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EDITORIAL

Autism: a review

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Abstract

This is a review of autism spectrum disorders. It presents the symptoms of the disease discussing the age of diagnosis and first symptoms encountered. It is a polygenic disease that occurs mainly in boys. The importance of early diagnosis is emphasized. The assessment scales used for early diagnosis are discussed. The anatomic basis of the disease is detailed. The molecular genetic aspects, and the techniques employed are reviewed. Special emphasis is placed in chromosome abnormalities observed in autism. Its incidence worldwide is increasing dramatically. This is considered to be due to epigenetic events. Several hypotheses for such epigenetic processes are discussed. Finally the state of intervention in autism and its paradigms are detailed. (J Pediatr Neurol 2003; 1(2): 55-67).

Key words: autism, clinical and genetic aspects of autism, intervention in autism.

Introduction

Autism is a behavior disorder. It is a central nervous system (CNS) disease the etiology (ies) of which is unknown. There is growing clinical as well as molecular genetic evidence that the pathway connections in CNS are aberrant. Each of its symptoms may be explained from this point of view.

As to be discussed in detail later, its incidence is increasing logarithmically. At present a worldwide epidemic of autism exists. Like any other behavioral disorder there is no medical cure but only behavioral intervention. From a public health point of view, what make it most interesting are both the present epidemic as well as the availability of intervention measures.

In fact the first intervention was tried in early 1980's. A visit to Internet sites and reading stories by parents of autistic children, one immediately becomes aware of truly numerous autistic children who now are late adolescents / adults leading an independent life holding jobs earning their living. This became a reality because of intervention. While in countries outside West, this is not true. An autistic individual remains psychologically crippled. The difference is like day and night.

This review will focus on clinical, intervention and research aspects of autism.

What is Autism?

Autism is an umbrella term for a wide spectrum of disorders sometimes referred as "Autism Spectrum Disorders" or "Pervasive Developmental Disorders". It ranges from the very severe infantile form to the mildest, the Asperger syndrome. In between various types of speech, attention deficit, hyperactivity disorders are placed. These latter conditions might not always share the same genetic milieu but definitely some share symptomatology of typical autism. One should not be astonished at such diversity since we now know that autism is a polygenic disease; therefore theoretically there might be more than the outlined phenotypes.

Autism affects three core areas of behavior: social skills, communication and behaviors of interest. Its first signs are usually observed by 3-years of age. Although there may be warning signs before 1-year-of age. Most educated and attentive

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parents will first notice the delay or loss of any one of these skills by 15-18 months of age.

In most instances no visible physical stigmata are present. Except if it is associated with some chromosome abnormality or like in Rett syndrome where many abnormalities of the peripheral systems are present. Autism is an invisible disease, which makes it troublesome to parents and physicians. Its main appearance is a complete blackout to environmental inputs.

The disease is characterized by deficits in social reciprocity. These defects are most severe in early classical infantile autism, while in Asperger syndrome these defects are milder. In classical autism mental retardation might co-exist 40-75%, in Asperger syndrome language and intelligence are preserved. Nevertheless a patient with Asperger syndrome will be sparse in speech, tends to be a loner, doesn't like social contact and answers tangentially. Classical autism includes back-and forth-meaningless body movements, gestures and repetitive play patterns. The child will pay no attention to conversation. He is not deaf but doesn't register speech. He shows ritualistic and obsessive behaviors since they are a routine that he feels to be comfortable with. An autistic child might insist on lining up his toys rather than playing with them. Any change in their established routine might lead to anger attacks, temper tantrums and will encounter severe resistance. He may have under- or over-sensitivity to sounds. A 3-year-old autistic child might be interested in an infant-book but might not be able to play simple peek-a-boo. Another one might never have uttered a word but might use sign language effectively. These are all caused by wrong connections of pathways in the CNS.

Autism has a strong genetic component. However, the increasing incidence also suggests that epigenetic factors have a role; and that environmental factors affect the function of certain genes. It tends to run in families. In 1998 its incidence was 1/1000 births in general population, At that time point the incidence was 3-7% for subsequent siblings of a family who already had one autistic child. In dizygotic twins the concordance rate was 9% and in monozygotic twins it was 60% (1). This clearly suggests a genetic component. Autism is a "boys" disease. The ratio of boys to girls is 4 to 1. Most of the autistic girls have Rett syndrome.

In 1986 1/5,000 births produced one autistic individual, this number was 1/1,000 in 1998 and 1/250 in 2000. In USA, in certain areas it has been reported to be as high as 1/138 or 1/125. The reason for this increase is not clear. The living standards and environment have changed in the last 20 years. Factors as increased organophosphates use in agriculture, changing dietary habits that change the intestinal flora and the toxins they produce, plastic industry and plasticizers are all blamed. In certain instances when measles-mumps vaccine related autism cases were found, it was thought that thiomersal used as a preservative was responsible (2). The epigenetic factors will be discussed later.

