Developmental Disabilities – Impairment of Children's Brain Development and Function: The Role of Environmental Factors

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Summary

Learning disabilities, attention deficit hyperactivity disorder, developmental delays, and emotional and behavioral problems are among childhood disabilities of increasing concern. Interacting genetic, environmental, and social factors are important determinants of childhood brain development and function. For many reasons, however, studying neurodevelopmental vulnerabilities in children is challenging. Moreover, inadequate incidence and trend data interfere with full understanding of the magnitude of the problem. Despite these difficulties, extensive laboratory and clinical studies of several neurodevelopmental toxicants, including lead, mercury, polychlorinated biphenyls, alcohol, and nicotine, demonstrate the unique vulnerability of the developing brain to environmental agents at exposure levels that have no lasting effect in adults. Historically, understanding the effects of these toxicants on the developing brain has emerged slowly while generations of children are exposed to unsafe levels. Unfortunately, with few exceptions, neurodevelopmental toxicity data are missing for most industrial chemicals in widespread use, even when populationwide exposures are documented. The personal, family, and communitywide costs of developmental disabilities are profound. In addition to the need for more research, a preventive public health response requires mitigation of exposures to potential neurodevelopmental toxicants when available evidence establishes the plausibility of harm, despite residual toxicologic uncertainties.

The Scope of the Problem

In the United States nearly 12 million children under 18 years of age (17%) suffer from deafness, blindness, epilepsy, speech deficits, cerebral palsy, delays in growth and development, emotional or behavioral problems, or learning disabilities (Boyle et al. 1994). Learning disabilities alone affect 5-10% of children in public schools (Parrill 1996). Attention deficit hyperactivity disorder (ADHD) conservatively affects 3-6% of all school children. (Goldman et al. 1998.) A recent survey from the Centers for Disease Control and Prevention (CDC) reports that parents of approximately 1.6 million elementary school-aged children (7 percent of children 6-11 years of age) reported ever being told by a doctor or health professional that their child had ADHD.

The incidence of autism may be as high as 2 per 1,000 children. The number of children entered into the California autism registry increased by 210% between 1987 and 1998,

and the rate in increase continues to rise. (California Health and Human Services 1999; Byrd 2002). According to the California Department of Developmental Services, the latest figures show that autism accounted for 36% of all the intakes during the first quarter of 2002. Improved reporting and differing diagnostic definitions undoubtedly explain some of the increases in disorders of neurological development (neurodevelopmental disorders) but do not explain for the entire pattern (Byrd 2002).

Causes

Genetic, environmental, and social factors interact in complex ways to determine how the brain develops and functions. Heredity alone accounts for, at most, about 50% of the variation in cognitive, behavioral, and personality traits among individuals (Plomin et al. 1994).

Among genetic factors, single gene disorders are uncommon causes of impaired brain development. An example is phenylketonuria (PKU), a condition that results from an inherited inability to metabolize the amino acid, phenylalanine. PKU causes mental retardation unless it is recognized early and phenylalanine is removed from the diet soon after birth. Every child born in the US is tested for PKU at birth. More commonly, however, multiple subtly acting genes working together exert smaller influences over neurological development. But even after these are taken into account, environmental and social factors are responsible for the other 50% of variability in these traits.

Challenges to Understanding

Interactions among these various influences are important and must not be overlooked. For example, expectant mothers and children living in poverty or decaying urban environments are often disproportionately exposed to harmful environmental contaminants such as lead or industrial air pollutants. Inherited genetic factors influence the capacity of individuals to metabolize and excrete toxic chemical compounds like, for example, some pesticides that can damage the developing brain or other nerve tissue. (Rosenman and Guss 1997; Costa et al. 1999) These interactions make it difficult to identify precisely the contribution of each genetic, social, or other environmental factor to the risk of a disability in a given individual.

