Abstract

The causes of pervasive developmental disorders have yet to be resolved. Needless to say, the etiology is complex as are the individual factors, especially in regard to autism. Certain findings may be integrated into early coherent models, but the heterogeneity of findings remains a central feature of autism. The present review examines contemporary areas of research and a few prominent theories specifically dealing with autism. The areas under scrutiny are divided into common academic compartments, such as biological, environmental. Autism represents a very timely topic due to its rising incidence in the population as well as changes in previous concepts occurring at this time. Besides the neurological, biological and epidemiological factors contributing and possibly initiating this disorder we discuss the possible involvement of endogenous morphine, especially in regard to depression and limbic functions. Lastly, we advance the theory that dysfunctional mitochondria appear to be involved in autism as well, explaining the widespread occurrence of its characteristics within the construct of susceptibility to stress and trauma. Thus, the diffuse manifestations of Pervasive Developmental Disorder occur potentially by altering energy processes.

Keywords: Autism; Pervasive developmental disorders; Causes

Abbreviations: PDD: Pervasive Developmental Disorders; ASD: Autism Spectrum Disorders; PDD NOS: Pervasive Disorder Not Otherwise Specified; CDD: Childhood Disintegrative Disorder; FRAXA: Fragile X Syndrome; MRI: Magnetic Resonance Imaging; SPECT: Single-Photon Emission Computed Tomography; EEG: Electroencephalography

Introduction

Pervasive developmental disorders (PDD), or autism spectrum disorders (ASD) currently have a high rate of occurrence worldwide, however, the causes of PDD are still under investigation. The umbrella term pervasive developmental disorder was first used in the 1980s, describing a class of disorders with the following characteristics: impairments in social interaction, imaginative activity, verbal and nonverbal communication skills and a limited number of interests and activities that tend to be repetitive [1]. Interestingly, these characteristics are found in respective normal behaviors of people, however, in autism they are exaggerated or diminished in their expression levels. This latter point has caused some investigators to regard autism as a mere manifestation in personality behavioral diversity, without using the term disorder [2]. However, it is our belief that this is a disorder since individuals afflicted with it can not-function, lacking the ability to communicate and therefore, requiring medical and social services intervention. Pervasive developmental disorders are, according to the DSM-IV, categorized into 5 subtypes: autistic disorder, pervasive disorder not otherwise specified (PDD NOS, also called atypical autism), Rett's disorder, childhood disintegrative disorder (CDD) and Asperger's disorder. ICD-10 defines 8 subtypes of PDD: childhood autism; atypical autism; Rett's syndrome; other childhood disintegrative disorders; overactive disorder associated with mental retardation and stereotyped movements; Asperger syndrome; other pervasive developmental disorders and other pervasive disorders. DSM-V includes autism as it expresses itself in neurodevelopmental disorders and centralized autistic disorder, Asperger's disorder, and pervasive developmental disorder into autism spectrum disorder. The ratings of the symptoms of these disorders as a single continuum of mild to severe impairments in the two domains of social communication and restrictive repetitive behaviors/interests rather than being distinct disorders appears to be appropriate given their presence in normal time behaviors [3]. Additionally, confounding accurate diagnosis to evaluate individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder may be more appropriate in the social (pragmatic) communication disorder category. Current estimates of PDD prevalence are around 20 in 10,000 and the prevalence for PDD NOS is around 30 in 10,000 [4]. Thus, PDD (for various reasons and from a wide range of perspectives) has become one of the most frequent neurodevelopmental disorders in childhood. However, as indicated above, that data supports the hypothesis that this disorder is one of degree of negative behavioral expression of normal behaviors. Thus, given the central nervous systems (CNS) functional architecture, expression of the components of this affliction may be alone or in combination also being complicated by the degree of the various abnormalities “blend” into the final behavioral “output”. Taking this into consideration, other research has aimed at a wide spectrum of specific areas and topics involving autism. Tsai asserts that based on behavioral and biological studies there is sufficient evidence to claim that PDD NOS are caused by a neurological abnormality but no specific causes were identified. According to Trottier the manifestation of autism is caused by a pathophysiologic process, arising from the interaction of an early environmental insult and a genetic predisposition, which was not defined [5]. Volkmar surmised that autism is thought to be one of the most heritable of all psychiatric conditions [6]. The issue today is simply what causes autism, if indeed it is one single event. In this regard, the current theory trend is a major step forward from the sensory and perceptual theories prevailing in the 1960s and 1970s, involving brain...
stem abnormalities [7]. A number of proposed current causes have been described, including medical conditions (e.g., phenylketonuria, fragile X syndrome, and tuberous sclerosis), perinatal impairment, and autoimmune disorders. Genetic origins are currently the focus of intensive research. Clarke postulates autism is one abnormality of behavioral expression, involving the normal spectrum of behaviors, which may be expressed abnormally [8]. The following discussion considers a modest speculation on the origin of autism (Table 1).

