1 – Autism's multiple etiologies

Autism has multiple etiologies, predispositions, or associated medical conditions. Some of these conditions are summarized in table 1 and also listed as headers for references [1-16]. Autism is not the only outcome of any of these. All of the associated disorders must however affect a common vulnerable brain system under some special circumstance to result in autism – sometimes referred to as “a final common pathway.” The medical conditions associated with autism include anatomical anomalies as in tuberous sclerosis or neurofibromatosis. Temporal lobe involvement in tuberous sclerosis is associated with more cases of autism than tubers in other brain areas [7b]. How development (or maturation) of the temporal lobes might be curtailed by other disorders associated with autism should therefore be considered.

The temporal lobes, like other higher cortical areas are not fully myelinated or mature until after the third or fourth postnatal year [17a]. Maturation of the cerebral cortex depends on integrity of the subcortical structures that transmit sensory and autonomic signals to these higher centers of cognitive processing during early childhood. Maturation of the auditory language circuits in the temporal lobes must be dependent upon integrity of the brainstem auditory pathway, which is myelinated and functional by 29 gestational weeks in the human fetus [17b]. The time span of myelin formation in the human brain is shown in figure 6 from Yakovlev and Lecours (1967), which shows that myelination of the acoustic radiations to the temporal lobes is ongoing during the first four years of life. Learning to speak during this period of early childhood is essential for all subsequent stages of human development.

More rare genetic causes of autism are being reported on a regular basis, and the hunt for "autism genes" is the focus of much current research, but it seems unlikely that a unique genetic flaw (or predisposition) that underlies all or most cases of autism will be found. It is illogical to try to link factors like prenatal infections or exposure to alcohol and drugs during gestation to genetic conditions or predispositions. Isn’t it just as illogical to presume that genetic predispositions contribute to complications at birth? Birth has always been recognized as difficult and dangerous. Experiments with monkeys on the effects of asphyxia at birth were undertaken to try to better understand the hazards of birth, and to minimize these hazards. The monkeys subjected to asphyxia at birth had no genetic predisposition for the resulting brain damage.

How the brain is affected by all of the conditions associated with autism should be the focus of research. How infections, alcohol, mercury, lead, toxic chemicals, and oxygen insufficiency affect the brain is known and recorded in the medical literature. Auditory nuclei in the brainstem have repeatedly been found vulnerable. The inferior colliculi in the midbrain are most severely affected by any factor that leads to a catastrophic disruption of aerobic metabolism, whether by a poisonous substance, suffocation, circulatory arrest, or an especially virulent infection [18-23].

Unfortunately much of the evidence reported in the past is ignored by many researchers, because they tend to limit searches for background information to the past five, ten, or twenty
years. Important data, like those on brain damage caused by asphyxia at birth, are all but lost in the dustbin of forgotten history; and these experiments can never be repeated because of restrictions on use of laboratory animals.

References

Etiologic Conditions Associated with Autism

Non-genetic Predispositions for Autism:

1. Prenatal exposure to alcohol and/or other drugs
   h. Stromland K et al. (1994) Autism in thalidomide embryopathy: a population study.

2. Infectious encephalitis
   d. Townsend JJ et al. (1975) Progressive rubella panencephalitis: Late onset after congenital rubella.
   e. Weil et al. (1975) Chronic progressive panencephalitis due to rubella virus simulating subacute sclerosing panencephalitis.


3. Lead poisoning
   c. Eppright TD et al. Attention deficit hyperactivity disorder, infantile autism, and elevated blood-lead: a possible relationship.

4. Seizure disorder/ neurologic damage

5. Perinatal complications
s. Badawi N et al. (2006) Autism following a history of newborn encephalopathy: more than a coincidence?
w. Jangaard KA et al. (2008) Outcomes in a population of healthy term and near-term infants with serum bilirubin levels of \( \geq 325 \) micromol/L (\( \geq 19 \) mg/dL) who were born in Nova Scotia, Canada, between 1994 and 2000.

Genetic/Metabolic Predispositions for Autism:

6. Neurolipidosis  

7. Tuberous sclerosis  

8. Neurofibromatosis  
   b. Gaffney GR et al. (1987a) Midsagittal magnetic resonance imaging of autism.  

9. Phenylketonuria (PKU)
   b. Williams RS et al. (1980) Autism and mental retardation: Neuropathologic studies performed in four retarded persons with autistic behavior.
   e. Leuzzi V et al. (1995) Biochemical, clinical and neuroradiological (MRI) correlations in late-detected PKU patients.

10. Fragile X syndrome

11. Chromosomal disorders

12. Leber's Congenital Amaurosis

13. Adenylosuccinate Lyase Defect

14. Lactic Acidosis

15. Krebs Cycle (aerobic metabolism) Defects

16. Mitochondrial Disorders

**Brain maturation and vulnerability to toxic substances, infections, and anoxia**

17. Maturation of the brain

18. Effects of alcohol

19. Infections
   a. Jereb M et al. (2005) Herpes simplex virus infection limited to the brainstem.

20. Lead

21. Mercury
   Oyanagi et al. (1988) The auditory system in methyl mercurial intoxication: a neuropathological investigation on 14 autopsy cases in Niigata, Japan

22. Toxic substances

23. Anoxia
   b. Janzer RC & Friede RL (1980) Hypotensive brain stem necrosis or cardiac arrest encephalopathy?
**TABLE 1: Medical disorders associated with autistic behaviors**

<table>
<thead>
<tr>
<th>Disorders</th>
<th>Citations</th>
</tr>
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<tbody>
<tr>
<td><strong>Metabolic/ Constitutional:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Neurolipidosis</td>
<td>Creak (1963), Darby (1976)</td>
</tr>
<tr>
<td>12. Intestinal Inflammation</td>
<td>Wakefield et al. 1998</td>
</tr>
<tr>
<td><strong>Prenatal Exposure To Drugs:</strong></td>
<td></td>
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<tr>
<td>2. Valproic Acid</td>
<td>Christianson et al. (1994), Williams &amp; Hersh (1997), Williams et al. (2001)</td>
</tr>
<tr>
<td>3. Thalidomide</td>
<td>Stromland et al. (1994)</td>
</tr>
<tr>
<td><strong>Infectious Encephalitis:</strong></td>
<td></td>
</tr>
<tr>
<td>1. Prenatal Rubella</td>
<td>Desmond et al. (1970), Chess (1971), Townsend et al. (1975), Weil et al. (1975), Chess et al. (1978)</td>
</tr>
<tr>
<td>3. Epstein-Barr virus</td>
<td>Domachowske et al. (1996)</td>
</tr>
<tr>
<td><strong>Obstetric Suboptimality:</strong></td>
<td></td>
</tr>
<tr>
<td>1. In Twins</td>
<td>Folstein &amp; Rutter (1977), Steffenburg et al. (1989)</td>
</tr>
<tr>
<td>2. Meconium Aspiration (?)</td>
<td>Matsuishi et al. (1999)</td>
</tr>
</tbody>
</table>
Figure 6:
Time span of myelin formation in the human brain from fetal months through the third decade of life. Note that myelin continues to form in the intra-cortical association areas (25) into the third decade, as does the reticular formation in the brainstem (9). Myelin formation in the stato-acoustic tectum (3) appears to be complete before birth, whereas myelinization of the acoustic radiations (17) continues during the first four years of life when learning to speak is essential for ongoing development. From Yakovlev and Lecours 1967 [17a].