Studying these problems in children is challenging for a variety of other reasons as well. Professionals often use different definitions for common terms like, for example, attention deficit hyperactivity disorder (ADHD), autism, or learning disabilities. Differing definitions complicate efforts to compare conditions in groups of children and to follow trends over time. The use of diagnostic labels is also quite inconsistent when the severity of symptoms varies. Behavioral problems, for example, may range from mild attention deficits to severe conduct disorders. A child may have only mild impairment of social skills or severe and disabling autism. Learning-related disorders may be mild or associated with severe mental retardation. Moreover, some traits typical of one diagnostic category are likely to be found in another as well. For example, up to 50% of children with ADHD have a learning disability and 30-80% have a conduct disorder (Baumgaertel et al. 1996).

When studying the contribution of toxic environmental chemicals to these disorders it is important, but frequently difficult, to accurately measure or estimate exposures to toxic chemicals. This is particularly problematic when the relevant exposure may have occurred in the fetus during pregnancy or during early childhood but the impact did not become apparent until much later. Finally, even when there appears to be an association between exposure to a toxic chemical and abnormality of brain development, researchers often disagree about when a cause-and-effect relationship has been demonstrated or how large an exposure is necessary to cause the effect. As a result, there is often considerable debate and disagreement about the role that environmental factors play in some commonly encountered disorders of brain development and function.

Varying Scientific Approaches

Toxicologists interested in studying the impacts of chemicals on brain development typically attempt to identify specific traits rather than syndromes that result from exposures. These traits may include attention deficits, specific learning or memory problems, or discrete behavioral problems like impulsiveness or aggression. Conversely, healthcare providers and educators are more likely to search for diagnostic categories that describe the collection of traits that they identify in an individual. ADHD, for example, is a mixture of problems of paying attention and controlling impulsive behavior. Autism can be a complex mixture of impaired social interaction, repetitive patterns of behavior, hyperactivity, and attention deficits.

Toxicologists can more easily study the impacts of chemicals on specific tests of attention than on a mixture of attentional and behavioral problems. Similarly, toxicologists can study specific learning or memory skills or behaviors as traits that are then sometimes grouped together to form a diagnosis like, for example, autism, Asperger's syndrome, pervasive developmental disorder, or non-specific learning disabilities. For the purposes of studying the causes of developmental disabilities and opportunities for prevention, explicit consideration of traits, as well as diagnostic categories, provide important insights.

Brain Development and the Impact of Specific Toxicants

Brain development begins early in embryonic life and continues well beyond birth into adolescence. During development, brain cells divide, migrate to the proper place in the brain, differentiate into specialized cell types, establish connections (synapses) with other brain cells to form circuits, and undergo programmed cell death (apoptosis) in an orchestrated sequence of events controlled by many different brain chemicals.

As nerve cells mature, they are coated with a fatty material called myelin that facilitates nerve impulse transmission. Nerve impulses are transmitted from cell to cell by means of chemical messengers called neurotransmitters. These neurotransmitters not only transmit nerve impulses but also play important roles in guiding the development of the brain during fetal life, infancy, and childhood. Interference with any stage of this cascade of events may alter subsequent stages, so that even short-term disruptions may have long-term effects later in life. For this reason, the timing of exposure to neurotoxic chemicals is as important as the size of the exposure. Even a relatively small exposure to a toxic

chemical during a window of vulnerability can have a permanent impact that might not occur if the same exposure happened at another time.

A large amount of research has examined the various ways in which neurotoxic chemicals can interfere with brain development. Chemicals that interfere with cell division, migration, differentiation, synapse formation, programmed cell death, neurotransmitter levels, or combinations of these are well documented. For example, lead interferes with nerve cell differentiation, myelinization, programmed cell death, and nerve impulse transmission. Alcohol interferes with each of these plus cell division, migration, and synapse formation.

Despite the challenges of studying neurodevelopmental disorders in children, a large amount of evidence conclusively documents the effects of a few environmental agents (Schettler et al. 2000). For example, fetal or infant exposure to lead, alcohol, or nicotine impairs normal brain development (Nulman et al. 1988; Eskenazi and Castorina 1999; Rice 1998). With respect to the availability of toxicity information, however, lead, alcohol, and nicotine are the exception rather than the rule. Several additional chemicals, profiled below, have been studied fairly extensively, and incomplete data are available for a few more. The vast majority of chemicals to which people are commonly exposed, however, have never been examined at all for their impacts on the developing brain. Given the vulnerability of the developing brain to chemical exposures, this lack of information is extremely unfortunate and keeps us from more fully understanding the magnitude of the public health threat.

