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Autism as a sequence: from heterochronic germinal cell divisions to abnormalities of cell migration and cortical dysplasias

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Abstract

The considerable heterogeneity in the number and severity of symptoms observed in autism spectrum disorders (ASD) has been regarded as an obstacle to any future research. Some authors believe that clinical heterogeneity results from the complex interplay of the many genetic and environmental factors that themselves define a condition as multifactorial. However, it is important to note that neuropathological findings in both idiopathic and syndromic autism suggests a single pathophysiological mechanism acting during brain development: the heterochronic division of germinal cells and subsequent migrational abnormalities of daughter cells to their target fields. Multiple exogenous (e.g., viruses, drugs) and endogenous (e.g., genetic mutations) factors are known to disrupt the division of germinal cells and provide for an autism phenotype. The variety of endogenous and exogenous factors, their timing of action during brain development, and the genetic susceptibility of affected individuals (a Triple Hit hypothesis) may all account for the clinical heterogeneity of ASD.

Keywords

autism spectrum disorders; germinal cells; heterotopias; migrational abnormality; brain development

INTRODUCTION

It was Leo Kanner's intent when describing a case series of autistic individuals to suggest the presence of a medical disorder based on the association of several signs and symptoms (1). Kanner's view was supported by detailed behavioral observations on a few patients, which to his credit, he attempted to follow-up longitudinally. In the decades following Kanner's insightful article only a few things from his original description merited

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CONFLICT OF INTEREST STATEMENT

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modification. One observation deserving further scrutiny is the marked heterogeneity in clinical presentation among diagnosed individuals. Indeed, Robert Schultz once remarked that autistic children are like snowflakes, no two alike (2). The marked heterogeneity of signs and symptoms among affected individuals seemingly undercuts diagnostic efforts like those of Kanner or, more recently, the Diagnostic and Statistical Manual (3).

It has been said that the concept of autism as a unitary disorder (i.e., one resulting from a common cause) is close to being abandoned (4). Autism is now being called “autisms” and current textbooks invite us to rethink our understanding of the condition from the standpoint of variation and complexity of the available clinical, genetic, and neuroimaging data (5, 6). It is thus unsurprising that Holt and Monaco have proposed that autism should not be considered a set of discrete disorders, but rather, a continuous range of individually rare conditions (7). This point of view argues that the autisms are comprised of conditions that differ among themselves in both degree and kind.

Prompts to validate our conceptual nomenclature from “autism” to “autisms” are based on the putative presence of multiple pathophysiological mechanisms. However, the guiding heuristic in science is to first disprove the explanation with the fewest assumptions. In this case the null hypothesis should be that autism is the result of symptom divergence where one single pathophysiological mechanism stands at the root cause of the condition. In this regard, Margaret Bauman has emphasized that researchers “should be hunting for what is similar, for the unifying characteristic [of autism]” (8). In unison with Bauman, Pelphrey and colleagues believe that most cases of autism can be explained by a single pathological lesion: one that impairs social cognition (9).

The concept of a condition wherein a large number of offending agents are funneled through a singular pathophysiological mechanism is well known in the field of neuropathology. In autism, John K. Darby is credited with having made the earliest and most comprehensive neuropathological review in the medical literature (10). In this pioneering study Darby described a number of conditions (e.g., tuberous sclerosis, cerebral lipoidosis) that provided for an autism phenotype. Many years later Darby elaborated on his initial findings in a letter to the editor of the American Journal of Psychiatry. The letter was entitled, “Autism Syndrome as a Final Common Pathway of Behavioral Expression for Many Organic Disorders” (11). In that letter the authors pose the difficulties, if not impossibility, of isolating neuropathologies based on behaviors. According to Darby, multiple etiologies lead to autistic behaviors but links to causation can’t be retraced backwards. Darby’s idea recapitulates John Hughlings Jackson’s argument that while localization of a lesion may be possible, it is much more difficult to localize a function (12).