As a result of this newly merging epidemic, for example in USA a large number of funds were made available by the Centers for Disease Control and Prevention (CDC) to do research on the causes of autism. A large number of sites are now present in Internet. A recent search indicated 1,630,00 sites, 763 books and 626 magazine articles on autism that appeared in recent years. Some of those addresses for autism are:

Autism Research Institute
Autism Research Review (http:/www. Autism.com/ari)
First signs of Autism (http:/www. Firstsigns.org)
Autism Society of America
Interdisciplinary Council for Developmental and Learning Disorders Spectrum.

Diagnosing Autism

In the west many efforts are spent to come up with reliable and accurate as well as universally acceptable assessment scales (3).

Screening tests: In order to have available a screening tool for case finding, the Social Communication Questionnaire (formerly the Autism Screening Questionnaire) appears to be adequate. The SCQ is a questionnaire for caregivers, built on the structure of Autism Diagnostic Interview that takes approximately 20 minutes to complete. The SCQ was developed by Cathy Lord and Mike Rutter who also have developed the ADI and ADOS (4,5). It is considered to be the best currently available screening instrument. However, the data for its sensitivity and specificity are limited. The criteria listed by International Classification of diseases (ICD-10) should be available to interviewers; 8 of the 16 criteria must be present before the child is referred to a clinic specialized in autism, for a more careful assessment (3).

Autism assessment scales: The large number of assessment instruments as detailed by Le Couteur (3) indicates that there is no universal agreement for a reliable scale. Some of the scales that found broad usage are as follows:

Childhood autism rating scale (CARS): The CARS (6) rates behaviors in 15 domains, with scores ranging from 1 (within normal limits) to 4 (severe autistic symptomatology). Total scores less than 30 fall in the nonautistic range, while those 30 and above are considered indicative of autism. A high degree of internal consistency has been found for the CARS (coefficient alpha of 0.94), as well as adequate test-retest reliability (r = 0.88) over a one

year period.

Autism diagnostic interview-revised (ADI-R) by Lord, Rutter, and Le Couteur (7) is a semistructured, investigator-based interview for caregivers of children and adults for whom autism or pervasive developmental disorders is a possible diagnosis. It has 35 items covering three domains: Qualitative Abnormalities in Reciprocal Social Interaction; Qualitative Impairments in Communication and Language; and Restricted, Repetitive Behaviors and Interests. It also has a 66-item pre-school version. Reliability and validity are generally excellent (Kappas are greater than 0.63; retest reliability exceeds 0.91; Cronbach's alphas ranged from 0.06 to 0.95, but were mostly above 0.70). ADI reliably differentiated autism from mentally retarded/ language impaired subjects in 24 of 26 cases.

Autism diagnostic observation schedule (ADOS) by Lord et al (8) is a standardized protocol for observation of social and communicative behavior associated with autism. The instrument consists of a series of structured and semistructured presses for interaction, accompanied by coding of specific target behaviors associated with particular tasks and by general ratings of the quality of behaviors. Interrater reliability for five raters exceeds weighted kappas of 0.55 for each item and each pair of raters for matched samples of 15 to 40 autistic and nonautistic, mildly mentally handicapped children (mean IQ = 59) between the ages of 6 and 18 years. Test-retest reliability is adequate.

Early Diagnosis

The main objective of practice in autism is to find reliable early predictors of autism. Rutter (5) in his summary of a recent conference on "Autism: The State of the Science," sponsored by the National Institutes of Health in the USA, noted that, in spite of three decades of burgeoning research on autism, one of the top clinical priorities for research is still the validity of the diagnosis of autism in very young children under the age of two years. There is now little doubt that such a diagnosis is possible; the only question that remains is its accuracy, sensitivity, and specificity. The issue is important because of recent emphases on intense early intervention programs such as that espoused by Lovaas (9). Follow-up studies of very young children comparing those with diagnoses of autism vs. other developmental disorders when they are older are needed (4).

Why is this important? Early diagnosis means early intervention. This translates in most instances to an autistic child growing to adulthood, leading an independent life scale, holding a job and having a near normal lifestyle. Over and over it was demonstrated that autism intervention gives best results if given before 5-years of age, the earlier the better.

Age of first manifestation of autism is a matter of some dispute (10). Probably the modal age where parents become seriously concerned about autism is at two years of age (11) when language delay becomes a concern. However, several retrospective studies show that parents note abnormalities by 12 months of age or earlier. Examples are: lack of anticipation for being picked up, eye-to-eye gaze for social signaling, joint attention, reaching for a familiar person and imitating other people's actions, e.g., waving good-bye or clapping hands. Retrospective studies of home movies at 9–12 months and at first birthdays Osterling and Dawson (12) corroborate these findings.

Stereotyped movements are a particularly interesting set of motor behaviors prevalent in about one third of people with autism. A significant proportion of stereotyped movements (c. 40%) in autism are also self-injurious (SIB), such as head banging (13). SIB is a devastating disorder the prevalence of which in autism is estimated from 10-40 percent. Both SIB and stereotyped behavior are manifested at a very early age (14), in normal infants, however, they rapidly decrease by one year and are rarely seen beyond five years of age. In infancy, stereotypies are often viewed as promoting motor development, but beyond one-year of age, they are viewed as seriously pathological and indicative of underlying neuropathology.

