There is also some relationship between autism and Tuberous Sclerosis, a genetic condition that causes abnormal tissue growth in the brain and problems in other organs. Although Tuberous Sclerosis is a rare disorder, occurring less than once in 10,000 births, about a fourth of those affected are also autistic.

DIAGNOSIS

Autistic disorder by definition begins prior to the age of 3 years. The diagnosis requires presence of disturbance in three domains:

1) Social interaction

2) Communication

3) Restricted interests and stereotyped patterns of behavior [1].

Autism is a hetereogeneous disorder, diagnosed subjectively on the basis of a large number of criteria [12].Children with dimorphic features, congenital anomalies, mental retardation or family members with developmental disorders are those most likely to benefit from extensive medical testing and genetic consultation. Pediatricians must diagnose autism spectrum disorders expeditiously because early intervention increases its effectiveness [41]. The work of Courchesne et al. suggests that children at risk for autism might easily be diagnosed by head circumference measurements as early as the first few months of life. While dysfunctional face recognition may be one of the more devastating symptoms for caregivers, it is also one of the most promising avenues for research to determine how autistic brains process their world differently [23].

Children with an absence of joint attention like including proto declarative pointing and gaze monitoring and pretend play at 18 months were at high risk of autism. Early identification and intervention have proved to be beneficial. The original version of the Checklist for Autism in Toddlers (CHAT) was a simple screening tool for identification of autistic children at 18 months of age in the United Kingdom Our study suggested that the Checklist for Autism in Toddlers -23 is able to distinguish between children with and without autism. The high sensitivity and specificity of the criteria noted in our study suggested that Checklist for Autism in Toddlers -23 may be used to identify children with autism [78]. Another helpful approach is to identify more immediate biological effects of these putative susceptibility genes.

Postmortem examinations and studies using magnetic resonance imaging have found larger volumes of white matter in general and subtle structural changes in cell density and alignment, particularly in the limbic system. Functional imaging studies have also reported atypical activation of the amygdala and surrounding structures in response to social stimuli [6].

Early diagnosis of children with autism spectrum disorders is critical but often delayed until school age. Few studies have identified factors that may delay diagnosis [79]. Autism spectrum disorder strikes between one and six out of every 1,000 children around the world but diagnosis and treatment are currently limited to developed countries. Autism is four times more prevalent in boys than girls but makes no racial, ethnic or socioeconomic distinctions [23]. It is characterized by three main symptoms: impaired language, social and communicative deficits, repetitive and stereotyped behaviors such as hand flapping, rocking and unusual responses to sensory stimuli.

Autism spectrum disorders can be broken down into other categories such as low-functioning autism (Intelligence quotients below 70), high-functioning autism (Intelligence quotients above 70) and Asperger syndrome (similar to high-functioning autism but with no language deficit) [23].

Table 1: Criteria for the diagnosis of autism* (derived from DSM-IV-R) [41]

A. Impairment in social interactions

1. Lacks eye-to-eye gaze, facial expression, gestures while interacting
2. Fails to develop peer relationships
3. Does not share interests with others like no bringing, or pointing out objects
4. Lacks social or emotional reciprocity

B. Impairment in communication

1. Has delayed development of speech
2. Does not initiate or sustain conversation
3. Has stereotyped and repetitive language or idiosyncratic language
4. Lacks make-believe play or social imitative play

C. Repetitive behaviors and stereotyped behavior patterns

1. Has stereotyped, restricted patterns of interest, abnormal in intensity or focus
2. Has inflexible adherence to specific, non-functional routines or rituals
3. Has stereotyped and repetitive motor mannerisms like hand or finger flapping
4. Has persistent preoccupation with parts of objects

Diagnosis of autism is usually made by the age of 3. Early diagnosis and treatment often helps to improve outcome for patients. Diagnosis includes the following:

a) Physical examination may include neurological examination
b) Medical history includes family history, birth history, and early development
c) Medical tests to rule out other conditions

Physicians use various screening tools to evaluate development, communication and language skills, and interaction with others. They usually question caregivers about the child's development like did the child babble, point, wave and grasp objects by 12 months of age and observe the child closely during office visits. The Differential Ability Scales (DAS) and the Autism Diagnostic Observation Schedule (ADOS) were used to examine profiles of verbal and nonverbal abilities and their relationship to autistic symptomatology [4].

In diagnostic schemes, the criteria for identifying autism in these domains include overlapping features. One approach to interpreting this overlap is to consider that social and communicative impairments reflect the same underlying cognitive deficit referred to as the 'theory of mind' hypothesis of autism [3].