Darby’s espoused concept reminds us of a similar and earlier proposal by Leopold Bellak who claimed a “final common pathway” to the nature of schizophrenia (13). In schizophrenia, according to Bellak, a variety of insults are somehow funneled to provide a similar set of manifestations. Bellak’s view has been updated to provide a framework that links risk factors and genes to increased presynaptic dopaminergic function (14). In essence, the modern version of the final common pathway of schizophrenia has been the further

elucidation of the dopaminergic hypothesis. The significance of this concept is derived from the major implications it has had over the years for treatment interventions.

During the last decade the number of presumed risk genes in autism has escalated from a handful to several thousands, comprising about one-sixth of our genome. Behavioral traits in idiopathic autism thus appear to be the result of combined hereditary effects and some undisclosed environmental exigencies. The complex interaction between a large number of presumably deterministic factors often makes it difficult to distinguish associated features from those having causal inferences. Adding to the confusion, the mechanistic role of single genes has been difficult to disambiguate. Functional attributions of defective synaptogenesis or dendritic arborization to abnormalities of individual genes are usually made without the recognition that these mechanisms have been exapted from evolutionary precedents involving cell division and motility. The role of the *CNTNAP2* (contactin associated protein-like 2) risk gene for ASD, as an example, has been traditionally related to synaptogenesis (15). However, temporal lobe resection for epilepsy in patients with a homozygous mutation of *CNTNAP2* shows abnormalities of neuronal migration (16). Similarly, the risk gene *BDNF* (brain-derived neurotrophic factor) has a recognized role in synaptogenesis and synaptic plasticity mechanisms underlying learning (17). However, *BDNF* has a similarly important role in neuronal migration as changes in gene expression are associated to heterotopias and aberrant cortical lamination (18).

It is generally acknowledged that autism is a neurodevelopmental disorder of multifactorial causation where involved genes and environmental factors vary among affected individuals. Multifactorial conditions are, in general, difficult to study because our understanding of them evolves as we gain increasing knowledge of the underlying risk factors. Unfortunately, the identification and understanding of all applicable risk factors is a feat that has rarely been attained for any complex condition. Nevertheless, in the case of autism spectrum disorders, it is the position of this author that multiple agents may funnel their effects through a single pathophysiological mechanism. More importantly, there are critical research findings that presently enable us to define that underlying pathophysiology. Our research suggests that the basic mechanism accounting for both syndromic and idiopathic autism is the same, namely that heterochronic germinal cell divisions during brain development causes migrational abnormalities of neuroblasts to the cerebral cortex and brainstem/cerebellum. Differences in the nature and severity of the inciting exogenous factor, timing of action during brain development, and the genetic susceptibility of the individual provide for the clinical heterogeneity observed in ASD (a Triple Hit hypothesis) (19).

AUTISM AS A SEQUENCE RATHER THAN A SYNDROME

Although often used interchangeably the terms “syndrome” and “sequence” have different meanings. In a syndrome the required commonality of signs and symptoms are usually related to a factor that gives rise to multiple but otherwise independent anomalies. An example of a syndrome is the genetic condition caused by a trisomy of chromosome 21. This condition, Down syndrome, provides a recognizable phenotype even when all characteristic anomalies are not present in a given individual. Down syndrome has a single genetic cause,

even when the additional genetic material can be acquired in different ways. A significant number of syndromes have multiple causes.

Usually, when clinicians do not know a lot about a condition, there is a tendency to label them as syndromes. It is only when they realize that the term needs broadening that the alternative descriptive name of sequence comes into consideration. In a sequence, the different features of a condition are all connected to a factor (genetic or not) that sets up a cascade of obligated events leading to a variety of signs and symptoms. This means that in a sequence (contrary to a syndrome) manifested anomalies are all serially related to some type of developmental abnormality (Figure 1). An example of a concatenated medical problem is Potter's sequence where a decreased amount of amniotic fluid (oligohydramnios) often leads to the compression of body parts while the baby is developing inside of the womb. Oligohydramnios causes the forceful apposition of the baby's face against the uterine wall and restricts the mobility of his or her extremities. Neonates with Potter sequence therefore have flattened facial features and malformed hands and feet. Another well-known example of a sequence is the Pierre Robin malformation. In this particular sequence a smaller-than-normal jaw leads to a tongue that falls back in the throat prompting breathing and feeding difficulties.

