Environmental Factors and Limbic Vulnerability in Childhood Autism

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Abstract: The rise in prevalence of autism spectrum disorders (ASD) is suggestive of a new etiology. Diagnostic substitution alone is unlikely to account for the increase, while genetic association with detoxification gene alleles points to an environmental contribution. Subtle structural anomalies in the ASD brain are widespread but limbic damage seems important for the development of behaviors diagnostic of ASD. The limbic brain is especially susceptible to environmental challenge: internal sensing, physiological feedback and neuroinflammatory processes may underlie this sensitivity to insult. Primary damage leading to ASD in later life is likely to take place in utero and/or in the immediate postnatal period. Despite evidence of heavy metal involvement, a causal connection may not yet be concluded because subjects exposed to metals tend to be exposed to other environmental agents. Because maternal minerals and lipids are supplied to the unborn child, historic toxic exposure of the mother may be pivotal. A two-hit combination of genetic susceptibility and environmental challenge is argued to underlie the rise in ASD.

Key words: Autism, autism spectrum disorder (ASD), environment, heavy metals, hippocampus, limbic system

INTRODUCTION

Autism spectrum disorder (ASD) case numbers have risen markedly. In London, prevalence is now 116 children per 10,000[1] while ASD rates in the USA approach 1% in younger age groups[2]. Most cases are of moderate to high severity, with 53% requiring prescription medication and up to 75% in sub-85 IQ bracket[2,3].

There is no consensus regarding the cause of the increase in case numbers. Widening diagnostic criteria and diagnostic substitution could lead to subjects once not diagnosed in this category now being allocated to ASD. There was an apparent fall in mental retardation cases as ASD increased[4]; this assertion was found to be incorrect[5] and was withdrawn[6]. A subsequent large survey ruled out concomitant decline in the separate categories of either mental retardation or speech and language disability, concluding that "these data do not support the hypothesis of diagnostic shifting"[7]. This study also reported an increase in attention deficit disorder paralleling the rise in ASD.

Using identical diagnostic criteria, autism prevalence rose 10-fold over a decade in Olmsted County, Minnesota[8]. Byrd and colleagues[9] in California addressed and excluded many possible confounding issues (earlier age of diagnosis, broadening criteria, migration), pointing to a real rise.

ASD rates also increased progressively when younger children were studied[7,8,10-15].

Systematic survey in Canada[16] recorded a 10% annual increase, with highest rates (107 per 10,000) in the younger children. The figures are underestimates: special schools providing services for children with mental retardation (an important subset of ASD) were excluded from the survey. The authors suggested that changes in diagnostic criteria, with increased awareness and referral, contribute to the rise. This was disputed by Taylor[17] who stated "diagnostic transfer is not the major explanation for the increased prevalence of autism", concurring with Fombonne and colleagues[16] who observed that the ASD rise is accompanied by an identical increase in the subset of strictly-defined autistic disorder where misclassification is unlikely. Both exclude vaccine effects including measles-mumps rubella (MMR) and thimerosal preservative as major causes of the rise in ASD. Nevertheless, environmental influences cannot be ruled out[16].

Indicators of a real rise in the prevalence of ASD have been reviewed, including the changing spectrum of impairments, apparent increases in twin concordance rates, and the decline in a specific genetic contribution (Fragile X) within the ASD population[18]. It has not been possible, on the basis of the available data, to refute the rigorous conclusion that there has been a real rise in prevalence, dubbed "new phase autism"[18], that

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suggests environmental influences. There is as yet no body of evidence sufficient to reject the role of environmental agents[19,20].

GENETIC AND BIOCHEMICAL MARKERS IN ASD

Up to 10% of ASD cases are associated with genetic abnormalities including the Fragile X expansion, mutations in genes causing tuberous sclerosis, and a further diversity of rare metabolic deficiencies (as reviewed[21-23]), but in no case is the genetic or biochemical deficiency sufficient to cause ASD in all carriers, pointing to environmental factors.

Genetic predisposition to environmental toxicity is consistent with differential representation of alleles of detoxification genes in ASD subjects versus controls. These genes include methylene tetrahydrofolate reductase (MTHFR), reduced folate carrier (RFC), transcobalamin II (TCN2), catechol-O-methyltransferase (COMT) and glutathione sulfotransferase GST-M1[24,25]. Skew in allele frequencies for paraoxonase (an organophosphate detoxifying enzyme, PON1)[26] and glyoxalase I (GLO1)[27] in ASD is suggestive of chemical exposure, while bias of ferroportin (SLC40A1/SLC11A3) and metal-activated transcription factor (MTF1) alleles[28] is consistent with heavy metal involvement. No genetic studies have been reported for prominent metal-susceptibility enzymes delta-aminolevulinic acid dehydratase (ALAD), coproporphyrinogen oxidase (CPOX), and stannin (SNN). Bias in histocompatibility haplotypes[29-33] may be indicative of exogenous infectious or inflammatory agents as contributory factors in autism.