On this view autism involves primary difficulties in identifying mental states in other people, and in interpreting behavior and action in relation to a person's mental state. Studies on the relationship between social behavior, communicative functioning and theory of mind in children with autism are reviewed; emphasizing the connections between these areas of impairment that are central to the definition of the autistic syndrome. More significantly some aspects of language impairment in autism are also not likely to be the result of impairments in theory of mind. In one study, they found that subgroups of children with autism showed significant delays in language beyond what would be expected for both their age and cognitive level. In this the data illustrate that not all aspects of the language deficit in autism are explained by the "theory of mind" hypothesis. While many of the social and communicative symptoms may be theoretically interpreted as reflecting underlying deficits in the development of theory of mind, autism is not just a disorder in this cognitive domain [3].

The average age of diagnosis was 3.1 years for children with autistic disorder, 3.9 years for pervasive developmental disorder not otherwise specified and 7.2 years for Asperger's disorder. The average age of diagnosis increased 0.2 years for each year of age.

Rural children received a diagnosis 0.4 years later than urban children. Near-poor children received a diagnosis 0.9 years later than those with incomes greater than 100% above the poverty level. Children with severe language deficits received a diagnosis an average of 1.2 years earlier than other children. Hand flapping, toe walking and sustained odd play were associated with a decrease in the age of diagnosis, whereas oversensitivity to pain and hearing impairment were associated with an increase. Children who had 4 or more primary care physicians before diagnosis received a diagnosis 0.5 years later than other children, whereas those whose pediatricians referred them to a specialist received a diagnosis 0.3 years sooner.

These findings suggest improvements over time in decreasing the age at which children with autism spectrum disorders, especially higher functioning children receive a diagnosis.

They also suggest a lack of resources in rural areas and for near-poor families and the importance of continuous pediatric care and specialty referrals. That only certain autism spectrum disorders - related behaviors, some of which are not required to satisfy diagnostic criteria, decreased the age of diagnosis suggests the importance of continued physician education [79].

Evidence abounds that autism results from multiple gene mutations. Genetics researchers estimate that autism is the result of mutations in anywhere from 2 to 20 genes. By studying the commonly inherited pieces of chromosomes in autistic siblings, geneticists have identified a handful of chromosome hotspots. Daniel Geschwind, a neurogeneticist at UCLA, has already completed such a study. It reveals an association of a gene or genes linked to this disorder between language deficits and a hotspot region on Chromosome 7 [23].

This practice parameter reviews the available empirical evidence and gives specific recommendations for the identification of children with autism.

This approach requires a dual process:

1) Routine developmental surveillance and screening specifically for autism to be performed on all children to first identify those at risk for any type of atypical development, and to identify those specifically at risk for autism.

2) To diagnose and evaluate autism, to differentiate autism from other developmental disorders [80].

Differential Diagnosis

Conditions that cause symptoms similar to autism include the following:

1) Asperger disorder

2) Childhood disintegrative disorder
3) Rett disorder
4) Pervasive development disorder-not otherwise specified (PDS-NOS)
5) Childhood psychoses like schizophrenia
6) Fragile X syndrome (more common in males; may cause mental retardation)
7) Hearing loss
8) Metabolic disorders
9) Checklist for Autism in Toddlers (CHAT)

Tests performed to rule out other conditions include the following: [19]

a) Blood tests to rule out metabolic disorders that affect amino acids and lipids in the blood
b) Chromosomal analysis to rule out genetic disorders
c) Comprehensive hearing test to rule out deafness as the cause of abnormal language development
d) Electroencephalogram (EEG) to rule out seizure disorder
e) Magnetic resonance imaging scan to rule out brain disorders
f) Image analysis
g) Measurement of the Intracranial Volume
h) Measurement of the Cerebral Volume and the Ventricles

Asperger disorder is sometimes considered a variation of autism. It is more common in boys, usually develops after the age of 3, and usually does not require lifelong care. Children with Asperger have narrow interests, repetitive routines, and are at increased risk for developing depression and anxiety. Symptoms include the following:

a) Excellent rote memory (usually)
b) Excellent musical ability (often)
c) Inability to use language to communicate
d) Lack of facial expressions and emotion
e) Limited interests and an intense interest in one or two areas
f) Severely impaired social interaction
g) Undeveloped motor skills

The deletions encountered in the autism linkage study were unexpected, since similar findings have not been reported for other large linkage studies.