Lead

The impacts of lead on the developing brain have been studied for many years. Lead exposures during infancy and childhood cause attention deficits, hyperactivity, impulsive behavior, IQ deficits, reduced school performance, aggression, and delinquent behavior. (Rice 1998; Needleman et al. 1996) A historical review of our understanding of the impacts of lead on the developing brain shows that exposure levels that were once thought to be "safe" are actually associated with brain damage when children are carefully studied. Even today, the Centers for Disease Control (CDC) is contemplating whether or not to further lower the screening threshold from 10 migrogm/dl blood to 5 microgm/dl blood since impacts have now been documented at these lower levels. (Lanphear et al. 2000)

Mercury

Mercury (Hg) is a potent neurological toxicant and is particularly harmful to the developing brain at low levels of exposure. Dietary fish contaminated with mercury (in the form of methylmercury) is, for many people, the largest source of exposure. Mercury easily crosses the placenta and enters the fetal brain where it disrupts many different processes necessary for normal brain development. (Atchison and Hare 1994; Sager 1988; Sager and Matheson 1988).

Large prenatal methylmercury exposures cause psychomotor retardation, seizures, developmental delays, and mental retardation (Harada 1978; Amin-Zaki et al. 1976). Much smaller prenatal exposures can impair IQ, language development, visual-spatial skills, gross motor skills, memory, and attention in offspring (Crump et al. 1998; Grandjean et al. 1997).

As with lead, a historical review of our understanding of the toxicity of mercury in the developing brain shows that more refined testing has resulted in a steady decline in the exposure level thought to be "safe" and without adverse effects. The U.S. Environmental Protection Agency (U.S. EPA) has recently developed a reference dose for mercury of 0.1 µg Hg/kg/day. Maternal exposures at or below this level are thought unlikely to increase the risk of harm to the developing fetal brain. A committee of the National Academy of Sciences supports the validity of this reference dose (National Research Council 2000). Unfortunately, according to the EPA, 52,000-166,000 pregnant women in the United States consume fish contaminated with mercury at levels at or above this reference dose (U.S. EPA 1997). A population survey conducted by the CDC indicates that more than 10% of women of reproductive age in the US have blood mercury levels that may increase the risk of impaired brain development in their children (CDC 2001). [An more extensive survey published in 2003 suggests this percentage may be closer to 8%.]

Manganese

The toxicity of manganese (Mn) in the brain from workplace exposures is well known. Symptoms include gait and movement disorders, and in some cases, inappropriate behavior. More recently, the toxicity of manganese in the developing brain has come under increased scrutiny. In several small studies of children, manganese hair levels are associated with ADHD (Collipp et al. 1983; Pihl and Parkes 1977; Crinella et al. 1998). Exposure to manganese in developing laboratory animals is also associated with hyperactivity (Boyes and Miller 1998).

At low levels, manganese is an essential dietary trace element. That is, we need small amounts in order to develop normally and stay healthy. Concerns center, however, on the effect of getting too much manganese. The concentration of manganese in human breast milk is about 6 µg Mn/L, whereas infant formula may contain 77-100 µg Mn/L, depending on whether it has been supplemented. Soy formula may naturally contain as much as 200-300 µg Mn/L because soybean plants easily extract manganese from the soil. (Dorner et al. 1989; Lonnerdal 1994). Compared to adults, children and immature animals absorb more and excrete less manganese (Mena 1974; Dorner et al. 1989). Moreover, in infants, manganese easily gains access to the developing brain.