Early motor behavioral abnormalities are often the first signs noticed, e.g. lack of joint attention, imitation, or motor coordination; presence of abnormal stereotyped movements, etc. These may be related to neuropathologies in the cerebellum, basal ganglia, and elsewhere.

Cognitive and communication abnormalities are a salient aspect of autistic disorders

There is considerable neurobiological evidence from neuropathological, immunological, and imaging studies that people with autism have a higher incidence of brain and neurochemical abnormalities, especially ones related to movement dynamics. The question remains, however, as to how they combine with environmental events to produce the behaviors observed in autism.

There are likely comorbid risk factors that can be detected very early in the neonatal period. Certain genetic syndromes, e.g. Fragile X syndrome, rubella, and tuberous sclerosis, etc. co-occur more frequently with autism. Autistic-like behaviors, e.g. stereotypy and self-injury, are higher among people with more severe mental retardation. Thus, congenital defects resulting in severe retardation may also be a risk factor for autism.

In summary: The sensory motor behaviors in the developmental sequence are the prerequisite for organized action, communication, and cognition,

Table 1. Hypothesized neural substrates for early symptoms of autism [a]

Symptoms	Possible impairment	Proposed substrate [b]
Orienting to social stimuli	Recognition of affective significance of stimuli	AMYG
	Social stimulus-reward associations	AMYG
	Disengage/shift attention	CER
Motor imitation	Perception of body movements	AMYG
	Cross-modal association	AMYG
	Long-term memory	AMYG, HIP
	Representation of action plans	FL
	Motor planning and execution	FL, BG
Joint attention	Orienting to social stimuli	See above
	Perception of gaze direction	AMYG
	Rapid shifts in attention	CER
Empathy	Perception of emotion	AMYG
	Motor imitation	See above

[a] Parts of this table were included in Figure 3 of "From mind to molecule: Researches try to unravel the complexity of autism," Journal of NIH Research, 7, 1995. Dawson (1995) is the original source of this material. It is condensed.
[b]AMYG: Amygdala; HIP: Hippocampus; CER: Cerebellum; FL: Frontal lobe; BG: Basal ganglia.

and that these abnormalities will be the best early neuro-behavioral predictors that can be linked with genetic and other neurobiological predictors of autism.

Neurologic Aspects of Autism

In recent years there have been many excellent integrative reviews of the clinical, genetic, neuropsychological and neurobiological perspectives on autism (10,15-17). Perhaps the most comprehensive review is the summary of the 1995 NICHD conference on "Autism: the State of the Science," published in the April 1996 issue of the Journal of Autism and Developmental Disorders. In his summation of this conference, Rutter (5) notes that two relatively understudied but high clinical priorities for research are early diagnosis of autism (p. 260) and the study of repetitive stereotyped behaviors or unusual cognitive skills found in individuals with autism (p. 261).

Persons with autism have neuropsychological impairments in a wide range of domains suggesting that multiple brain regions and neural networks may be involved (15). Many of the dysfunctions appear to involve social information processing. There may be different predictors of autism at different ages during development. Early in life, they involve attention to social stimuli, imitating body actions, pointing and gesturing, etc., i.e., while, in later life, they involve forming a theory of mind and comprehending pragmatic language rules. Table 1 summarizes some of the hypothesized neural substrates for early symptoms of autism.

Most of the tools necessary for social functioning are in place early in life (18). By five months, infants can distinguish affective vocalizations independent of visual information. The motor programs for facial
expressions, gestures, and gaze are present at birth. Eye contact, joint visual attention, recognition of facial expression, response to touching and holding, autonomic arousal in response to social signals are fully functional by six months of age. In autism these functions are impaired at a very early age.

The presence of cyclicity in the occurrence of aberrant behaviors is certainly noteworthy and important to caregivers. The theoretical explanations for cyclicity and stereotyped behavior are still a matter of much speculation (19). There have been no direct observations of neural pattern generators in the CNS. They must be inferred indirectly from behavioral or neurophysiological methods. This will be a growing area for research in the future.

Genetics and Molecular Genetic Aspects of Autism

As presented before there is little or no doubt that there is a genetic basis for autism. The research also indicates that there is no simple genetic model for autism. It is highly likely that as many as 63 genes play a role (20). The genetic linkage studies indicated that in each family or ethnic group one of these genes to play the major role. When tested in others it will not be found to be associated with the disease. The best example is autism associated with chromosome 15q11-q13 region abnormalities.

At least 15 such patients were reported. But, when tested on a large scale in Poland, no association to that site was found (21). Again another study done among UK autistic patients found linkage at chromosome 7q, while it was not present among non-UK patients (22). These studies clearly suggest that in each family or ethnic group a different gene predominates.

Where does the information for the molecular genetics in autism come from?

There have been two types of approach. In the first type, standard linkage and association was searched for in a genome-wide screen with chromosome markers in large families or in families with multiplex autism cases. In the second approach, first a chromosome abnormality was detected and then detailed genetic studies were conducted in the narrowed region of chromosome. Although the second approach has provided better identification, in most instances neither the first nor the second approach gave reproducible results. Whatever was found for one family or ethnic group could not be confirmed for another family or ethnic group. Table 2a and 2b summarize chromosome abnormalities in association with autism. It only contains the last 6-7 years publications when molecular studies could be coupled to karyotyping findings.