Thus, it is not possible to evaluate the statistical significance of the deletion frequencies detected here. Since large-deletion alleles are not routinely detected by other methods for polymorphism discovery. Large-deletion–allele polymorphisms may be an underappreciated class of genetic variability in humans. Deletions of the size reported potentially could contribute to human phenotype variability, either by deleting one or more genes or by influencing the expression of neighboring genes. Thus, identification and characterization of large deletion –allele polymorphisms may be important for understanding the influence of genetic variability on normal and disease-related phenotypes. The deletion allele at D8S272 was found in all populations screened. No additional deletions were identified in any of the groups without autism. Thus, these deletions appear to be specific to autism kindred's and are potential autism-susceptibility alleles.

An alternative hypothesis is that autism-susceptibility alleles elsewhere cause the deletions detected here, possibly by inducing errors during meiosis [81].

Childhood disintegrative disorder causes marked deterioration of intellectual, social, and language skills around the age of 3 or 4. The disorder is associated with seizures and is more common in boys. Patients with the condition usually require lifelong care. Childhood disintegrative disorder causes loss of the following:

a) Bowel and bladder control
b) Language means ability to communicate and understand others
c) Motor skills
d) Social skills means ability to play, develop peer relationships

Rett disorder is a progressive neurological disorder that occurs only in girls. Symptoms of the disorder usually develop between 6 and 18 months of age. It is characterized by the following:

a) Abnormal gait
b) Inability to control hand movements
c) Inability to express feelings
d) Reduced brain size and weight (microcephaly)
e) Reduced muscle tone (hypotonia)
f) Seizures

Patients also may experience constipation, breathing difficulties, weakness of the extremities, and cognitive regression. There is no cure for Rett disorder, but symptoms usually can be managed with appropriate treatment.

Pervasive developmental disorder-not otherwise specified (PDD-NOS) is characterized by delayed development of social and communication skills. It usually develops between 2 and 12 years of age. Individual attention and medication to manage behavioral problems can be beneficial. Symptoms include:

a) Abnormal play behavior
b) Desire for sameness in their environment
c) Difficulty using and understanding language
d) Impaired ability to relate to people, objects, and events
e) Repetitive movement and behavior
f) Self-injury
g) Unusual mannerisms

Future research on the social, language, and cognitive functioning in children and adults with autism will bring about a more comprehensive understanding of this neuro developmental disorder, which will guide the development of new interventions and therapies to improve their daily lives [3].

TREATMENT

These current treatments for autism are considered palliative but not curative [82]. Autistic disorder and the group of related conditions defined as pervasive developmental disorders are chronic neurodevelopmental disorders starting in early childhood and affecting a significant number of children and families. Although the causes and much of the pathophysiology of the disorder remain unknown, in recent years a number of available medication treatments have been identified as holding promise in alleviating some of the most disabling maladaptive behaviors, associated with pervasive developmental disorders. However these treatments do not address the core symptoms of the disease and often their side effects outweigh their benefits. Therefore there is substantial need for new medications that are safer and more effective in addressing the behavior symptoms of autism [1].

Autism, also known as autistic spectrum disorder or pervasive developmental disorder (PDD), is of great concern to the practicing pediatrician [41]. Autism is a chronic and lifelong pervasive developmental disorder for which there is yet no effective cure, and medical management remains a major challenge for clinicians [10]. Autism is a chronic and lifelong pervasive developmental disorder for which there is yet no effective cure, and medical management remains a major challenge for clinicians. In spite of the possible similarities with conditions that have an established pharmacotherapy, and despite improvements in some associated "problematic behaviors" following the use of available medications, effective medical treatment for the core symptoms involving language and social cognition remains elusive [40]. Autism is a severe developmental disorder with poorly understood etiology [2].

Autism is an early developmental disorder. It leads to severe and durable disturbances. Given this problem, no treatment can be excluded a prior. Thus, many approaches are used to deal with autistic disorders. About medical treatments used in adolescents and adults with autism, they are classified in 3 categories:

Category I include drugs used for their neurochemical effects focusing on autistic signs.

Category II covers drugs used for treatment of behavioral disorders frequently associated with autism.

Category III corresponds to a wide range of drugs or vitamins for which only few case studies exist reporting irregular positive effects [83].