These observations raise questions about the wisdom of supplementing infant formula with manganese and the widespread use of infant soy formula containing naturally high concentrations of manganese. They also further concerns about the use of gasoline supplemented with an organic manganese compound as an octane enhancer in the United States and Canada. The Ethyl Corporation (Richmond, VA, USA), the U.S.-based manufacturer of the additive, claims there is no evidence to support concerns that

manganese in gasoline represents a threat to public health--an argument that is eerily reminiscent of their position on the use of tetraethyl lead many years ago. Under provisions of the North American Free Trade Agreement (NAFTA) (International Joint Commission 1972), the Ethyl Corporation brought legal action against Health Canada for blocking access to Canada's gasoline market. Health Canada ultimately decided to settle, not only allowing the additive onto the market but also agreeing to pay Ethyl Corporation an estimated $10 million for legal costs and lost income (McCarthy 1998). Meanwhile, available data indicate that the brain is vulnerable to long-lasting effects from developmental exposures to manganese.

Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are industrial chemicals used in the US and throughout the world for decades in electrical equipment, paints, and as lubricants. Their manufacture was banned in the US in 1977 because of concerns that they could cause cancer. Since then, additional health impacts have become apparent, including impairment of normal brain development. Unfortunately, PCBs are persistent in the environment. Consequently, most of the PCBs that were ever produced are still present somewhere, whether in an electrical transformer, soil, landfill, or river or lake sediments. PCBs are soluble in fat and tend to concentrate as they move up the food web. As a result, PCBs continue to contaminate the food supply. People are exposed primarily through eating PCB-contaminated meat, processed food, dairy products, or fish.

The impacts of polychlorinated biphenyls (PCBs) on brain development have been examined in several large human studies where exposures during fetal development were measured by sampling maternal or umbilical cord blood or breast milk. Fetal exposures to PCBs at current environmental levels cause impaired reflexes, delays in developing motor skills, delayed cognitive development, hyperactivity, and IQ deficits (Jacobsen and Jacobsen 1990; Jacobsen and Jacobsen 1996; Patandin et al. 1999; Lonky et al. 1996; Stewart et al. 2000). Impaired learning, altered behavior, and hyperactivity have also been demonstrated in laboratory animals (Rice and Hayward 1997; Rice 1999).

Many scientists are studying the mechanisms by which PCBs interfere with brain development. (Zoeller et al. 2000; Brouwer et al. 1999; Osius et al. 1999; Tilson 1997; Koopman-Esseboom et al. 1994) One mechanism that seems particularly important is interference with normal thyroid hormone function. Because thyroid hormone is essential for normal brain development, the effects of PCBs and other chemicals that interfere with thyroid hormone function are of particular concern. A recent study (Haddow et al. 1999) of women with hypothyroidism during pregnancy showed the extreme sensitivity of the developing brain to even mildly depressed or low-normal thyroid hormone levels. At 7-9 years of age, offspring of these women were more likely than the offspring of mothers with normal thyroid function to perform poorly on tests of attention and word discrimination.

Flame Retardants

Polybrominated diphenyl ethers (PBDEs) are widely used as flame retardants in consumer products and are detected in increasing concentrations in human breast milk

and fat tissue. (Meironyte et al. 1999) PBDEs are structurally similar to PCBs and also interfere with normal thyroid hormone function (Darnerud et al. 2001) Some pesticides, such as dicofol, pentachlorophenol, dinoseb, and bromoxynil, also interfere with normal thyroid hormone function. (Meerts et al. 2000). Animal tests show that PBDE exposures during brain development cause hyperactivity and interference with memory and learning when the animal grows up (Eriksson et al. 2002) The impacts of these chemicals on humans have not been studied, yet human exposures are widespread (Darnerud et al. 2001; Needham et al. 1995).

Pesticides

Limited data describe the effects of exposures to neurotoxic pesticides on the developing brain. In laboratory rodents a single low-level exposure to an organophosphate pesticide or a pyrethroid on day 10 of life causes permanent changes in the brain and hyperactivity when the animal is tested at 4 months of age (Ahlbom et al. 1995; Eriksson et al. 1991). Organophosphate and pyrethoid pesticides are among those most commonly used in the home and on gardens as well as in commercial agriculture. A study of Mexican children exposed to a mixture of agricultural chemicals showed impacts on motor skills, memory, attention, and learning (Guillette et al. 1998).