| A. Biological etiology |
|------------------------|
| 1. Genetic factors      |
| - fragile X syndrome   |
| - tuberous sclerosis   |
| - phenylketonuria      |
| 2. Chromosomal abnormalities |
| - chromosome 15        |
| 3. Genetic susceptibility running in families |
| 4. Non-genetic conditions |
| - infectious diseases  |
| 5. Dysfunctional Mitochondria |
| (Stefano and Kream 2015a,b) |

| B. Neurobiological factors |
|---------------------------|
| 1. Brain dysfunctions     |
| - reduced connectivity   |
| 2. Altered pattern of evoked response potentials |
| 3. Structural abnormalities in various regions of the brain |
| 4. Changes in temporal lobe |
| - temporal lobe damage   |
| - temporal lobe epilepsy |
| 5. Cerebellum and limbic structures |
| - alterations in neuronal size |
| - alterations in density |
| 6. Neocerebellum         |
| - reduction in granule and Purkinje cell density |
| 7. Changes in limbic system (amygdala, hippocampus) |
| - reduced density |
| - reduced cell size     |
| 8. Neurological abnormalities |
| 9. Neuroimaging          |
| - PET: deficiencies in coordinated interaction between the cortical and subcortical systems |
| - SPECT: hypoperfusion in the temporal region and the frontal lobe |
| - MRI: megalencephaly in males |

| C. Neurochemical factors |
|-------------------------|
| 1. Dysfunction of cerebellar-cortical serotonergic pathways |
| 2. Overactive brain opioid systems |
| 3. Changes in oxytocin neurotransmission |
| 4. Dysfunction of cerebellar-cortical serotonergic pathways |
| 5. Hyperserotonemia      |

| D. Pre- and perinatal conditions |
|----------------------------------|
| Hospitalization during the neonatal period |
| - thalidomide embryopathy |
| Maternal ingestion of anticonvulsants |
| Intrauterine effects |
| - high testosterone levels |
| - high androgen levels |
| Pregnancy complications |
| - severe infections |
| - second-trimester bleeding |
| Birth complications |
| - prolonged time of gestation |
| - neonatal cyanosis |
Biological Factors