1. **Behavioral and sensory integration interventions**
    a) Applied behavior analysis
    b) Computer use
    c) Multi stationary stimulation
    d) Neurofeed back
    e) Cranio-sacral therapy
    f) Non-coercive approaches
    g) Relationship development intervention
    h) Son-Rise
    i) The institutes for the achievement of human

2. **Biomedical interventions**
    a) Detoxification
    b) Drug therapy
    c) Gluten-free, Casein free
    d) Low salicylate diet
    e) Gold salt
    f) Occupational, auditory, visual therapy
    g) Tinted Lenses
    h) Other therapy
    i) Holistic healing
    j) Probiotic diets
3. **Non-medical views**
    a) Autism is not a disorder
    b) There is no one condition called autism
4. **Communication therapy**
5. **Dietary modifications**
6. **Medication**

PHARMACOLOGICAL TREATMENTS IN AUTISM [83]

Category I used for their neurochemical effects focusing on autistic signs

Selection signs 1 Active drug in the dopamine system.

Haloperidol (Dopamine antagonist): The effects of this molecule have been broadly studied in autism. Results indicate high efficiency in some symptoms of autism (lack in social behavior, stereotypical behavior) and in behavioral impairments that may be associated with autism (aggressive behavior, hyperactivity). Its side effects, particularly the risk of late dyskinesia, make atypical antipsychotics preferable because of their lower risks.

Risperidone (Dopamine and serotonin antagonist): Among several studies only few have been controlled. They indicate that risperidone has positive effects on the behaviour and is quite well tolerated. Risperidone, administered as an oral solution at a mean dose of 1.38 mg/d (range: 0.02–0.06 mg/kg/d) for 1 year, was well tolerated, safe, and showed maintenance of effect in the

treatment of disruptive behavior disorders (DBD) in children aged 5 to 12 years with subaverage intelligence quotients [84].

Sections sign 2 Active drugs in the serotonine system.

Clomipramine: after promising results, the medium-term efficiency has decreased and severe side effects have limited its use.

Fluvoxamine, Fluoxetine, Sertraline (Specific serotonine drugs): Their efficiency has been mainly tested through open studies and their results are contrasted. In some cases, social behaviours have improved and aggressiveness and stereotyped behaviours have decreased.

a) Fluvoxamine
b) Fluoxetine
c) Fenfluramine: At present, this drug is removed from the market. Yet, some studies have suggested that it improves behavioural disturbances as well as performances in autism.
d) Amitriptyline

Sections sign 3 Active drugs in the opiate system.

Naltrexone: Several controlled studies have indicated an improvement in social and aggressive behaviours. Nevertheless, these studies have used small size sample and have not been replicated.

Category II

This category correspond to drugs supposed to be active on neurochemical disturbances found in autism but their target symptoms are not autism specific signs as defined by the ICD 10.

Buspirone: This serotonine agonist may have a good impact on emotional disorders and sleeping confusions.

Methylphenidate: Most of the current studies about this noradrenergic drug concern children. The results are variable. Paradoxical effects may exist in children with severe mental retardation.

Propranolol: Some isolated studies have reported its efficiency on behavioural disturbances.

Clonidine: This adrenergic drug treats efficiently some cases of aggressive behaviour and hyperactivity.

Category III

This category contains a wide range of drugs, vitamins or method used in autism after sporadic observations of their positive effects.

Secretine: [1], [2]

An important improvement has been reported in isolated cases. However, controlled studies in children do not confirm these results**.**

Anecdotal reports on the efficacy of secretin in autism raised great hopes for the treatment of children with this disorder. No evidence is provided for the efficacy of repeated doses of porcine secretin in the treatment of children with autism [85].

Vitamins B_6, B_{12} and Magnesium salts: An improvement in socialization and behavioral disorders has been reported in some cases, but these results are not yet confirmed.

Lithium, Carbamazepine, Valproate: Results of some case studies have found it to be efficient in cyclic disorders.

Gluten and casein free diet: An improvement of social behaviour has been reported by some parents after these diets. No controlled study has validated this observation.

Although there many clinical observations, only few controlled studies have validated the efficiency and safety of these treatments. At present drugs are generally limited to severe disorders, for which usual psycho-educational approaches are insufficient [83].

Pharmacological interventions with serotonin reuptake blockers or with atypical neuroleptics that block both dopamine (D_2) and serotonin ($5\text{-}HT_2$) receptors seem to offer clinical benefit [16]. There is no cure for autism; however, with appropriate treatment and education, many children with the disorder can learn and develop. Early intervention often can reduce challenges associated with the disorder, lessen disruptive behavior, and provide some degree of independence. Treatment depends on the individual needs of the patient. In most cases, a combination of treatment methods is more effective. Autism usually requires lifelong treatment.