In both the Potter and Pierre Robin sequences multiple etiologies may lead to the same sequence of events. As an example, it is well known that amniotic fluid volume is determined by fetal urine production. In Potter sequence, a variety of events (e.g., cystic kidneys, obstructed ureters, absent kidneys) may result in reduced urinary production thus leading to deformation of the fetus which is manifested as clubbed feet and diminished lung development. Furthermore, the same signs and symptoms when associated with other recognizable features may be part of different syndromes, e.g., Fetal alcohol syndrome, Treacher Collins Syndrome, Velocardiofacial syndrome. These conditions, having accessory symptoms and other known causes, are given the appellation of "syndromic". In many of these syndromic conditions the sequence may be the result of extrinsic factors acting on the fetus. These extrinsic factors may provide for a sequence with a low recurrence risk even though the genetic underpinning of the syndromic condition itself may be hereditary.

Autism Spectrum Disorders should be considered a sequence, not a syndrome. The autism phenotype, although the result of varied etiologies, can be explained as a cascade of factors all derived from anomalous germinal cell divisions and their subsequent migration. In this regard different etiologies (e.g., germinal matrix bleeds in extreme premature infants, "candle guttering" heterotopic masses in tuberous sclerosis, periventricular cysts in congenital cytomegalovirus) all provide a pathological commonality (i.e., an abnormality of germinal cell divisions and migration) that could explain the manifestation of an autism phenotype.

A LOCUS MINORIS RESISTENTIAE IN AUTISM

The Latin phrase *locus minoris resistentiae* translates as the location of least resistance. It is widely used in infectious disorders to define the place of invasion by microorganisms or the

effect(s) of their toxins. In surgery the area of greatest weakness or *locus minoris resistentiae* is that formed entirely by connective-tissue structures, e.g., the inguinal canal and herniation of abdominal viscera.

In neuropathology the phrase has acquired a new meaning being used by Melvin Ball to identify the structure that seems universally involved in a given condition, e.g. the hippocampus in Alzheimer's disease (20, 21). In this regard the term makes mention of a lesion necessary for disease development and progression.

Revision of the medical literature suggests that the anomalous division of germinal cells and their subsequent progenitor migration offer a *locus minoris resistentiae* to autism spectrum disorders. Germinal cells in the periventricular matrix divide asymmetrically and generate daughter cells that migrate to the cerebral cortex where they provide the precursors to pyramidal cells. Within the lower laminae of the cerebral cortex pyramidal cells are derived from the ventricular zone while those in the upper laminae originate from the subventricular zone. The outer subventricular zone is a primate-specific anatomical structure that accounts for a significant portion of projection neurons participating in corticocortical networks (22). During encephalization the topographical layout of this corticocortical connectivity suggests a drive that emphasizes small-world attributes (23). The resultant bias in short vs. long corticocortical connections may provide an anatomical correlate to different cognitive styles seen in a variety of neurodevelopmental conditions (24).

The asymmetric division of periventricular germinal cells pursues a series of concatenated steps wherein daughter cells migrate out of their precursor field and follow a radial path through the white matter and subplate, progressing through the cortical plate, and stopping at the pia-glia barrier (25). When neuroblasts fail to move out of the periventricular zone, they remain behind as nodular excrescences into the ventricular wall. Neuroblasts that stall in their migration through the white matter remain behind as single misplaced neurons or as heterotopic cell clusters. If cells reach the cerebral cortex, migratory abnormalities are recognized by occasional gross malformations, laminar effacement, and the presence of supernumerary cells within the molecular layer.

Neuropathological tombstones indicating anomalies of cell division and migration are closely interlinked and often found together in different disorders. It is therefore not surprising that individuals with megalencephaly, similar to some autistic individuals, often display neuronal heterotopias, gyral abnormalities and corpus callosum dysgenesis. Clinical reports of patients with grey matter heterotopias originally focused on seizures and neurodevelopmental-related aspects of the disorder; however, modern research recognizes psychiatric complications including an autism phenotype (Table 1) (26).