Until the 1960s, autism was assumed to be of psychogenic origin but the high incidence of mental deficiency as well as epileptic seizures led investigators to incorporate biological factors into its definition. A review by Rutter et al. concluded that most cases of autism are not secondary to or associated with specific medical disorders [9]. By contrast, Freitag has suggested that non-genetic medical conditions are minor risk factors for autism but they may be its most relevant cause [10]. In other words, they represent phenocopies of the disorder. At the time, this seemed very appealing, however, the depth of the associated diagnostic characteristics and their expression levels may warrant other considerations, e.g., cellular internal dynamics manifesting themselves abnormally regionally. One of the first postulates for considering genetic factors as a cause or contributing component of autism was the twin study by Folstein and Rutter, which described a highly increased concordance rate for autism in monozygotic twins (4%) but not for dizygotic twins (0%) [11]. In 1989, Steffenburg et al. found even higher concordance rates for monozygotic twins (60%) in contrast to dizygotic twins (3%) [12]. Twin studies on autism resulted in heritability estimates of >90% for the phenotype of autism [10]. Interestingly, autism also can be associated with other medical disorders in 24.4% of the cases presented in those studies [13]. Genetic conditions such as fragile X syndrome, tuberous sclerosis, phenylketonuria can have a autistic comorbidity as with non-genetic conditions such as infectious diseases [14,15]. The frequency of these disorders in the population with autism is much greater than could be expected by chance, and importantly none are solely associated with autism. Thus, the heterogeneity of the autistic spectrum of disorders is widespread without an apparent connection. There are also a few findings about infectious diseases in relation to PDD, such as congenital rubella, acute encephalopathy, and cytomegalovirus [15]. Additionally, tuberous sclerosis and fragile X syndrome (FRAXA) are the most prevalent single-gene disorders in autism spectrum disorders. Gutierrez et al. described tuberous sclerosis in approximately 40% of autistic persons, mostly in those with moderate to severe mental retardation and/or a seizure disorder [16]. Epidemiological studies [17,18] demonstrate that the prevalence of tuberous sclerosis in children with autism is more than 100 times greater than expected. A number of authors [19,20] have reported that about 2%-5% of autistic children and adolescents carry a full FRAXA mutation or FRAXA mosaics. According to other genetic studies, there is an association between autism markers and brain development, such as 3 markers of the c-Harvey-ros oncogene and the homeobox gene EN2. The most common chromosomal abnormalities include duplication of chromosomal material, especially chromosome 15 or the sex chromosomes. Reports of single-case chromosomal abnormalities are questionable, except for the numerous reports of deletions and duplications of chromosome 15, especially in the 15q11-13 region [21]. The 15q region from the maternally-derived chromosome is supposed to be the most commonly affected in autistic individuals [22,23]. The genetic epidemiology is complicated by variable expressivity and heterogeneity as noted earlier. Thus, it has been difficult to establish not only the origin of autism but also its mode of transmission. The data do not support a single gene model for autism, implying greater gene numbers are involved [24]. This can also be surmised because a significant number of parents of autistic children exhibit impaired executive functions, such as inadequate planning skills and lack of the flexibility of attention, increasing the target gene pool. Studies describe clusters of personality characteristics, language abnormalities, and psychiatric disorders in families with autism [25]. These clusters of symptoms also may serve as a manifestation of an underlying genetic susceptibility to autism and/or improper cellular communication processes in the brain.

Pre- and perinatal Factors

Studies of prenatal and perinatal complications did not show any constant association with autism [26], although in some cases positive associations were found. Guillen emphasizes the high number of perinatal complications and a high proportion of hospitalizations during the neonatal period in children with autism spectrum diseases [27]. In Japan, the prevalence of autistic disorders has been reported to be 3 times higher in children hospitalized in neonatal care units than in the general population [28]. In some cases, autism is associated with insults early in gestation, including thalidomide embryopathy in 4% to 5% of cases, probably due to damage to the CNS in the early stages.
of gestation [29]. Autism occasionally occurs as a result of maternal ingestion of anticonvulsants [30]. Certainly, these reported studies imply strongly a neurochemical component in autism origination that appears to transcend abnormalities in normal behavior expression by an individual. Intrauterine effects may result from genetic conditions of the mother, endangering the development of the fetus. According to consistent findings, the affected children as adults have a higher rate of pregnancy and birth complications than their siblings or controls [31] and several studies found significantly increased rates of obstetrical complications in pregnancies [32-34]. The many similar and diverse abnormalities comprised in pre-, peri-, and postnatal complications: prolonged time of gestation, neonatal cyanosis, umbilical strangulation, and severe neonatal icterus shall require a compelling theory for such a negatively dynamic disorder. Juul-Dam et al. found a significantly higher incidence of uterine bleeding in mothers of autistic children, and in the PDD NOS group a higher incidence of hyperbilirubinemia, but again no unifying feature could be established [35]. Cederlund and Gillberg recorded abundant pregnancy complications in 31% of the patients (including severe infections, second-trimester bleeding, and pre-eclampsia) as well as perinatal complications in 60% of the patients, but severe perinatal complications were rare [36]. The findings of a Swedish study suggested that the pathogenesis of autism may be based on intrauterine and neonatal factors related to deviant intrauterine growth or fetal distress [37]. These results support previous findings by other investigators [38,39]. Perinatal stress may cause significant brain damage and therefore probably be involved in initiating autism. It is noteworthy to mention that the research findings stress that birth complications are relatively non-specific and can be observed in both children with autism and healthy children, indicating the presence of other factors in this autistic emergence or that the abnormalities being examined may arise from other factors than autism. Volkmar argued that if birth complications are an etiologically relevant factor, autism would be expected to occur with increased frequency in populations with an increased risk for birth complications. An increased rate of birth complications is also found in children with cerebral palsy, severe mental retardation [40-42], chromosomal aberrations, and genetic disorders [43,44]. Thus, we propose that this interpretation is simplistic since comorbidities represent a fraction of any disorder, suggesting that shared commonalities exist and can be complicated in their pattern of expression. Voracek also has reported on the importance of exposure of the fetus to high androgen levels in the context of developing autism [45]. High androgen levels occur in women who are chronically stressed [46], chronically fatigued [47] chronically depressed [48] or exposed to fear-relevant stimuli during pregnancy [49]. Cohen-Bendahan et al. have hypothesized the key increase of high testosterone levels affecting the fetus arise from the fetus (not the mother) [50]. This hypothesis is the subject of ongoing work [51]. Antibodies against myelin basic protein are often found in children with autism. Those children also have increased eosinophil and basophil response to IgE-mediated reactions, suggesting neuro-immune involvement. In autistic children there are abnormally elevated alpha interferon levels in the plasma, which possibly influence cell growth, activation, and proliferation [52] further supporting a neuro-immune pro-inflammatory state existed [53].