Occupational therapy and physical therapy are sometimes used to treat autism. Occupational therapy helps improve independent function and teaches basic skills like buttoning a shirt, bathing. Physical therapy involves using exercise and other physical measures like massage, heat to help patients control body movements.

OTHER TREATMENT STRATEGIES:

Autism is a pervasive developmental disorder that is aetiologically and clinically heterogeneous [16].

Behavior modification

There are several methods of behavior modification that are used to treat inappropriate, repetitive, and aggressive behavior and to provide autistic patients with skills necessary to function in their environment. Most types of behavior modification are based on the theory that rewarded behavior is more likely to be repeated than behavior that is ignored. This theory is called applied behavior analysis (ABA).

Behavior modification often involves highly structured, skill-oriented activities that are based on the patient's needs and interests. It usually requires intense, one-on-one training with a therapist and extensive caregiver involvement.

Sensory integration therapy

People who have autism often have sensory difficulties. In some cases, they are hypo- or hyper-reactive, or they lack the ability to integrate the senses. Sensory integration therapy, which is performed by occupational, physical, or speech therapists, focuses on desensitizing the patient and on helping the patient re-organize sensory information. If the patient has difficulties with the sense of touch, sensory integration therapy may involve handling materials with different textures. Patients who are over-sensitive to sound may undergo auditory integration therapy, which involves listening to a number of sound frequencies.

Before undergoing sensory integration therapy, the patient should be observed closely by the therapist to make sure the therapist has a clear understanding of the patient's sensitivities.

Playing Well with Others [3]

Social interaction is often affected by limited emotional development that is common in autistic patients. Play therapy is a type of behavior modification that is used to improve emotional development, which in turn, improves social skills and learning. Play therapy involves adult-child interaction that is controlled by the child. Social stories can also be used to improve undeveloped social skills. Stories are designed to help autistic patients understand the feelings, ideas, and points of view of others, or to suggest an alternate response to a particular situation. They also may be used to help patients understand and cope with their own feelings. Behavioral therapists can teach caregivers how to develop social stories.

Communication therapy

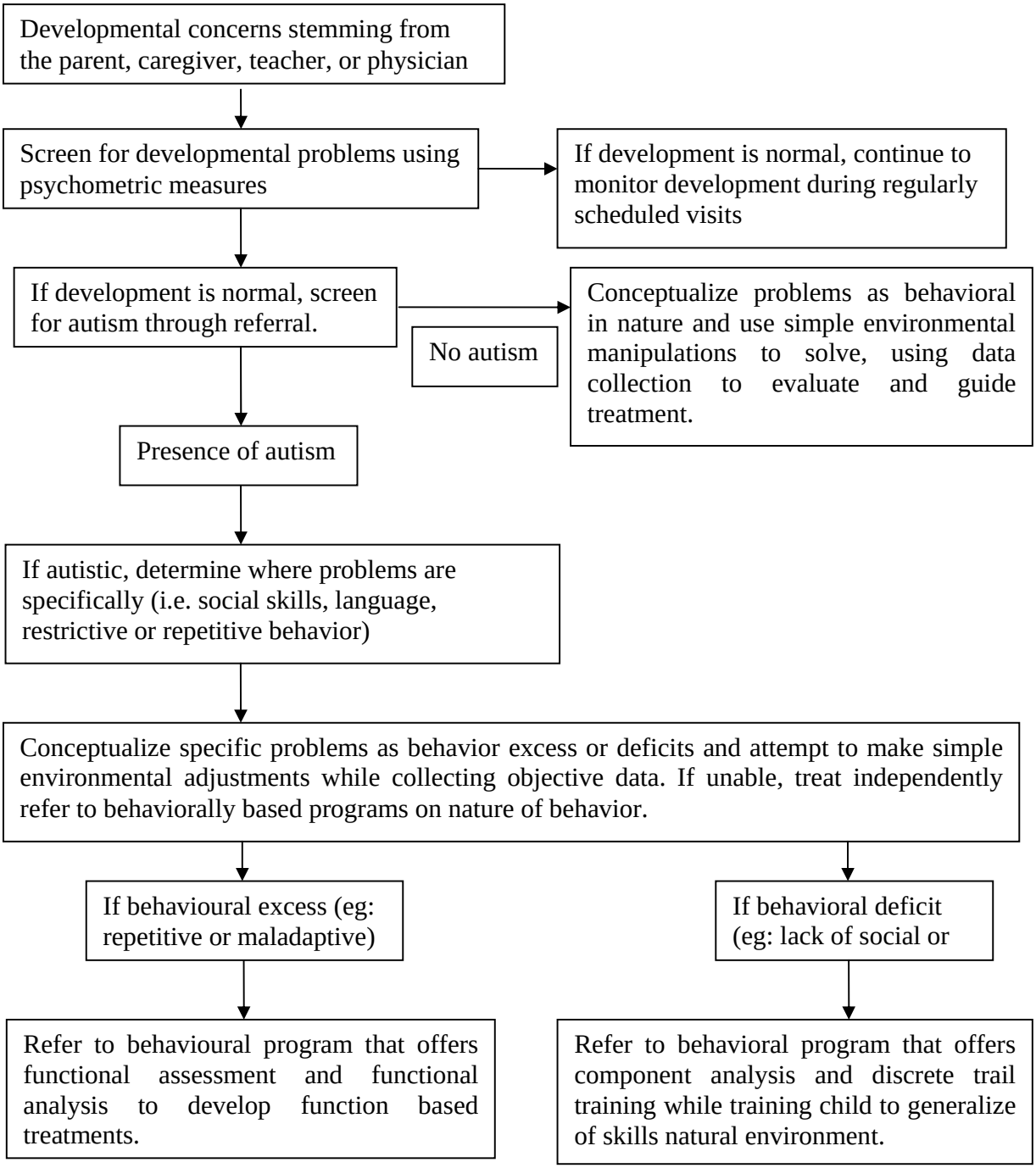
Communication therapy is used to treat autistic patients who are unable to communicate verbally, or to initiate language development in young children with the disorder. Speech therapy may be used to help patients gain the ability to speak.