The general lack of neurodevelopmental toxicity data for agricultural chemicals is of particular concern because of their widespread use and ubiquitous exposures. Population-based studies in the United States show that over 90% of children have detectable urinary residues of just one of the neurotoxic organophosphate pesticides. Specimens analyzed for residues of 30 pesticides showed that >50% of the population contained at least six (Needham et al. 1995). One study examined the meconium (first baby bowel movement) of newborns and found residues of organophosphate pesticides in each of them, documenting fetal exposure during critical periods of brain development. (Whyatt and Barr 2001)

Alcohol and Other Solvents

Alcohol and other solvents cross the placenta exposing the fetus during development. Fetal alcohol exposure causes hyperactivity and learning and IQ deficits. (Nulman et al. 1988). Depending on the timing and amount of the exposure, some fetuses exposed to alcohol develop fetal alcohol syndrome. They may have slightly abnormal development of their faces and heads and the most severely affected may be mentally retarded.

Toluene is another solvent that can impair brain development in ways similar to alcohol. (Kostas and Hotchkin 1981; Pearson et al. 1994; Jones and Balster 1997; Jones and Balster 1998; Hougaard et al. 1999;) Most studies of toluene have been done in laboratory animals, but some human studies have been done on children whose substance-abusing mothers sniffed glue during pregnancy. In these cases, their children showed deficits in learning, speech, and motor skills. The impacts of lower level exposures to toluene from consumer products like gasoline, nail polish, glues, and cleaning agents have not been adequately examined.

The impacts on the developing brain of other solvents like xylene, styrene, and trichloroethylene, among others, have not been studied in humans. These are solvents that are also widely used in glues, paints, resins, gasoline, cleaning products, or other consumer items. However, limited animal studies show that these, too, can impair normal brain development and function, sometimes at exposure levels that are similar to what pregnant women might encounter in the workplace or during use of some consumer products in the home. Offspring of these animals show altered activity levels and impaired motor skills, learning, and memory. (Dorfmueller et al. 1979; Mirkova et al. 1983; Taylor et al. 1985; Shigeta et al. 1989; Khanna et al. 1991; Hass et al. 1995).

Conclusions

Developmental delays, learning disabilities, ADHD, and behavioral disorders extract a terrible toll from children, families, and society (Cramer and Ellis 1996). Children with ADHD are at risk for failure in the classroom and later in the workplace. Individuals with learning disabilities have a more difficult time keeping a job, learning new skills, and getting along with co-workers. Children with learning disabilities are often alienated, isolated, and misunderstood. Some developmental disabilities increase the risk of substance abuse, delinquency, criminal behavior, and suicide.

Families of children with learning, developmental, or behavioral disorders experience additional stress. The costs associated with caring for these children can be high for families and society. Special education programs and psychological and medical services drain resources. When services are unavailable, children, families, and communities suffer in numerous ways.

The neurodevelopmental effects of relatively few compounds encountered in the ambient environment are well characterized. Yet, even these limited data highlight the profound vulnerability of the developing brain. Moreover, comparisons of animal and human data for lead, mercury, and PCBs show that laboratory animal studies tend to underestimate human neurodevelopmental sensitivity by 100-10,000 fold. (Rice et al. 1996). In each case, what was considered a "safe" exposure level was continuously revised downward as human data became available.

Unfortunately, neurodevelopmental data are lacking for the large majority of known or suspected neurotoxic chemicals. Regulatory agencies have generally failed to require neurodevelopmental testing of chemicals before they are marketed. None of the voluntary testing programs proposed by the chemical industry in the United States includes neurodevelopmental testing.

Although we can do little about genetic contributions to many of these developmental disorders, we have enormous opportunities to reduce exposure to chemical environmental contaminants that interfere with normal brain development. Sufficient evidence has accumulated to permit better understanding of the hazards of exposure to neurotoxic chemicals. Clearly, more comprehensive pre- and postmarket neurodevelopmental testing of chemicals to which humans and wildlife are likely to be exposed is essential. Residual scientific uncertainty, however, cannot be an excuse for avoiding precautionary action

when available evidence establishes the plausibility of harm. Exposures to these chemicals known or suspected to damage the developing brain can and should be reduced or eliminated.

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