Diminished supply of sulfur-containing amino acids in ASD may also affect susceptibility to environmental agents because these amino acids are critical for some detoxification reactions. Plasma methionine and cysteine were reduced by 39% and 20% respectively in ASD[24]; these are principally derived from the diet and gastrointestinal abnormalities (common in ASD) could be a contributing factor. The ratio of total reduced (GSH) to oxidized glutathione (GSSG) fell in ASD to ~50% of controls[24,34], suggestive of oxidative stress. Abnormal metabolic markers in ASD include deficiencies of dehydroepiandrosterone (DHEA) and oxytocin[35,36] and stochastic elevations of blood testosterone and cortisol[37,38]. Disturbed steroid endocrinology is a known outcome of environmental toxicity[39,40].

LIMBIC DAMAGE AND ASD

Structural studies on the ASD brain (post-mortem or imaging) have revealed a variety of changes that distinguish autistic from control subjects[41-43]. The most consistent alterations are seen in the limbic brain, centered on the hippocampus, amygdala and adjoining brain regions, but with significant perturbations in cerebellum and cortex[44,45].

Limbic damage in ASD: Limbic/temporal lobe damage has been causally linked to ASD development[46-51]. Subjects with early and selective damage to the hippocampus fulfilled ASD diagnostic criteria; Hauser et al.[46] suggested that dysfunction of the medial temporal lobe is a major factor in the pathogenesis of infantile autism. Bilateral hippocampal dysfunction in early life is associated with a profound failure of cognitive capacities, including language learning and the acquisition of complex social and adaptive skills; these deficits correspond to the cognitive deficits of severe infantile autism[52]. Abnormalities of the medial temporal lobes, encompassing the limbic hippocampal formation and amygdala, were argued to underlie the cognitive, perceptual and language impairments of ASD[53], and this is supported by the known roles of the limbic brain in anxiety, memory, pain sensing and physiological regulation, all disturbed in ASD[18].

Abnormalities in other brain regions in ASD: Abnormalities are seen in many other areas of the autistic brain, often in cerebellum. The cerebellum is centrally involved in physical coordination and postural control. Although ataxia is sometimes seen in subjects with ASD, this is unlikely to relate to the social, linguistic and behavioral deficits of these disorders, and is likely to be an incidental accompaniment. Other brain regions with possible involvement in the pathoetiology of ASD include hypothalamic and brain-stem nuclei, but these have not been well studied.

The deficits of autistic disorder are wider than limbic damage: The manifestations of ASD extend beyond the diagnostic triad to hyperactivity, brainwave abnormalities and frank seizure activity[18,54], network and complex processing abnormalities[55-57], weak central coherence[58,59], underconnectivity[60], and altered excitation/inhibition ratios[61]. Sensory abnormalities are also common[62]. Paradoxical responses include squinting, looking out of the corner of the eyes, gaze aversion, staring at the shadows of waving fingers[63] and a fixation on the sense of

smell[64]. These manifestations may be accompaniments to the primary damage that causes the diagnostic impairments of ASD.

ENVIRONMENTAL SUSCEPTIBILITY AND THE LIMBIC BRAIN IN ASD

The limbic brain (hippocampus, amygdala and functionally related brain regions) is especially vulnerable to toxic insult. Agents causing specific damage to the hippocampus include bacterial toxins[65,66], vitamin B1 deficiency[67,68], excess homocysteine[69,70], hepatic encephalopathy[71]; copper deficiency[72], glucocorticoid excess or deficiency[73-75], ethanol exposure[76], oxygen deprivation[52,77] and irradiation[78]. Limbic damage, particularly in the hippocampus, is the primary outcome of challenge, while other brain regions often largely retain their integrity. Nevertheless, other structures which potentially could be damaged (including the hypothalamus and brainstem) are difficult to study, and have been omitted from most screens, a significant limitation.

Toxic damage to the hippocampus is illustrated by exposure to trimethyl tin (TMT). From rats and mice to primates[79,80] including humans[81-84], systemic TMT exposure produces marked and selective destruction of the hippocampal dentate gyrus, with milder effects on hippocampal regions CA1-3, amygdala, subcortex, and cerebellum. TMT exposure thus causes selective damage in the same brain regions implicated in autism and ASD. TMT treatment of rats is reported to entrain an autism-like behavioral disorder[85].

