Perinatal complications

A lapse in respiration at birth has been shown to interfere with metabolic activity in auditory nuclei like the inferior colliculus [1]. Therefore the effects of birth injury should be considered relevant in cases of developmental language disorder. However, the research with monkeys subjected to asphyxia is now totally overlooked. The researchers themselves described the brainstem lesions caused by asphyxia as possibly responsible for “minimal cerebral dysfunction” (MCD), a condition apparently not regarded to have potentially bad long-term effects.

Ranck and Windle (1959) did note the similarity of the brainstem lesions caused by asphyxia to the pattern of brainstem nuclei stained by bilirubin in kernicterus [2]. Auditory problems of children with kernicterus (or erythroblastosis fetalis) had been discussed in the literature [3]. Gilles (1963) commented on the similarity of brainstem lesions caused by asphyxia to the neuropathology observed in Moebius syndrome, and he proposed that impairment of auditory nuclei by asphyxia at birth should be investigated as a possible cause of aphasis disorders in childhood [4]. Gilles’ comments were published in a brief abstract of conference proceedings, which is not even listed in the online PubMed Index, and does not seem to have published anything more on this subject since. Gilles appears to be the first person to suggest a possible link between auditory system impairment and developmental language disorder. The abstract of his presentation is shown in figure 7.

Children normally learn to speak “by ear,” and more easily than adults learn a second language before learning to read. Auditory problems have long been recognized in children with autism [5]. The possible association of auditory system dysfunction and difficulties learning to speak should therefore not be neglected.

Perinatal complications have been documented more frequently than any other medical condition in the records of children with autism, yet still are not viewed as a causal factor (see citations 5a-t in the section 1 above, and 6a-c below). Difficulties at birth are most often attributed to some vague hypothetical genetic predisposition. Statistics on complications at birth are tabulated with at best some passing remark about effects on the brain, with no consideration of how the disabilities so characteristic of autism might result.

Juul-Dam et al (2001) described the perinatal factors associated with autism as "mild" and without any unifying feature [6a]. But the unifying feature of all perinatal complications is the possibility of a lapse in respiration, and no lapse in oxygen delivery should ever be viewed as "mild." Oxygen is the most essential and urgent on-going need of all species dependent upon aerobic metabolism.

Table 2 is a list of excerpts from papers that point to complications at birth as a predisposition for developing autism. Many of these papers attempt to show that the problem at birth was due to some (as yet not understood) defect in the fetus or the mother. But problems like abnormal presentation, such as breech birth or being born with the umbilical cord around the neck, can happen in any birth. Birth has long been acknowledged to be hazardous both for
infant and mother. To place blame on the fetus or mother is senseless and stigmatizing. Children with classic autism (as described by Kanner) are physically perfect. Children identified with “minor birth defects” are likely those who suffered prenatal infection or exposure to alcohol or other toxic substances.

Bodier et al. (2001) in an investigation of 295 cases of autism in France, found only one third had no discernable medical condition, but perinatal problems had occurred in 77 percent of the children without other medical problems [6b].

Matsuishi et al. (1999) investigated the occurrence of autistic disorder in 5,271 infants followed after discharge from a neonatal intensive care unit in Japan [6c]. Of these infants, 18 were later diagnosed as autistic and 57 with cerebral palsy. The incidence of 18 among 5,271 (34 per 10,000) was noted to be more than twice the highest prevalence rate previously reported in Japan. The most significant risk factor associated with autism was meconium aspiration, which might indicate a degree of asphyxiation great enough for the infant to have begun gasping for air before birth. Different risk factors were found for cerebral palsy.

References

1. Auditory system damage caused by asphyxia at birth
   b. Myers RE (1972) Two patterns of perinatal brain damage and their conditions of occurrence.

2. Kernicterus-like damage caused by asphyxia at birth

3. Auditory impairments in kernicterus
   b. Keleman G (1956) Erythroblastosis fetalis

4. Childhood aphasis disorders?
   a. Gilles FH (1963) Selective symmetrical neuronal necrosis of certain brain stem tegmental nuclei in temporary cardiac standstill.

5. Auditory impairments in autism

6. Perinatal complications and autism
Selective Symmetrical Neuronal Necrosis of Certain Brain Stem Nuclei in Temporary Cardiac Standstill. F. H. Gilles, Baltimore, Md.