Picture exchange communication systems (PECS) enable autistic patients to communicate using pictures that represent ideas, activities, or items. The patient is able to convey requests, needs, and desires to others by simply handing them a picture.

Dietary modifications

Autism is not caused by diet and the use of dietary modifications and supplements to treat the disorder is controversial. Changing the diet or adding vitamin supplements may improve digestion and eliminate food intolerances or allergies, which may contribute to behavioral problems in autistic patients. Researchers have found elevated levels of proteins found in wheat, oats and rye contain gluten and casein contain protein in dairy products byproducts in patients with autism, suggesting that the incomplete breakdown or excessive absorption of these substances may affect brain function. Eliminating foods that contain gluten and casein from the diet may cause side effects and should not be done without the advice of a health care practitioner. Studies have shown that vitamin B, magnesium improves the effects of vitamin B, and cod liver oil supplements which contain vitamins A and D may improve behavior, eye contact, attention span, and learning in autistic patients. Vitamin C has been shown to improve depression and lessen the severity of symptoms in patients with autism.

ASSESSMENT AND TREATMENT OF AUTISM [86]



Prognosis

Patients with autism have normal life expectancies. With early intervention and appropriate treatment, some autistic patients can function productively and attain some degree of independence. Most patients require lifelong assistance.

There was much initial excitement concerning the use of the gastrointestinal peptide secretin in the treatment of autism. A series of randomized, double-blind, placebo-controlled trials of intravenous infusion of the agent followed. Indeed, secretin is the best-studied drug for treatment of autism, involving nearly 600 children. Although it is perhaps the best-studied treatment for autism, secretin is not effective.

A recently published case series describes 3 autistic children with gastrointestinal symptoms who underwent endoscopy and intravenous administration of secretin and were subsequently noted by their parents to demonstrate improved language skills over a 5-week period. With a total study completion rate across all participants of 96%, repeated measures analyses of variance revealed no significant increases in children's language skills from baseline across all 5 study time periods after a single infusion of secretin. Similarly, neither significant decrease in atypical behaviors nor increases in pro-social behaviors and developmentally appropriate play skills emerged. The results of our pilot study indicate that intravenous secretin had no effects in a 5-week period on the language and behavior of 20 children with autism and gastrointestinal symptoms [2].

Three children with autistic spectrum disorders underwent upper gastrointestinal endoscopy and intravenous administration of secretin to stimulate pancreaticobiliary secretion. All three had an increased pancreaticobiliary secretory response when compared with nonautistic patients (7.5 to 10 mL/min versus 1 to 2 mL/min). Within 5 weeks of the secretin infusion, a significant amelioration of the children's gastrointestinal symptoms was observed, as was a dramatic improvement in their behavior, manifested by improved eye contact, alertness, and expansion of expressive language. These clinical observations suggest an association between gastrointestinal and brain function in patients with autistic behavior [87].

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