Dividing cells: The unusual fragility of the central formation of the limbic brain, the hippocampus, requires an explanation. Considerable attention has focused on one striking feature of the hippocampus - the presence of dividing cells in the formation. Because dividing cells are especially sensitive to toxic damage, it seems intuitive to suggest that this could underlie the vulnerability of the formation. Though relevant to restorative processes, it will be argued that ongoing cell division is unlikely to explain susceptibility of specific brain regions in relation to ASD development.

Neurogenesis takes place into adulthood in the dentate gyrus of rodents, monkeys[86,87], and human[88]. Some late production of new neurons continues in other brain regions, including the olfactory system, amygdala, temporal cortex and cerebellum[89,90] but overall, late neurogenesis is principally restricted to the hippocampus (and olfactory system) in primates[91,92]. Mitotic cells are exquisitely sensitive to chemical toxins, as exploited by anti-cancer therapy, and dentate damage is often seen in subjects receiving radiation or chemotherapeutic treatments. Dividing cells are also preferred substrates for viral replication: dentate destruction takes place in experimental animals infected with bornavirus[93], and bornavirus infection has been proposed as an animal model of ASD[94,95].

Nevertheless, there is no one-to-one association between vulnerability to toxic insult and the presence of dividing cells. The type and location of limbic damage depends more on the nature of the insult than on the presence of dividing cells. Glucocorticoid excess and X-ray irradiation, like TMT, selectively cause loss of dentate granule neurons[75,78,96]. In contrast, early ethanol exposure selectively reduces neuronal number in the dentate hilar region, and not in the granule cell layer[76]. X-irradiation and chemotherapeutic agents cause loss of both subgranular progenitor cells and non-dividing dentate hilar oligodendrocytes[96-98]. The dentate gyrus can be unaffected - early beta and gamma irradiation reduces cell numbers in the CA1-3 regions[99,100] with additional damage in the cerebellum, but not in the dentate gyrus. Oxygen deprivation (as in cerebral ischemia) leaves the dentate intact but selectively destroys hippocampal CA region pyramidal neurons[101,102] as seen in some ASD subjects[52].

While these studies confirm the regional vulnerability of the hippocampus, clearly the location and type of damage does not depend on the presence of dividing cells. Indeed, neurogenesis is widespread in the developing brain, and not just in limbic regions. While preferential susceptibility of dividing cells to viral replication may underlie the late development of ASD as a result of viral infection of the brain in adolescents and adults[103,104] when neurogenesis is more restricted, other factors must underlie particular vulnerability of the limbic brain.

Internal sensing: The hippocampus is unusually responsive to metabolic signals. Receptors and signalling molecules are strikingly abundant in the hippocampus[105-109]. The hippocampus is a primary target for soluble ligands that reflect body physiology, including ion balance and blood pressure, immunity, pain, reproductive status, satiety and stress[110]. Selective expression may reflect internal sensing (enteroception, also interoception) in the reciprocal accommodation of brain function, motivated behavior, and body physiology. Region-specific limbic damage is predicted if chemical insults aberrantly target receptors selectively expressed in the hippocampal formation.

This may explain selective hippocampal destruction by TMT. Stannin, a mitochondrial metal-binding protein, is a prerequisite for TMT toxicity. In the absence of stannin, target cells are largely refractory to TMT[111,112]. Stannin is most prominently expressed in the hippocampus[113]. It is further induced by pro-

inflammatory cytokines[114], relevant to inflammatory processes taking place in ASD.

Blood-brain barrier: Intuitively, the tight junctions between epithelial cells in the brain microvasculature might direct environmental toxicity to regions that are unprotected. However, the functional development of the barrier is complex[115,116]. Even in the adult, there is active transport of polypeptides, molecules, and ions from the blood into the brain. In neonates subjected to excess of the toxic pigment bilirubin (kernicterus: leading in some subjects to mental retardation and ataxia), the hippocampus is one of the areas stained selectively and hippocampal volume loss has been observed[117]. The hippocampus (along with brain stem nuclei) seems to be particularly exposed to blood-borne substances.