Linkage studies: This is a statistical analysis that searches if alleles of two loci of genes travel together within a family more often than predicted. If they do, it means that those two loci are located close together on the chromosome. Most linkage analyses in autism are done with 400 such markers. Nowadays with the availability of a megabace system the number of markers is over 1,000. The results might reflect a true linkage or might be a statistical artifact. Two big studies found suggestions that autism genes exist on chromosome 1, 2 6, and 7 (59,60). The problem with linkage studies is the relatively small size of populations studied, and the noise introduced by genetic heterogeneity. The linkage studies identify large regions of chromosomes; then the question becomes which one of these genes among the numerous genes present in that area. The problem for the value of this type of analysis in autism has been the difficulty in reproducing it in a second study, in the same or another group of patients.

An extension of this method has been the candidate gene approach. In this approach, genes are identified either through juxtaposition with the chromosome region by their virtue of their physiologic or developmental role. Examples are GABA3 receptor gene on chromosome 15q13, or genes linked to the MECP2 locus identified on chromosome X in Rett syndrome.

Autism associated with chromosome abnormalities

The search for genes in autism is fortunate that so many children with autism have a chromosome rearrangement. When a chromosome break or duplication occurs, it can be assumed that the missing gene(s) at the region are responsible for the phenotype. Also several of these breakpoints correspond roughly to regions identified by linkage studies. Then the problem reduces to find which one of those genes at breakpoint is responsible for autism. At times this process becomes even more difficult if the translocation occurs between two chromosomes that carry putative autism genes, such as a translocation between chromosome 1 and 7. Several studies the delayed language development in autism is related to 7q31 (40). In a case with similar translocation Vincent et al (38) has identified a novel gene with unknown function at the breakpoint, FAY1 (or FAM4A1).

Another example is duplication of 15q11-q13 that occurs frequently in children with autism. Chromosome 15 is notorious for the amount of duplicated material. Wolpert et al (55) indicates a strong association between this region and autism. In another study Smith et al (39) found autism in association with a microdeletion at a more distant place on chromosome 15q22-q23. Molecular studies indicated that the distal region shared many DNA segments with the proximal region.

In summary: At present many candidate genes are identified through a combination of linkage and chromosome studies. Too many genes are implicated but the observations lack a testable research hypothesis. Autism is a complex polygenic disorder and establishing a good genetic hypothesis will not be an easy task.

Putative Autism Genes Involved in Development of Brain

A large number of studies suggest that certain genes predispose the fetus later to autism. These are:

1) HOXA1 gene
2) Reelin gene
3) RAY1 gene
4) Forkheadbox P2
5) Genes of Disheveled family of proteins

HOXA1 gene: Chromosome location: 7p.15-p14.2

The interest in this gene comes from some human pathology as well as from animal models.

This gene is expressed in the embryonic development only briefly. In humans this period is from day 20-24 and is related to the development of the hindbrain. The null mutation of this gene in mice leads to the reduction of neuron numbers in the facial nucleus, abduscens nucleus, superior olive that is an auditory relay nucleus, shortens the brain stem (61). Similar neuroanatomic abnormalities are

Table 2a. Chromosome abnormalities in autism other than those of chromosome 15q11-q13