Neurobiological Factors

The neurobiological involvement in autism encompasses data from the fields of neurophysiology, neurochemistry, neuroimaging and morphological research. A population-based study found 85% to 90% of autistic subjects show some indication of underlying brain dysfunction [54]. The pattern of evoked response potentials and conduction time is altered in autistic children and structural abnormalities have been found in various regions of the brain. A number of autistic behaviors have been reported in individuals with temporal lobe damage [55,56] both temporal lobe epilepsy and temporal lobe enlargement are frequent [57]. Compounding these abnormal characteristics are those showing reduced connectivity in the autistic brain [58]. Volkmar proposed this condition is brought about by generalized hypoactivation of a social processing brain network, indicating a pervasive lack of social interest, engagement, motivation, or reactivity [59,60]. A number of authors, including [61,62] emphasize the role of limbic system circuitry, particularly the amygdala and hippocampus, in causal models of autism. Postmortem studies repeatedly have described various abnormalities in these areas: such as; reduced density, cell size, and dendritic arborization in the amygdala, hippocampus, anterior cingulate, and mammillary bodies [63,64]. New to the consideration of autism etiology is the occurrence of endogenous morphine in these brain areas and its associated coupling to constitutive nitric oxide synthase stimulated nitric oxide release, which alters the physiological state of neurons and microglia [65,66]. Indeed, inappropriately stimulated macrophages and/or microglia can induced dysphoria [68,69] similar to psychiatric abnormalities noted in autism. Approximately 75% of autistic subjects show abnormalities on neurological examination [70]. About half of autistic patients have abnormal electroencephalogram results. Thus, autism may arise from abnormal CNS functioning. This hypothesis is based on the high incidence of epileptic seizures in autistic individuals. Tanguay reported that autistic persons show more EEG abnormalities than non-autistic controls, but the findings are varied and nonspecific as well as open to reinterpretation [71]. Singh et al. states that 58% of autistic individuals, compared with only 9% of controls, have antibodies reactive to myelin basic protein (anti-MBP) in their serum [72]. Minshew et al. suggested that the neural basis of autism is widespread cortical abnormalities sparing early sensory processes [73]. This hypothesis is based on models aimed at difficulties with complex information processing. A number of neurochemicals, including chemical messengers, have been investigated in respect to autism in the past several decades, but most abnormal findings have not been substantiated. Neurochemical studies have investigated the role of serotonin, epinephrine, and norepinephrine, since levels of these neurotransmitters are altered in autism [74]. Other hypotheses implicate overactive brain opioid systems and changes in oxytocin neurotransmission. Green et al. also have suggested that children with autistic disorder show alterations in the endocrine oxytocin system [75]. A frequently cited finding is the dysfunction of cerebellar-cortical serotonergic pathways [76]. Hyperserotonemia in autism is considered to be heterogenous, with some subjects having increased 5-HT uptake and another group having decreased 5-HT, binding [77].