In autism, abnormalities of cell migration are suggested from accounts of focal dysplasias, abnormalities in the thickness of the cerebral cortex, variations in neuronal density, minicolumnar alterations, the presence of supernumerary neurons in the molecular layer, irregular laminar patterns, poor differentiation of the gray/white matter interface, and heterotopias (19, 27, 28). The following paragraphs detail some of the research in this area.

RESEARCH STUDIES IN AUTISM SPECTRUM DISORDERS

MRI studies suggest that the prevalence of unidentified bright objects (UBOs) in nonsyndromic autistic individuals is higher than in neurotypicals (29). Unidentified bright objects (also called “white matter hyperintensities”) are common findings in MRI characterized by increased T2 signal intensity and isointensity on T1 weighted images. The signal’s profile, its lack of mass effect, calcification or surrounding edema, all suggest that UBOs are heterotopic in nature. The presence of heterotopias in ASD has been confirmed in postmortem studies.

Bauman and Kemper described indistinct lamination of the anterior cingulate gyrus in 5 out of their 6 autopsy cases (30). In a slightly larger series, Bauman and Kemper reported heterotopias of the inferior olive ($n = 9/9$) and an ectopic cluster near the inferior peduncle ($n = 1/9$) (31). Several years after Bauman and Kemper’s initial report, Bailey and colleagues were the first to recognize the significance of cortical abnormalities of a dysplastic nature in autism (32). In their original report 5 out of 7 cases exhibited widespread cortical dysgenesis and 4 out of 7 cases showed increased numbers of neurons within the white matter. Bailey et al. also described increased cellularity within the molecular layer in 1 case and indistinct lamination in 3 of their patients (32). Using Nissl and MAP2 immunocytochemistry Mukaetova-Ladinska et al. examined tissue from both BA9 and 10 for neuron morphometric screening using Image-Pro software (33). The results showed ill-defined cortical layers and reduced levels of MAP2 expression, in both neuronal soma and dendrites, in their 2 individuals with autism as compared to controls. Fatemi et al. linked the migration and lamination disturbances observed in autism to significant brain reductions of both Reelin and Bcl-2 (34, 35).

Hutsler et al. evaluated cortical thickness and layering in 8 ASD patients (ADI-R criteria) and an equal number of controls (36). All regions examined were examples of eulaminate cortex (i.e., BA7, 9, 21). There was no difference in cortical thickness but qualitative examination revealed cell clustering and supernumerary cells in both lamina I and the subplate. Later on, Avino and Hutsler used computerized image analysis to examine the same histology sections (37). Their results showed an indistinct boundary between cortical layer VI and the adjacent white matter. The authors attributed the indistinct boundary to the presence of supernumerary neurons within the subplate region and/or the lack of resolution of this transient zone in autistic individuals (38).

Wegiel et al. used serial whole hemisphere coronal brain sections of 13 autistic and 14 age matched controls to qualitatively screen for developmental abnormalities (39). In the autistic cohort the authors described periventricular nodular heterotopias in 1 patient and thickening of the subependymal layer in 2 individuals. The most common developmental change detected was focal dysplasias in 11(85%) of their autistic subjects. It should be stressed that genetic conditions (e.g., mutations of the *FLNA* gene) usually give rise to generalized heterotopias that involve both hemispheres. Focal heterotopias that vary in location from patient to patient, like those reported by Wegiel et al., are more consistent with environmental factors (e.g., X-ray induced), hence their name “epigenetic” heterotopias (25).

Courchesne et al. used stereological methods to analyze the dorsolateral and medial prefrontal cortex of 7 autistic children and 6 controls (40). Results of the study indicated increased neuronal density (67% more) in autism as compared to controls even when taking brain weights into consideration. Similar to Courchesne's result an earlier study done by Casanova et al. described a 34% increase in neuronal density in the dorsolateral prefrontal cortex of autistic individuals (41). In addition, the Casanova et al. study found similar findings of increased neuronal density in areas outside of the prefrontal cortex wherein pyramidal cells also exhibited reductions in size. The latter authors explained their findings based on an increased number of cell minicolumns. The presence of smaller projection neurons in autism would serve to bias neuronal networks towards an "intrahemispheric modus operandi" (42).