References (Ref. No)	Chromosome abnormalities	Clinical details
Borg et al (23)	Deletion of 2q35 with loss of 13 genes. The breakpoint at 8q21.2 was in MMP 16 gene	Developmental delay, autism
Sultana et al (24)	Translocation (7;20) (q11.2;p11.2). An autism susceptibility gene (AUTS2) was identified at the breakpoint of 7q.11 translocation	Monozygotic twins Concordant for autism and
Smalley et al (25)	A locus for ADHD was localized at a 12-cM region on chromosome 16p13. It overlaps with another region associated with autism	203 families with ADHD were studied for genetic linkage
Wolff et al (26)	A deletion in subtelomeric region of Chromosome 2q	10 autistic individuals with a deletion at 2q subtelomeric region
Shao et al (27)	Genetic linkage to a marker in chromosome 2 at D2S116	Found among 82 sibpairs with autism in 45 families
Auranen et al (28)	Significant linkage at chromosome 3q25-27 in the vicinity of D3S715 and D3S3037. It is 58 cM distal to a previously described autism susceptibility locus AUTS1	38 Finnish families sharing ancestral alleles; stronger among regional isolates
Badner et al (29)	Susceptibility locus on chromosome 7 with multiple-scan probability analysis on published results	Meta-analysis of previously published data
Alarcon et al (30)	Speech development is linked to Chromosome 7q and the repetitive behavior is localized to an overlapping region linkage analysis	152 families with autism by nonparametric multipoint
Ogilivie et al (31)	By karyotyping no deletions at 22q11	103 autistic children
Wolpert et al (32)	Inverted duplication of 7p11.2-p14.1 The patient was partially trisomic due to this extra DNA segment	25-year-old man with autism. Only 30 patients are known
Buxbaum et al (33)	Linkage found at chromosome 2	95 families with two or more autistic children
Steel et al (34)	46XY, del (13)(14q22)	18 y. old male with autism
IMGSAC (22)	Linkage at D7S477 and another one 27 cM distance both on chromosome 7. They used a 5cM grid in multiplex families Among 153 sibpairs; 125 in UK and 28 in non-UK countries	Strong linkage among sibpairs in UK, weaker linkage among non-UK countries
Tentler et al (35)	Balanced reciprocal translocation t (5;7)(q14;q32) with a breakpoint involving SSBP and T2R. No methylation defect	Autistic families
Nasr et al (36)	Balanced translocation t(4;12)(q21.3;q15)	Monozygotic twins with autism severe MR and affective disorder
Yan et al (37)	Familial translocation 1(1;7)(p22;q21) Breakpoint associated with polymorphic markers D7S630/ D7S492 and V2410/ D7S646	A child with schizophrenia and autism; co-segregating among family members with psychopathologies
Vincent et al (38)	Translocation t(7;13)(q31.3;q21) It interrupted a novel gene RAY1 the gene contains 16 exons with evidence for alternative splicing spanning 220 kb at 7q31.3	An autistic individual
Smith et al (39)	In order to define the extent of Chromosome deletion at 2q37, they used 22 different BAC's identifying microsatellite markers. They found four new polymorphic markers	
Warburton et al (40)	A balanced chromosome rearrangement involving 7q31.3 A breakpoint at 1 cM interval between CFTR and D7S643 showing strong linkage to autism	A family with one speech and one language development disorder
Mc Lean et al (41)	A boy with ring chromosome 22 46XY; r(22) (p11.31-q13.31 to approximately 13q13.33)	2 22 Chromosome abnormalities with autism
Ashley-Koch et al (42)	Paracentric inversion at Chromosome 7 inv (7)(q22-q31.2) Unisomic inheritance Significant linkage D7S2527 and D7S640)	Three sibs with 7q inversion They confirmed the linkage in 76 multiplex families as well
Lauritsen et al (43)	Autism candidate regions Re: 7q21, 10q21.2, 15q11-q13, 16q23, 17p11.2	Danish cytogenetic registry, literature review
Grumbacher et al (44)	HyperIgE with autism. Small deletion at 4q21. Analphoid ring chromosome; DNA piece lost between D4S1569 and 30120	

Ghaziuddin et al (45)	Deletion in distal portion of Chromosome 2 at 2q37	Autism with dysmorphia
Lassig et al (46)	Transmission dysequilibrium test for allele specific PCR for Serotonin receptor. (HTR7). None found	53 trios of autistic children and their families
Carratalla et al (47)	20/22 translocation with interstitial deletion within	A 3- year-old boy with no speech,
Michaelis (47)	thew region 22q11. A 45 XY, -22, +der (20), t) 20;22) (q13.3;q11.2). Deleted region is associated with Di George; not in patient	mild dysmorphia and hypoperfusion of left temporo-parietal cortex
Michaelis et al (48)	Interstitial deletion of 20p11.22-p11.23. A deletion of 5-6 cM proximal to Allagille region. A region related to neural development	Hirschprung and autism
Ishikawa-Brush et al (49)	X; 8 translocation occurring within the GRPR gene and the 3' to the SDC2 gene. Breakpoints are in the first intron of GRPR and 30 kb distal to the Syndecan gene	Autism, MR, epilepsy and multiple exostoses
Vostanis et al (50)	1)Interstitial deletion of Chromosome 17 (p11.2-p11.2) 2) Unbalanced translocation of Chromosome 5 resulting in monosomy for part of the short arm (5pter→5p13)	1) 14 year old boy autistic 2) 19 year old autistic man

Table 2b. Abnormalities of chromosome 15q11-q13 in autism

References (Ref. No)	Chromosome abnormalities	Clinical details
Slopien et al (21)	No abnormalities in 15q11-q13 were found in 20 families	20 probands 4-27 years old
Chibuk et al (51)	NDNL (MAGE-3) gene in susceptibility locus. Not imprinted and pathogenic	
Menold et al (52)	Three GABA-receptor subunit genes. Pedigree Dysequilibrium test shows significant association of SNP's within GABBRG-3 gene	Linkage dysequilibrium test in 226 families with autism
Bass et al (53)	Linkage to 15q11-q13 with increased recombination. GABA-A receptor gene is the candidate	63 multiplex families with autism
Smith et al (54)	One chromosome 15 had only part of PML genes. The single PTPN9-SLP1 gene is expressed only in brain and codes for non-receptor protein tyrosine phosphatase	Autism, mild dysmorphia and developmental delay
Wolpert et al (55)	Three different patients with isodicentric chromosome 15. The Karyotype 47XX +idic (15)(q11.2) ; 47XX +idic (15q(q11.2) and 47XY + idic (15q)(q11.2) in three patients stereotypic behavior	Three unrelated probands with autism with delayed motor, speech, social reciprocity and
Salmon et al (56)	Linkage studies with eight microsatellite markers. They found no linkage to the GABRB3 gene	139 multiplex autism families
Maddox et al (57)	They studied the evidence for 15q11-q13 involvement in autism. They found linkage with markers D15S156, D15S219 and D15S217. They studied with PAC and BAC clones the 1.2-Mb region of the GABA Receptor gene cluster. Methylation is involved	
Schroer et al (58)	In South Carolina the single most common factor associated with autism was Chromosome 15 abnormalities. Candidate genes included Ubiquitin-protein ligase (UBE3A, the gene of Angelman syndrome) and three genes of GABAreceptor units. All were unisomic inheritance from the mother	100 families with autism