Studies of dopaminergic and catecholaminergic systems in autism have not yielded consistent results [78]. However, with dopamine serving as the major endogenous morphine precursor a new examination is in order. The evidence from neuroimaging studies indicates that dysfunctions in the cerebellum and possibly the temporal lobe and association cortex occur in autistic subjects. Recent studies found abnormalities in autism CNS at several levels, including the brain stem, cerebellum, limbic system, and association cortex [79]. Postmortem studies of autistic brains have not detected gross pathology, but recent studies have described alterations in neuronal size, density, and dendritic branching in the cerebellum and limbic structures [80] with the most consistent conclusion being the reduction in granule and Purkinje cell density in the neocerebellum [81]. Positron-emission
tomographic studies have shown deficiencies in coordinated interaction between the cortical and subcortical systems that are involved in directed attention capabilities [82] with the consequence of impaired social communication skills. Cederlund and Gillberg reported that the most common SPECT finding was hypo-perfusion in the temporal region and the frontal lobe. A recent MRI study concluded that autistic subjects exhibit a specific sex-dependent pattern of cortical lobe enlargement-megalencephaly (an abnormally large brain)-accounting for increased brain size in autistic males.

With respect to macrocephaly (an abnormally large head, with megalencephaly being one of the potential causes) Lainhart et al. based on retrospective data, found that macrocephaly was not present at birth, but developed in early and middle childhood [83]. The cause of the increase in size has not yet been explained. Longitudinal MRI studies of the phenomena are needed. On the other hand, Deb and Thompson have stated that MRI studies have not confirmed brain abnormalities in autism and Tanguay suggests neural imaging results should be viewed with skepticism [84]. Then again, the absence of results using this technology may suggest the abnormal occurrences may be at the chemical communication level, including altering neuro-immune respective cellular behavior.

Environmental Factors

Gardener et al. has suggested that human migration is a risk factor for autism and this theory has been confirmed by others [85-88]. It has been theorized conditions in the countries of origin and the attempts to cope with Western society are stressful. We surmise this type of perceived stress creates a local neural environment manifesting itself as a proinflammatory state in susceptible individuals that if not alleviated becomes chronic potentially leading to autistic development depending on the functions affected. Indeed migration may just serve as a marker for this stressful event, in that other stressor may originate the process [89]. Dealberto also emphasizes the additional risk of autism to offspring of veiled women. Similarly, Zhang et al. have described a "maternal unhappy emotional state" as a risk factor for autism [90]. James has suggested that the association between maternal migration, the accompanying stress, and autism is mediated by high maternal adrenal androgen concentrations [91]. Furthermore, race is reported to be independently associated with a high risk for autism and pregnant black women have reportedly higher testosterone levels [92]. James has suggested that the higher risk for autism in the offspring of black women is the higher androgen level.

In yet another stressor, Gardener et al. has suggested that birth order is another risk factor for autism and that firstborns are at greater risk than children born later. The reason is supposed to be a stronger influence of maternal testosterone in the first trimester [93]. This can also be interpreted as stress being transmitted unintentionally to the baby by the mother reflecting nervousness concerning inexperience in mothering. Jaspers et al. identified early childhood aspects predictive of ASD: male gender, low level of education of the mother, low birth weight, social behavioral problems, language, psychomotor and eating problems in toddlers [94]. These results might serve as additional stress cues. Lucarelli et al. found that in autistic children, antibody reactivity to certain common foods is higher than in healthy subjects, again imposing stress on a susceptible individual [95]. Elimination of those foods from the diet substantially improved the behavioral symptoms. Mazurek et al. suggest that gastrointestinal problems are interrelated with and possibly have common underlying mechanisms with anxiety and sensory over-responsivity in ASD children [96]. Others have recently supported this hypothesis as well [97-99]. In a mechanistic approach these recent works support the 1994 study by Stefano and colleagues, who suggested inappropriately activated immune cells could and do wander into the brain releasing common chemical messengers and that in so doing stimulates abnormal behavioral outcomes, e.g., autism-like.

