Neurologic Concepts of Lead Poisoning in Children

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Two important changes in the approach to childhood lead poisoning occurred in 1991. First, the Centers for Disease Control lowered the "concern" blood level for lead exposure in children from 25 μg% to 10 μg%. This change was made in response to clinical studies showing adverse neurobehavioral outcomes in children with low-level lead exposures. Because more than four million children in the United States exceed this new standard, an enormous number are now officially recognized as at risk for neurologic deficit from lead in the environment. Exposure to these low levels of lead in utero and during the first 5 years of life are thought to be most damaging, and the deficits in neurologic function appear to persist into adulthood.

The second change for 1991 was a therapeutic one with the approval by the Food and Drug Administration (FDA) of a new oral chelating agent for the treatment of lead poisoning. Dimercaptosuccinic acid (DMSA) was approved for general use in early 1991 as an orphan drug alternative for calcium ethylenediaminetetraacetic acid (EDTA), the parenteral administration of which has been standard therapy for lead poisoning during the past 30 years. In initial trials, DMSA was well tolerated with a low incidence of serious side effects. Transient elevations of liver enzymes and rare instances of mild leukopenia at recommended doses and lightheadedness at high doses have been recorded. Because of its orphan drug status, only a few hundred patients have been treated with DMSA under the auspices of FDA reporting. Because DMSA is a sulfur drug, the allergic reactions noted with similar agents should be expected as more children are given DMSA. At present, chelation...
therapy using either DMSA or EDTA is recommended when blood lead levels exceed 45 µg% or are rapidly rising, implying a risk for acute encephalopathy and its neurologic complications.

The approval of a new oral chelating agent for the treatment of undue lead exposure occurring almost simultaneously with the official recognition of the risk for subtle but lasting neurobehavioral problems from lower lead exposures has opened a controversy about the management of children with blood lead levels between 10µg% and 44 µg%. These children are not at immediate risk for acute encephalopathy, and the ability of chelation therapy to alter their neurobehavioral outcome is unknown.

A study of the potential use of DMSA for the prevention of neurobehavioral deficits rather than prevention of acute encephalopathy is currently under consideration by a review panel at the National Institute of Environmental Sciences. The efficacy of this treatment may be difficult to evaluate given the complex interplay of other environmental and social issues that influence cognition and behavior in children. Added to the challenge is the fact that many children return to lead-contaminated homes after chelation therapy. It should be pointed out that the administration of chelator therapy while a child is living in a lead-containing environment is potentially dangerous because these agents can enhance the intestinal absorption of lead. At present, the best management for most children with modest elevations above the new 10 µg% guideline is removal of the child from the ongoing exposure to lead followed by repeat blood monitoring. Avoidance of exposure in the first place has to be the ultimate goal, and this will involve a concerted effort to identify, avoid, or abate the two million housing units in this country contaminated with unstable lead surfaces. Studies are currently underway to evaluate different approaches to housing abatement and identify the least dangerous and most cost-effective approach.

Lead has been recognized as a potent neurotoxicant since antiquity, but the clinical syndrome of acute lead encephalopathy of childhood was not appreciated until its description in Australia during the early 1890s. The association between lead paint as the primary source of exposure for children was made soon thereafter, and lead was banned from interior house paint in Australia and most of western Europe in the early 20th century. Unfortunately, the United States was much slower to act and did not ban lead from house paint until 1973. The reasons for this delay are reviewed elsewhere. Like the many advertisements for white lead paint correctly claimed, lead paint lasts a very long time and is the predominant source of exposure today for children living in homes built prior to 1973. Lead paint was even used on baby cribs until prohibited by legislation. Until recently, gasoline was another major source of lead contamination of the environment and is now known to have contributed to a considerable fraction of human exposure. With the introduction of lead-intolerant catalytic converters and subsequent elimination of lead from gasoline, this exposure decreased and blood lead levels dropped.

The nature of lead absorption from the gastrointestinal tract and the pulmonary epithelium is not fully understood despite years of investigation. It is generally agreed that iron deficiency, poor nutritional status, low calcium intake, and immaturity are all risk factors associated with enhanced absorption and retention of ingested lead. Attention to these factors, including treatment of the commonly associated iron deficiency, are important components of programs aimed at decreasing lead toxicity in children.

Once absorbed, lead is transported in the blood largely within erythrocytes. The relatively small fraction of lead present in the plasma is mainly bound to protein and other organic molecules leaving very little as the free hydrated ion. The exact mechanism of transfer from these interacting blood pools into bone, brain, and other soft tissues is complex and poorly defined. In some tissues, calcium transport systems may be subverted by lead for its entry into specific cell types. Furthermore, some transporting barrier tissues may accumulate lead and this selective affinity may enhance the vulnerability of transporting epithelium (eg, renal tubular cells) while protecting the parenchymal cells. Such appears to be the case in the brain where lead must traverse the endothelial cells making up the blood-brain barrier before reaching the neurons and their synaptic connections, the probable target site for the neurobehavioral deficits associated with low-level toxicity.