a part of Moebius syndrome. The rate of autism in Moebius syndrome is about 25% as compared 1/ 1,000 in general population (62). In Sweden thalidomide was used before the awareness of its teratogenic effects. The offspring exhibited the same neuroanatomic dysfunction aforementioned; the frequency of autism in those offspring was approximately 30% (63). In some thalidomide children Duane syndrome was found. In this syndrome the innervation of the lateral rectus is by the oculomotor nerve rather than abduscens. It occurs when abduscens nerve is weak leaving its target area to invasion by the nearby oculomotor nerve. This raises the possibility that wrong connections might be established after the disruption of formations in early embryo (64). The teratological affects of valproic acid are similar to thalidomide (65). In rat valproic acid reduces the

number of neurons in tegmental nuclei, shortens the brain stem, and reduces the numbers of cells in inferior olive (66). The similar changes were observed in the autopsies of autistic patients (67). The decrease in number and volume of Purkinje cells in cerebellum, which are formed after 24 days decrease secondary to the defective inferior olive, which loops to cerebellum (68). It also leads to aberrant neurological connections in the brain stem (69). The best support for this was increased eye-blink conditioning. In almost all instances of brain damage this conditioning slows. While in autism and valproate given rats it increases. This process is known to be mediated solely by loops between brain stem and cerebellum (70). In South America a medicine used as abortifacient, misoprostol has created an epidemic of Moebius syndrome as well as autism (71). This is a prostaglandin that contracts the uterus producing ischaemia in uterus thus injuring the brain stem at the critical stage of neural tube closure.

Molecular genetic findings

HOXA1 is a transcription factor. A string of histidine residues were identified in a critical region for its function. A variant was found with the substitution of G in A (68). This substitution changed the code of histidine for arginine interrupting this sequence. In some individuals this substitution led to a deletion of three histidine codons. This variant is called G; it is uncommon in the general population. The inheritance of G rather than A in families was significantly different from 50/50. This deviation from the Hardy-Weinberger proportion suggested a role of this mutation in the pathogenesis of autism. This deviation was not observed in families with other polygenic diseases. (68). It is a rare allele. The homozygous G/G in a child resulted in a severe case of autism. The trait appears to be maternally transmitted (69). This in turn suggests a role in methylation of the gene.

Conclusion

Teratological events around day 20-24 neural tube closure such as valproic acid, thalidomide, misoprostol, or congenital conditions that affect the same way like Moebius syndrome, Duane syndrome lead to abnormal development of the brain stem which have the later consequences in cerebellar development through loop-connections. This appears to be one of the several genetic events that create susceptibility to autism.

Reelin gene: *Chromosome location:* 7q22

This gene spans 450 kB with 63 exons. It is a pivotal signaling protein that plays a role in the migration of several neuronal cell types. The evidence for the participation of this gene as a susceptibility locus in autism comes from several observations (72): 1) In Reelin knock-out mice the topography of the brain overlaps with the cytoarchitectonic changes described in the brains of autism. 2) The Reelin protein becomes detectable at extracellular level around fifth week of gestation, which coincides with the window of maximal vulnerability, 3) the Reelin locus maps within the portion of chromosome 7q and most tightly linked to autism.

Persico and Keller (72) found a significant linkage between a polymorphic GGC repeat located at the 5' untranslated region of the Reelin gene, immediately upstream of the AUG translation start codon. Approximately 90% of the Caucasian population have 5 to 10 repeats. Long (>11 GGC repeats) appear to be transmitted to the autistic offspring but not to the unaffected one (73). The latter authors hypothesized that owing to the formation of stable hairpin structures in this region, the translation of the mRNA must be considerably slower. They have confirmed this hypothesis in detecting rate differences in a luciferase reporting gene attached; the longer the GGC repeats, the slower the rate of synthesis was (72). Reelin has serine protease activity, which is preferentially inhibited by organophosphates, by commonly used insecticides and pesticides. Thus a decreased reelin might create a susceptibility to autism later in life due to the exposure to these compounds.

When reelin +/- mice are studied, only male mice displayed a decreased number of Purkinje cells, a characteristic of autistic cerebella (74) which goes hand in hand with the male susceptibility to autism. In families of autistic children the E2 apolipoprotein allele is preferentially transmitted to offspring as evidenced by the Hardy-Weinberg equilibrium. The reduced binding to VLDL/apoliprotein ER2 receptors by functionally defective factors such as reelin, or WNT2 gene product (75) may lead to enhanced risks of infertility and miscarriages in families with autism common to those families (76).