Findings of an increased number of minicolumns in autism can be traced to the supernumerary divisions of periventricular germinal cells. Compartmentalization of the minicolumn has shown that width appears to be reduced primarily within its peripheral neuropil space (43). The reduction of the peripheral neuropil space across all cortical laminae suggests involvement of an anatomical element-in-common across the width of the cerebral cortex (44). The peripheral neuropil space contains, among other things, the majority of inhibitory elements that serve to provide a so-called "shower curtain of inhibition" to the minicolumn (43). A possible explanation to the reported minicolumnopathy of autism involves the heterochronic division of periventricular germinal cells causing neuroblasts (future pyramidal cells) to migrate to the cortex and mature asynchronously to other anatomical elements that translocate tangentially from subpallial domains, i.e., interneurons (28, 45, 46) (Figure 2). The resultant excitatory/inhibitory bias may account for some of the symptoms observed in autism: e.g., seizures, sensory abnormalities (28, 45). When the germinal cells involved are those of the rhombic lip a number of brainstem and cerebellar nuclei may be affected.

An excitatory/inhibitory imbalance similar to the one proposed for autism (see above) may be propitiated by interrupting the development of interneurons. This appears to be the case when mutations target the mouse gene *Plaur* which encodes the urokinase plasminogen activator receptor (uPAR). The mutation disrupts the ontogeny of the forebrain's inhibitory neurons by arresting the migration of inhibitory parvalbumin containing interneurons in their early trajectory from the medial germinal eminence (47). Mice genetically manipulated for this defect show spontaneous seizures, anxiety related behaviors, and impaired extinction of cued fear conditioning (48).

Throughout encephalization the overall increase in cortical modules (minicolumns) have required that the growing metabolic requirements of the brain be balanced by decreased demands of other body systems, primarily the gut (49). The brain monopolizes a significant share of energy from the body to fulfill its need (50) making metabolic homeostasis a tightly controlled process with small tolerances for deviation. Many pathological conditions are related to cumulative oxidative damage and metabolic stress (51). An increased number of minicolumns, as in autism, may lower the threshold needed to maintain the brain's dynamic metabolic balance. The lowered threshold confers a susceptibility rendering affected brains vulnerable to injuries such as febrile convulsions and/or mitochondrial defects (52, 53).

SYNDROMIC VS. IDIOPATHIC AUTISM

Those cases having a known etiology for patients exhibiting an autism phenotype are called syndromic. Idiopathic or non-syndromic cases are those where an underlying cause for the condition is lacking. Idiopathic cases constitute by far the majority of individuals with an autism spectrum disorder. It is my belief that by looking for commonalities among the known neuropathologies of syndromic cases that the core features of idiopathic cases will become evident (Figure 3).

An autism phenotype is frequently seen in several genetic conditions such as tuberous sclerosis, Ehlers-Danlos, Lujan-Fryns, and the Smith-Lemli-Opitz syndrome. Neuropathological studies reveal the presence of migratory disturbances in all of these conditions. Among these disorders, the relationship between tuberous sclerosis and ASD has been the most extensively studied. About 40 to 45% of patients with tuberous sclerosis exhibit comorbidity with autism (54). Tuberous sclerosis is a dominantly inherited disease associated with wart-like protrusions of the cerebral cortex, clusters of neurons within both the white matter and periventricular zone., and subependymal giant cell astrocytomas. Neuropathological studies indicate that the presence of tubers (dysplastic cortex) within the temporal lobes appears to be a necessary but not sufficient risk factor for the development of ASD (55). Magnetic Resonance Imaging (MRI) occasionally reveals radial migration lines, thought to represent heterotopic glia and neuron, in association to cortical tubers (56).