In order to be thorough it should be mentioned that the mumps-measles-rubella vaccine had been considered as a possible cause of autistic disorders but epidemiological and case-control studies deny any increased risk caused by vaccination [100-102]. Therefore, this kind of vaccination cannot be considered as a risk factor for the development of autism. Season of birth has been linked to autism as well, citing factors such as the effects of weather, differences in nutrition, and season-specific medical problems during pregnancy [103]. On the contrary, Tanguay stated that no consistent seasonal trends emerged; children with autistic-like conditions were most often born in May and November but seasonal influences on the development of autism are weak and not consistent. In all probability seasonality does impose stress, again autism may emerge in individuals prone to developing this disorder because, in part, they are stress susceptible, as noted earlier. Higher maternal age used to be considered as a possible risk factor but recent studies have not found consistent evidence of this [104]. Coleman stated that the possibility of postnatal toxicities has been added to the list of environmental concerns in autism [105]. Clarke opens up very interesting discussion about the real influence of mercury pollution that may be directly connected to IQ increase/decrease but also autism symptoms. In our interpretation this again represents a stressor impacting a susceptible individual, targeting areas associated with autism behavioral characteristics.

Co-morbidity Indicative Factors

Volkmar described heterogeneity both etiological and genetic (the etiological heterogeneity being the involvement of both genetic and environmental etiologies, and the genetic heterogeneity being the involvement of either several different mutations at a single genetic locus or by several genes at different loci). There is considerable evidence that autism is both etiologically and genetically heterogeneous. In the 1990s, Clarke and Baron-Cohen introduced the "theory of mind". Here, the social dysfunction in autism is the result of impaired processes specifically in conceiving of other people's and one's own mind. Thus, it may be looked at as a personality disorder not a full blown neurological abnormality.

A number of scientists, such as Bolton et al., report a higher incidence of major depression and social phobia in first-degree relatives of autistic persons; 64% percent of the depressed parents had their first episode prior to the birth of the autistic child [106]. Mazefsky et al. refers to broader autism phenotype in family members of individuals with ASD as well as high rates of affective psychiatric disorders [107]. We also speculated that limbic involvement is present, in that presentation of the abnormal behaviors occurs within a dopamine defined disorder, e.g., depression, where endogenous morphine is involved [108-113]. Over expression of the dopaminergic driven behaviors may be do, as noted in these cited reports, to a morphine insufficiency condition, which may be a contributing factor in autism.

Conclusion

Autism currently represents one of the most discussed diagnostic categories in the area of psychopathology. Multifactorial etiology opens the door to new questions not answers. It is one of biggest "biomedical
problems” in psychiatry. Causal contributions to the manifestation of pervasive developmental disorders may be classified into six categories: biological etiology, neurobiological factors, neurochemical factors, pre- and perinatal conditions, environmental and comorbidity factors. Accordingly, the underlying etiological mechanisms responsible for the manifestation of complex autistic behaviors are by nature multifactorial and include disproportionately unknown genetic, developmental, and environmental components [114,115]. Preferential evidence favoring genetically driven etiological factors is compelling, is inherently complex, but perhaps underestimates the contribution of environmental determinants [116,117]. Along these lines of evidence, neuroimaging studies have indicated the involvement of broad and developmentally interrelated neural systems, contradicting the notion of single core deficits. We surmise this indeed is the case. We further presume that the future aim of research defining and specifying causes of pervasive developmental disorders is to gradually narrow the scope of research to those key areas of discovery based on prevailing concepts and their commonalities. However, given the complexity of autism, we may indeed be faced with an abnormality that manifests itself from varying altered structures and brain areas. The tendency to “lump” all into a single event may be fatally flawed for autism [118-128].

Recently, another theory has emerged, which is quite compelling in its ability to explain the multitude of widespread characteristics that exist in defining autism as well as other psychiatric disorders. This involves the mitochondrion an important eukaryotic cellular organelle involved with generating ATP, powering the cells many reactions, normally without abrupt interruptions. It is surmised that mitochondrial dysfunction when it occurs targets the CNS because of its level of oxygen utilization. In so doing stress, trauma, any negative stimulus or stimuli would damage neurons initiating neural and neuro-immune disorders, e.g., autism. Indeed if genetic susceptibilities are present the target becomes more specific as opposed to a more diffuse manifestation of abnormality. Given the universal presence of mitochondria in CNS cells this theory provides for a credible explanation for the complications and characteristics that emerge in autism.

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