Conclusion

Evidence suggests that a slowed rate of synthesis of reelin protein create a susceptibility to autism in the offspring.

Autism and Environment

Genes don't operate in a vacuum. We are becoming more and more aware that the environment shapes how, when and how efficiently a gene functions later in life. Unless we are more knowledgeable for the role of genes participating and the environmental influences, there can be no rationalistic pharmacologic intervention in autism.

It is likely that epigenetic factors play a significant role in autistic children. Indirect evidence for this hypothesis exists both for abnormalities in chromosome 15q11-q13 as well as Rett syndrome. Clearly, at least in these two syndromes, methylation, acylation / deacylation results in loss of suppression / suppression of transcription factors which in turn lead to the emergence of the disease. Such methylation and acylation processes are epigenetic events. They will take place during gametogenesis / meiosis. The environmental factors exert significant affect on methylation of genes in other disorders such as acute lymphocytic leukemia. A detailed study of these co-morbidity genes will contribute to our understanding of the emergence of autism in childhood and might even provide rationalistic interventions. Certainly these studies should provide a solid basis, a stimulus to detail the role of environmental factors in autism. Therefore they are of utmost importance.

Genomic imprinting is an epigenetically controlled form of gene regulation leading to the preferential expression of one parental gene copy. A good example of this is the autism susceptibility locus at 15q11-q13 area. This area contains other genetically imprinted sites such as those related to Prader-Willi and Angelman syndromes. At the end of 2001, approximately 40 imprinted genes had been reported that were exclusively or predominantly expressed from either paternal or maternal allele. The population of imprinted genes is estimated to be 0.3%. This form of control is exerted by the addition of a methyl group to CpG nucleotides that occur as an island in the promoter region, mostly in house keeping genes.

Finally a special case for the pivotal role of methylation is Rett syndrome.

Patients with Rett syndrome: *Chromosome locus:* Xq28- Methyl-CpG-binding protein

This is a variant of autism observed only in girls; boys usually don't survive the pregnancy except in some rare instances (77). It is characterized by a set of systemic phenotypic features in addition to autism. It is due to a mutation of the methyl-CpG-binding protein (MECP2). The interest in this syndrome is the recent demonstration of Carney in his study of 69 autistic girls. He found two patients who had a mutated MECP2 gene but no systemic findings of the disease (20).

All identified mutations of MECP2 gene are de novo with no premutations such as expansion of trinucleotide repeats (78). Amir et al (79) suggested that partial loss of function of MECP2 would decrease transcriptional repression in some genes. The epigenetic events as related to MECP2 gene are of pivotal importance for understanding various phenotypes of Rett syndrome.

The importance of the regulation of the epigenetic events related to MECP2 in Rett syndrome is of utmost importance. Nan et al (80) showed that MECP2 repressed transcription in vitro from methylated promoters but did not repress non-methylated promoters. The action of this gene on specific transcription factors remains to be elucidated. Transcriptional repression in vivo is relieved by the deacetylase inhibitor trichostatin A. This indicates that deacylation of histones (and/or other proteins) is an essential component of this repression mechanism. The data suggested that, two global mechanisms of gene regulation, DNA methylation and histone deacylation can be linked to MECP2.

The phenotype of mutations in MECP2 may vary greatly (81). Such are the presence of male patients like a 46 XX, male with Rett syndrome, and somatic mosaicism in boys with Rett features, etc. Other examples are preserved speech variant (PSV) (82) and poor prognosis in early-truncating mutations while emergence of classical Rett in missense mutations or late-truncating mutations (81).

Conclusion

Some, maybe the majority, of the molecular genetic mechanisms related to epigenetic phenomena in autism may be related to methylation of the CpG islands at the promoter sites of the genes.

What are the Environmental Causes Implicated in Autism?

As mentioned before the incidence of autism in the world is increasing logarithmically. Most investigators agree that numerous genes are involved acting in concert, predispose or confer fragility toward the appearance of autistic clinical picture. The paradigm is akin to celiac disease. The genetic susceptibility may exist but unless the patient consumes gluten no discernible symptoms will emerge.

Hypotheses may be derived if we consider what factors have changed in our lives in the past 20 years (2).

1) Infectious diseases: the whole pattern of infectious diseases as well as many new vaccines in the form of dead forms of the infectious agents are introduced in ever-greater quantities and at earlier stages of life. Most of them are combined into multi-component mixtures. Either the preservatives used such as thiomersal or the structure of the vaccines with potential to alter immune function in a dramatic way, might also trigger the emergence of autism.

2) Pesticides: Unless one specifically seeks out "Organic foods" and water, every drop of water we drink or every particle of food we consume will have some pesticide residue as organophosphates, or fungicide or herbicide. It is noteworthy that in New

York, they found organophosphate residues in the meconium of newborn. More Rett syndrome was observed among the fathers of Rett patients who worked in organophosphate industry.