Selective symmetrical neuronal necrosis of certain tegmental nuclei of the brain stem was found in 3 individuals who had survived temporary cardiac standstill for variable periods of time. Included among these nuclei were sensory and motor nuclei of several cranial nerves, including the third. Necrosis also occurred in cells of the inferior colliculi, certain cell groups of the reticular substance, and in the lateral cuneate nuclei; occasionally, entire nuclei were destroyed. The basis pontis remained intact in all cases. In 2 of the cases, cerebral cortex, basal ganglia, thalamus, and cerebellar cortex showed the expected necrosis. In one case, an 18-month-old child who had had cardiac standstill following drowning, the cerebral and cerebellar cortex remained virtually intact. The distribution of the lesions was not dependent upon specific arterial supply areas, nor did it follow the pattern of "secondary" alterations observed in brain swelling and increased intracranial pressure caused by space-occupying lesions. The distribution pattern of the tegmental pathology is compared with that of nuclear lesions described in experimental neonatal asphyxia and in human cases of kernicterus. The suggestion is made that certain congenital brain stem nuclear "aplasias," for example, Moebius syndrome, may be related to temporary prenatal or perinatal cardiac failure.

Figure 7:
Abstract of Gilles' presentation describing brainstem damage in three cases of cardiac arrest, comparing these to lesions caused by neonatal asphyxia [in experiments with monkeys] and in human cases of kernicterus, and suggesting that "congenital brainstem aphasias," or developmental language disorders might be the result in human conditions like Moebius syndrome.
Table 2: Perinatal complications associated with autism
Excerpts from each paper are quoted.

   “During childhood and adolescence, VLBW children are reported to exhibit greater internalizing and externalizing behavior problems than their peers, as well as attentional difficulties and hyperactivity. Difficulties with social integration including excessive shyness, withdrawn behavior, and poor social skills are also described. ... we have identified several factors that seem to increase the risk for positive MCHAT scores in these children, including lower birth weight and gestational age, male gender, prenatal infection...”

   “Infants were excluded if they had documented Rh factor isoimmunization, significant congenital anomalies, severe peripartum asphyxia with Apgar scores of <3 at 5 minutes of age, or documented hypoxic-ischemic encephalopathy.” Outcomes of 56019 infants were analyzed. “During the study period, there were no reported cases of kernicterus... The risk of cerebral palsy was not increased significantly in the hyperbilirubinemia group... The risk of developmental delay was significantly increased in the moderate hyperbilirubinemia group... There was a significant increase in the risk of attention-deficit disorder... A nonsignificant increase in the risk of autism was seen with exposure to moderate and severe bilirubin levels.”

   "Most outcome studies have focused on neurological functioning and severe deficits in young children (<4 years). In general, very few children with mild encephalopathy show neurological impairments or have developed severe mental or motor retardation at preschool age. ... Only a few studies looked at the behavioral consequences of NE. Those studies found elevated rates of hyperactivity and autism in children with moderate NE."

Table 2 – continued on next page

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Table 2, page 2


"According to our review, 3 parental characteristics and 2 obstetric conditions emerge as potential risk factors for autism: namely, paternal age, maternal age, maternal immigration, growth restriction, and newborn hypoxia. In analyses that adjusted for confounding variables, these factors usually remained statistically significant."


"We also found strong associations between children with infantile autism and mothers with foreign citizenship, children with congenital malformations and children who needed treatment at Neonatal Intensive Care Unit (NICU) after birth. When the caesarean sections were categorized into scheduled and unscheduled procedures, we found only scheduled caesarean sections to be associated with infantile autism."


"... in a population-based study of moderate and severe term newborn encephalopathy (NE) in Western Australia ... infants with NE were 5.9 (95% CI 2.0–16.9) times more likely to be diagnosed with an ASD than controls... this was not an expected association at the outset of the study"


“The mean gestational age of the autism group was significantly older than that of the controls. The mean birth weight of the autism group was also significantly higher ... Frequent neonatal complications included hyperbilirubinemia, history of phototherapy, premature birth (less than 37 weeks), asphyxia, post-term birth of 42 weeks or longer, fetal distress, and complications of respiratory distress ...”