Physiological feedback: Peripheral insults also have a toxic inpact on the limbic brain, notably through the induction of neuroinflammation. Acting by vagal relay, systemic administration of inflammation-inducing lipopolysaccharide (LPS) or of interleukin IL-1 boosts the levels of neurotoxic pro-inflammatory cytokines in hippocampus and hypothalamus[118,119]. Peripheral (respiratory) infection with *Bordetalla pertussis* or systemic administration of broken *Shigella dysenteriae* results in persistent hippocampal and hypothalamic expression of markers of inflammation including IL-1β and tumor necrosis factor (TNFα[120,121]. Organometal (TMT) treatment of the post-natal mouse produces specific elevations in hippocampal pro-inflammatory cytokine mRNAs[122,123].

In ASD, striking increases in brain pro-inflammatory cytokine molecules have been observed[124,125]. The cause of ASD neuroinflammation has not been established, but peripheral inflammatory processes relay to the brain. Gut inflammation is common in autistic patients, notably with large excesses of particular Clostridial species[126-128]. Gastrointestinal anomalies are frequent: in one study, 91% of ASD subjects were affected[128]. Inflammatory processes taking place in gut, compounded by immune system deficiencies[30,129-132] may contribute to brain inflammation in ASD.

Oxidative stress: Local inflammation is associated with oxidative stress (OS); a role for this process in the pathoetiology of ASD has been proposed[133-135]. Oxidative stress equates to interference with mitochondrial electron transport processes[136], leading to the accumulation of reactive free radical species. Both LPS and TMT are potent inducers of oxidative

stress in the brain[137-140] as are other environmental agents such as the herbicide paraquat[141] and heavy metals generally[142-144]; the presumption is that these molecules cause mitochondrial damage, particularly in the vulnerable hippocampus.

Evidence for OS and mitochondrial damage in ASD includes attenuated GSH-GSSG ratios[24,34] and excess urinary porphyrins[145], the latter marks inhibition of heme synthesis of especial relevance to heme-dependent cytochromes and their key role in mitochondrial electron transfer. The most convincing demonstration of OS in autism disorders is the reproducible elevation of urinary isoprostanes[146,147], a reliable marker of oxidative stress[148]. Isoprostane elevation is also seen in methylmercury exposure[149].

ENVIRONMENTAL EXPOSURE IN ASD

ASD is typically diagnosed between two and four years of age, but retrospective analysis has revealed anomalies from earliest time-points. It seems likely, therefore, that prenatal or perinatal insult is pivotal, concurring with other strong evidence of major risk factors timed during gestation and the perinatal period. Early toxic exposure appears to be critical. Thalidomide exposure during gestation is a known risk factor for ASD development, but there is no evidence that thalidomide administered to older children (as an anti-cancer agent) predisposes to autism disorders. Gestational exposure to anticonvulsant medication, tobacco, alcohol or cocaine, as well as to thalidomide, predisposes to ASD development in the child[150-157]; exposure in later life appears to present no specific risk factor for the condition.

Prenatal insults may include maternal infection: in an animal model, respiratory infection during pregnancy (but without fetal infection) was associated with later behavioral deficits in progeny reminiscent of autism[158,159]. A role for prenatal injury associated with maternal psychosocial stress has been discussed[160,161]; mild maternal stress in mice aggravates excitotoxic brain injury induced post-natally[162].

Perinatal brain injury alone can predispose to ASD: Birth complications are generally more frequently recorded in subjects later diagnosed with ASD[151,163,164]. Some rare ASD cases have been attributed to congenital infection with rubella[165] or cytomegalovirus[166-168]. Early postnatal oxygen deprivation in rats causes later autism-like behavior[169]. A small group of children injured by perinatal hypoxia (and with selective limbic damage) developed severe infantile autism[52]; one of Hans Asperger's original

patients, Hellmuth L, also endured perinatal hypoxia.

Later in infancy, brain insult does not generally seem to result in ASD-like conditions. In oncology referrals treated with anti-cancer therapy including ionizing radiation and chemotherapeutic agents, brain disturbances include epilepsy, attention and working memory deficits, intellectual impairment, and sensory perturbations including ocular and auditory problems, often with peripheral neuropathy[170-173]. Full-blown ASD (fulfilling the diagnostic triad) is rare in survivors of anti-cancer therapy with the possible exception of younger children recovering after aggressive therapy of brain tumors (Wallace, H., pers comm).

Identity of the environmental agent(s): It was suspected over many years that lead (Pb) poisoning might be associated with ASD[174-181]; this has been confirmed in some specific cases[182]. Attention has moved to organomercurials (notably methylmercury) found in some immunological reagents, because methylmercury (like TMT) can cause limbic damage in susceptible animal models[183].