3) Dietary changes: Nowadays the common diet is based on eating more wheat-based foods and milk only from Friesian/Holstein cattle. Additives are used to enhance the flavor or to prevent food from microbial contamination. We might not genetically equipped in terms of enzymes to cope the food we now eat. The increased rate of autism seen among Japanese and Scandinavian who immigrate to USA might be du to this change of diet.

4) Dysbiosis: The food we eat now and the antibiotics we use profusely might have changed our intestinal flora. It should increase the anaerobes as clostridia or yeast in the gut. . This new group of organisms might produce unusual and toxic tryptophan metabolites such as indole-acrylic acid, or might produce potent opioids as dermorphins and deltorphins.

5) Plasticizers: Nowadays everything is stored and sold in plastics. The manufacture of plastic involves toxic catalyzers. There is no study how much contamination of fluid and food occurs by these chemicals. In fact we all know by experience that the flavor of some drinks acquire a different flavor from plastic containers.

6) Drugs and medicine residues: The drugs we use are persistent in the environment. Themselves or their metabolites passed out in the urine will eventually appear in the water supplies. Drugs such as beta-blockers or hormones used in the contraceptive pills are very potent in low doses.

7) Toxic chemical pollutants: Residue from burning the fossilized fuel, pollutants from incinerators such as chlorobenzenes and dioxins are very toxic substance. They persist in the environment and are potentially very harmful.

8) Heavy metals: Although heavy metals as lead, cobalt and mercury in the environment have been eliminated, the quantity of mercury in vaccines has increased dramatically (Thiomersal). This might be responsible in some cases the autism observed inn relation to measles-mumps vaccination.

Each one of these issues must be subjected to careful research in their relationship to autism.

Intervention in Autism

Like other behavior disorders there is no medical cure but requires behavioral intervention. More recently Chez et al (83) found beneficial effect of donepezil hydrochloride which is an acetylcholynesterase inhibitor. They attributed this effect to increase of the diminished acetylcholine receptor activity in autistic brain. In addition to this drug, other medications might find usage in future.

Efforts of intervention were first tried in 1980's. Now nobody doubts that this is an effective way of management. The evidence for it is the presence of lots of autistic kids in their late teens or early adulthood who live independently and who hold jobs. The Internet sites are full of parental stories attesting to the efficacy of intervention.

It also became apparent that behavioral intervention must be performed early, never more than 5-years-of-age. Careful studies in the West, clearly indicate that those children who had intervention before 5 fared much better than those who were intervened later than 5 years. It must be started before maladaptive patterns of behavior and communication are firmly engraved in the child's brain. The best results are obtained if the intervention is performed before 2-years-of-age. The behavioral management is a life-long process. The parental stories in the Internet also indicate that different manifestations, minor neurological symptoms keep appearing later during life. Obviously, mal-connections in the brain are all pervasive and needs behavioral attention at all stages of life of an autistic kid.

The intervention must be comprehensive not only having psychologists, therapists, teachers, but also will be closely helped in its functions by the medical staff. This is a must since autism is a brain disorder with neurological and psychological abnormalities. Intervention will help them to straighten the wrong information processing. This resembles to a wrong electric wiring in a house; when the sitting room light switch is pressed the bedroom lights go on. The circuitry must be corrected, so does the maladaptive pattern.

Principles of Early Intervention

Autism is a syndrome of behavioral deficits and excesses that have a neurological basis yet are amenable to change in response to multifaceted structured quality intervention. Additionally, children with autism look normal, however, exhibit distinctive behavior patterns that make them more dependent on others and challenge their caregivers. In fact, the autism is a complex topic that debates professionals, creates many misconceptions and diverse treatments.

By offering timely and intensive intervention, many children can overcome a wide range of developmental problems (84,85). The proper intervention requires parental education and support (86). Thus, parental education and involvement is a key aspect for successful early intervention (84,86). Those children within autism spectrum are no exception, and some assessment programs are far less effective at the age of 2-and 4 years. Interestingly, there is a wealth of research to

support the notion that autistic children experience more gains when treatment is provided to them at an early age. Some research indicates that the early years are crucial for the developing language and social behavior in autistic children. Whereas, early diagnosis and interventions are also essential to ensure that families and caregivers to have access to appropriate services and professional support (87).

Research suggests that quality intervention is more likely bring positive effect on the well being of such children. their families, and community as well. Autism is a syndrome of behavioral deficits and excesses that have a neurological basis, yet are amenable to change in response to specific constructive interactions with their environment. These children are hard to manage, tend to depend on others, thus, challenge caregivers. Therefore, any types of support to such population is a must regardless of age, severity of the disabilities, and/or culture (88).

Summary

Autism is a polygenic disorder and encompasses a wide variety of disorders under its umbrella. It is a behavior disorder caused by faulty connections in CNS. It appears that its incidence is increasing dramatically thereby creating a major health care problem for almost all societies. There is no medical treatment available at present but behavioral treatments are effective in high functioning cases before the wrong behaviors are engrained. Recent advances in genetic techniques have created important leads to the genes that are involved but no clear-cut conclusions yet. It is safe to conclude that significant findings will soon emerge from such genetic research in near future.

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