"In the unadjusted analyses, breech presentation, low Apgar score (less than or equal 7) at 5 minutes, low birth weight (less than or equal 2,500 g), gestational age at birth of less than 35 weeks, and being small for gestational age were associated with a statistically significantly increased risk of autism..."

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   "Five children had an Apgar score of 6 or under at 1, 5, or 10 minutes, and 3 of these had scores of 1 or 2 (i.e., they had severe postnatal asphyxia). ... Of the 100 individuals, 58 had one or more remarks in their birth- or perinatal records about a serious problem in the peri-/neonatal period."

   "For 58 of 99 children, some kind of abnormality was noted in their neonatal record. ... Twenty-two had had hyperbilirubinemia (plasma bilirubin more than 200μmol/l), ... Hyperbilirubinemia occurs in about 10% of newborn infants... Forty-five of 92 children (49%) for whom fairly detailed data about early language development were available, clearly did not have normal language development at 2 years of age. It cannot be concluded that the remainder had normal language development."

   "Cases were more likely to have experienced fetal distress during labor (OR, 1.64; 95% CI, 1.15-2.34). Apgar scores calculated at 1 minute showed that significantly more cases achieved a score of 6 or less (54 [19.5%] of 277 cases with data recorded since 1991)."
   "[12.9%] of 512 control subjects with data recorded since 1991 (OR, 1.6; 95% CI, 1.1-2.4), and cases were more likely to have taken more than 1 minute before the onset of spontaneous respiration (OR, 1.4; 95% CI, 1.0-1.9)."

   "... 5 items were found to significantly predict group membership (prescriptions taken during pregnancy, length of labor, viral infection, abnormal presentation at delivery, and low birth weight)."

   "The risk of autism was associated with daily smoking in early pregnancy (OR = 1.4; CI = 1.1-1.8), maternal birth outside Europe and North America (OR = 3.0; CI = 1.7-5.2), cesarean delivery (OR = 1.6; CI = 1.1-2.3), being small for gestational age (SGA; OR = 2.1; CI = 1.1-3.9), a 5-minute Apgar score below 7 (OR = 3.2, CI = 1.2-8.2), and congenital malformations (OR = 1.8, CI = 1.1-3.1). Note: The OR (odds ratio) was greatest for 5-min Apgar score below 7."
Table 2, page 4

"Children with autism spectrum disorders have lower optimality (higher rates of complications) than unaffected siblings..."

"In a sample of families selected because each had exactly two affected sibs, we observed a remarkably high proportion of affected twin pairs, both MZ and DZ..."

"Among the children with a serious medical condition, 34.4% also had ante- or perinatal antecedents. Among the 33% without any medical factor, 77% also had ante- or perinatal antecedents."

"... specific complications that carried the highest risk of autism and PDD-NOS represented various forms of pathologic processes with no presently apparent unifying feature."

"AD was identified in 18 of the 5,271 children and the incidence was 34 per 10,000 (0.34%). This value was more than twice the highest prevalence value previously reported in Japan. Children with AD had a significantly higher history of the meconium aspiration syndrome (p = .0010) than the controls. Autistic patients had different risk factors than CP." Note: CP (cerebral palsy) occurred in 57 of the 5,271 children."
Table 2, page 5

"...[obstetric] optimality score (OS), were compared in two groups: 78 families containing an autistic proband (ICD-10 criteria) and 27 families containing a down syndrome (DS) proband... RESULTS: Autistic and DS probands had a significantly elevated OS compared with unaffected siblings, regardless of birth order position. The elevation was mainly due to an increase in mild as opposed to severe obstetric adversities."

"Males with AS showed a trend toward lower Apgar scores at one minute."

"These data provide slight support for the contribution of nonspecific pre- and perinatal factors to other etiological bases of autism."

"In most of the pairs discordant for autism, the autistic twin had more perinatal stress."

"Abnormal presentation at birth is the only factor that occurred more frequently for the autistic sample..."

"There were more complications of labour in the experimental group than the controls (p=0.001) ...Abnormal conditions of the child noted at delivery occurred significantly more frequently in the experimental group, e.g. difficulty with resuscitation, cord around neck, fractured skull, cyanosis, head moulding, bruising, jaundice (p<0.0004)."

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