Elevated body levels of heavy metals are reported in some ASD subjects[174,175,184,185], with excess of mercury in early baby teeth[186]. Urinary porphyrin levels (a marker of heavy metal toxicity) were significantly elevated in children with autistic disorder[145]. Removal of heavy metals by chelation reduced urinary porphyrin levels[145] pointing to, but not proving, a cause-effect relationship. A later report reiterated the porphyrin excess in ASD subjects[187] but further work is required to confirm the generality of these observations.

Despite the focus on heavy metals, a combination of exposures is likely. Generally, a combination of agents can cause significant damage even when each is at sub-threshold or "safe" levels, exemplified by multiple xenoestrogen exposure[188]. Environmental chemicals appear to synergize with heavy metals to increase the extent of damage produced[189]: synergy between mercury and polychlorinated biphenyl toxicity has been reported in dual-exposed children[190]. Specific evidence for chemical toxicity in ASD is provided by increased levels of trichloroethylene and toluene[191], polychlorinated biphenyls and dioxins[192], further underscored by evidence of genetic linkage to chemical detoxification gene alleles.

Though local atmospheric mercury correlates with ASD rates in Texas[193], conjoint exposure emerged as a significant factor in the California association study - there was a 5-fold elevation in ASD rates in highest versus lowest exposure regions when overall exposure was considered (including heavy metals and chemical toxins)[192]. The increased prevalence of ASD in urban versus rural areas[193-195] supports this conclusion.

Susceptibility to toxic damage: Deficits in detoxification may explain why only a proportion of children develop ASD. There is evidence of a heavy metal mobilization deficiency in affected children. Hair is a significant export route for mercury, but mercury was largely absent from first baby hair of children who went on to be diagnosed with ASD[196]. Comparing 94 ASD samples with 45 age-matched controls, mercury levels were over 7-fold higher in samples from control children. Levels of mercury varied inversely with severity of the disorder – the children with the least hair mercury were subsequently those most severely affected[196]. Reduced metal levels in hair of ASD children have been confirmed[197]. Children may be especially at risk if they are unable to mobilize organometals.

Present versus historic exposure: 5% of inner-city minority children had unsuspected elevations of urinary mercury[198] but the route of exposure is difficult to decipher. Early-life (gestation/lactation) exposure to mercury has been expressed as an algorithm of maternal dental amalgams, sea-food consumption, and a specific maternal immunoglobulin (rhoD or rhesus: generally administered at 27 weeks gestation) that contains a organomercury preservative[196]. However, there are major complexities in evaluation. Metals, like lead and tin (but mercury less so), are deposited in bone over decades. During pregnancy and lactation, turnover of maternal bone supplies the unborn child and infant with minerals[199]. 5-10% of maternal skeletal mineral is lost during lactation alone[200]. If maternal heavy metal burden is significant, there will be toxic exposure of the unborn or breast-fed child[201,202].

Chemical exposure is also widespread[203], with some alarmingly high levels in human organs[204]. These agents accumulate with maternal age[205,206], predominantly in fatty tissues. Maternal lipids, like metals and minerals, are passed to the child during gestation and lactation[207]: mobilization of accumulated lipid-soluble residues is likely to contribute to early-life exposure. In support of a specific maternal contribution, ASD rates are elevated in the children of older mothers[150,164,192,208] though other studies have queried this finding[151,209]. The age-effect could relate to accumulated toxic exposure. An association with paternal age has also been reported[210].

The possibility that ASD in offspring might result from accumulated toxicity over more than one generation is worthy of consideration. It is notable that

in fetal anticonvulsant syndrome (overlapping with ASD), a known genetic vulnerability (specific MTHFR alleles) was found in the mothers, but not in the affected children themselves[211]. Indeed, parents of ASD children can themselves manifest behavioral idiosyncrasies that fall short of meeting the diagnostic criteria of autism[212,213], and which could be consistent with historic parental exposure.

Two critical factors: environmental exposure and genetic susceptibility: It is argued that increasing ASD prevalence rates can be ascribed to early environmental toxic exposure, notably in utero, combined with genetic susceptibility and the regional sensitivity of the limbic brain. The "two-hit" model[214] proposes that an external trigger factor must be combined with genetic predisposing factors to produce this disorder. The genetic factor may be in the child, for instance low-activity alleles for key neurodevelopmental genes where environmental challenge can expose sub-clinical genetic deficiencies that culminate in new developmental phenotypes[215,216]. Where susceptibility genes affect detoxification pathways the genetic factor may be in the mother as well as in the child. Further research is warranted to determine the precise identity of the specific environmental agents responsible[217] in order to devise appropriate preventative/therapeutic interventions.

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