Connective tissue disorders like Ehlers-Danlos and the Lujan-Fryns syndromes (i.e., Marfanoid body habitus, intellectual disability and dysgenesis of the corpus callosum) manifest abnormalities of brain development. The finding is not unexpected as the matrix proteins (as in germinal tissue) and those related to cell attachment are affected. Failure of neurons to migrate from their birthplaces along the lining of the lateral ventricles results in their accumulation as nodular malformations. Neurological disorders associated with periventricular nodular heterotopias are seen with mutations in the filamin A (*FLNA*) gene which is involved in cytoskeletal organization. Mutations in the *FLNA* gene have recently been described in a family with periventricular nodular heterotopias who were identified as having Ehlers-Danlos syndrome (57, 58, 59). The presence of heterotopias in Ehlers-Danlos syndrome appears to be related to both seizures and dyslexia (60).

The Smith-Lemli-Opitz syndrome is an autosomal recessive disorder linked to a defect in cholesterol metabolism. Studies indicate that the majority of patients with the disorder have some variant of autism (61). Neuroimaging and postmortem studies of Smith-Lemli-Opitz syndrome indicate small brain size with enlarged ventricles and an overall reduction in size (dysgenesis) of the corpus callosum. Microscopic examination reveals abnormalities of migration in both cerebral hemispheres and cerebellum (62, 63).

Congenital viral infections are among the oldest known causes of syndromic autism. The best association to date is between congenital rubella and autism. Fortunately the MMR immunization vaccine has reduced the number of individuals infected by the rubella virus as well as the number of syndromic cases caused by this infection (64). Cytomegalovirus (CMV) is the most common congenital viral infection affecting 1 in every 100 live births

(65). The first description of syndromic autism and congenital CMV was by Stubbs (66). Autistic patients infected with either rubella or CMV have germinal cysts on neuroimaging examination (67). Germinal cysts result when necrotic lesions cavitate as a result of a neurotropic infection, or more commonly, a subependymal hemorrhage (68).

Damage to the germinal matrix and/or corresponding migrational abnormalities can lead to an autism phenotype. Germinal matrix hemorrhages with or without extension into the ventricles represent the most common and important neurologic injury in preterm neonates. Researchers usually explain the abundance of this pathology based on the developing brain's inability to autoregulate cerebral blood pressure. This is of outmost importance for germinal tissue where an abundance of immature blood vessels exhibiting a paucity of pericytes, thinned basal lamina, and reduced number of ensheathing astrocytic end-feet all suggest a frail microvasculature (69).

Recent studies in survivors of extreme prematurity (born more than 3 months before the expected date of delivery) have shown an increased prevalence of an atypical social profile suggestive of an autism spectrum disorder (70). In addition, circumstances associated with extreme prematurity, including multiparity (twins, triplets) and fertility drugs, are also risk factors for autism spectrum disorders (71). Extreme prematurity is commonly associated with both germinal matrix hemorrhages and lesions in the surrounding white matter (e.g., infarctions and periventricular leukomalacia) (72). Injuries to the germinal matrix limit the number of dividing progenitor cells while lesions of the surrounding white matter interfere with the migration of neuroblasts. The risk for a low birth weight infant developing ASD is dependent on the severity of the underlying white matter injury. In a prospectively followed cohort of 1105 low birth weight infants screened perinatally by ultrasound those infants who exhibited ventriculomegaly had a seven-fold risk of later screening positively for an ASD diagnosis (73).

Researchers have looked at several drugs that, when taken during pregnancy, may increase the risk of an infant developing an autism spectrum disorder. What appears interesting is the commonality among these drugs and other risk factors for autism. As an example, a significant percentage of children exposed to cocaine or misoprostol (a synthetic prostaglandin) *in utero* manifest a Moebius sequence (74, 75). All of these agents (prenatal cocaine, misoprostol, Moebius sequence) may provide for behaviors in the adult associated to autism spectrum disorders. The finding in some cases of concomitant dysplasias (e.g., olivary) in Moebius sequence clearly indicates a migratory abnormality. The neuropathology of misoprostol is unknown as of present, but prenatal cocaine exposure disturbs brain growth, early corticogenesis and development of cortical lamination (76). Recent work has shown that prenatal cocaine exposure alters progenitor cell markers in the subventricular zone of the adult rat brain (77).

It should be noted that exogenous factors that are known to act in various stem cell populations are likely to have systemic effects. Prenatal ultrasound was deregulated in the early 1990's and an eightfold increase in energy was allowed by the FDA in order to better visualize the fetus. This increase closely parallels the rise in prevalence observed for autism spectrum disorders (78, 79). It is well known that high frequency sound waves affect various

stem cell populations and are capable of regulating a number of growth factors (78, 79). Ultrasound is known to trigger tissue regeneration in bone fractures and has similar effects on cartilage. Prenatal ultrasound has been shown to alter learning, social behaviors, and locomotor activity in young mice and has been proposed as an animal model of autism (80). Stanton et al. have shown that ultrasound exposure in mice provides a statistically significant reduction (22%) in the number of mitotic figures and an increase in apoptotic bodies (153%) in the small intestine (81). A study of the effects of prenatal ultrasound in rodents demonstrated abnormalities in neuronal migration to the cerebral cortex (82).

CONCLUSIONS

The statement that autism is a disorder of brain development is not a matter of debate. Convergent evidence from the perspectives of epidemiology, neuroimaging, and neuropathology clearly support this point of view. In this article we have provided evidence to sustain the presence of a common pathophysiological mechanism for both syndromic and idiopathic autism. The presence of focal asymmetric dysplastic processes and heterotopias suggest the influence of an environmental exigency acting during brain development. In the case of syndromic autism, these environmental exigencies are well known, e.g. drugs, viruses. Although, the main risk factor associated with idiopathic autism has not been properly identified the same must act by disturbing germinal cell division and the subsequent migration of neuroblasts towards their target fields. Even though based on a single pathological mechanism, clinical heterogeneity in autism spectrum disorders could still be engendered based on differences in the underlying genetic susceptibility of the individual, the type of exogenous factors, and the timing during which the exogenous factor(s) acts during brain development (19).

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Figure 1.

A schematic of the concatenated pathology proposed for autism spectrum disorders. Idiopathic cases exhibit abnormalities of germinal cell divisions, migration and cortical dysplasias. Syndromic cases exhibit a known cause and additional manifestations. In the absence of a known cause (symbolized by an X on the figure) we tend to speak of cases as syndromes rather than sequences.

Figure 2.

Coronal section of the human brain during embryonic development. The clear arrowheads illustrate the tangential migratory pathway of cells (future interneurons) from the lateral and medial ganglionic eminences (LGE, MGE) to the cortical plate. Interneurons may also originate from the retrobulbar neuroepithelium of the lateral ventricle and from the cortex itself. Those interneurons fated for the cortex acquire a superficial and deeper pathway in order to avoid the embryonic striatum. A set of dark arrowheads illustrate how neuroblasts migrate out of the ventricular zone and into the cortical plate (future pyramidal cells) following a radial pathway. An excitatory/inhibitory imbalance may result from desynchronization of cells as they undertake their radial and tangential migrations. Because interneurons are generated at such distant sites their migration may be susceptible to disruption from a large variety of sources.

Figure 3. Manifestations of syndromic autism spectrum disorders exhibit a common neuropathology. Abnormalities in germinal cell divisions may lead to changes in corticocortical connectivity, seizures and sensory/motor abnormalities (28).

Table 1

Neuropathological and clinical manifestations associated with subependymal and subcortical heterotopias

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- Cortical malformations, e.g. schizencephaly
 - Gyral malformations, e.g., polymicrogyria
 - Changes in brain size
 - Changes in size of the corpus callosum
 - Enlarged ventricles
 - Seizures, often intractable
 - Mental retardation
 - Developmental delays
 - Dyslexia
 - Schizophrenia
 - Schizoaffective disorder
 - Major depression
 - Anxiety disorders
 - Attention deficit hyperactivity disorder (ADHD)
 - Obsessive compulsive disorder
 - Self-injurious behaviors
 - Autism spectrum disorders
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