The blood-brain barrier (ie, the brain capillary bed) not only influences lead entry into the brain but is also a determinant in the action of chelators. One goal of chelation therapy is to lower blood levels of lead and mobilize and remove lead stored in skeletal tissue. By limiting the entry of lead into the brain, the risk for further neurologic damage is reduced, and cases of acute encephalopathy are avoided. An additional goal of chelation therapy is removal of lead from the brain. Whether this actually happens is not yet known. Calcium EDTA, for example, does not
cross the blood-brain barrier, and any lowering of brain lead levels in response to EDTA is probably a result of diffusion in a reversal of the entry process. Such a reversal depends on the ability of lead within brain cells to "sense" a concentration gradient driving release from the neurons to the interstitial fluid and then across the brain endothelium back to the bloodstream. Given the complexity of the barrier systems involved, it is possible that lead in neurons does not respond to a drop in blood levels. Once in the brain, lead may remain long after the return of blood lead levels to an acceptable range. Interest in the new chelating agent, DMSA, is enhanced by the suggestion that it may remove lead from the brain.17,18

When blood levels of lead in young children exceed 60 μg% and continue upward toward 100 μg% or greater, the risk for onset of acute encephalopathy dramatically increases.1 Intervention at this point is critical because the encephalopathy may evolve quickly over days from mild lethargy, ataxia, and confusion to coma, convulsions, and severe brain edema. Children who reach this stage may die from complications of increased intracranial pressure, and survivors are often left with major intellectual and behavioral disorders.

Screening programs of environmentally at-risk children without overt signs of encephalopathy have largely eliminated acute encephalopathy with its attendant complications from the contemporary scene. Despite the current emphasis on awareness of lead poisoning, many children are still seen with blood levels that put them in this very high risk state. For example, at the Kennedy Krieger Institute in Baltimore, Dr Julian Chisolm treated four children in 1991 whose blood level exceeded 60 μg% (unpublished data). An additional 29 children were given chelation therapy for blood levels greater than 45 μg% but less than 60 μg%. These numbers do not represent the entire experience of Baltimore City, which has less than 40,000 children between 1 and 6 years of age. Thus, at least one toddler per 1000 in this city was treated for lead poisoning in 1991. The problem is not limited to children living in inner-city poor homes but includes referrals from the more affluent suburbs where older homes are under renovation.

The pathogenesis of acute lead encephalopathy involves a failure in blood-brain barrier function.19 When lead accumulates in the brain microvasculature above a critical threshold, disruption of normal capillary function ensues. The biochemical steps in the cascade of injury appear to involve alterations in cellular calcium metabolism and second messenger signaling systems. Anatomically, the tight intercellular junctions that seal brain endothelial cells together separate and cease to provide a blood-brain barrier. With opening of the tight junctions, there is a rapid influx of plasma into the brain. Because brain tissue does not have lymphatic drainage, fluid accumulates and brain edema rapidly develops. Although the cerebellum and occipital lobes of the cerebrum appear particularly vulnerable, the process is widespread and causes both increased intracranial pressure and disturbances in the normally precise ionic homeostasis of brain interstitial fluid. Brain lead levels also rapidly increase at this time. Coma and convulsions ensue, and irreversible neuronal loss also may occur.

Blood lead levels peak at approximately 18 months of age with a wide band of increase between 6 and 36 months.5 A good correlation exists between this peak in blood lead levels and the normal hand-to-mouth activities seen in toddlers. It is this activity in a house and backyard contaminated with lead in the dust and dirt that provides most of the absorbed lead in children. Although pica of paint chips has the potential for much greater intake of lead, it is a less common source.

Two other factors place the toddler age group at particular risk for injury from lead poisoning. First is the relative efficiency of the gastrointestinal tract in absorbing lead at this age, which may be related to a sharing by lead of the calcium absorption sites that are especially active during rapid growth. Second is the pattern of developmental change in synaptic density that occurs in the toddler brain just when blood lead levels are at their highest.5

At the time of a term birth, all large neuronal cell bodies are in place in the cerebral cortex and basal
ganglia.\textsuperscript{20} The neurons are generated during the first trimester of gestation and then migrate to their adult location before the end of the second trimester.\textsuperscript{21} Synaptic connections among adjacent neurons are sparse prior to birth after which multiple connections and formations of neural networks are made functional. As shown in Figures 1 and 2, these connections become so dense that by 2 years of age, the density and synaptic activity is almost twice that of a normal adult.\textsuperscript{22} Although the actual peak in this process of synapse formation varies in different cortical layers and regions, the pattern remains one of overproduction of connections during the toddler years followed by a progressive pruning of selected synapses until the adult density is achieved late in childhood.\textsuperscript{23} This process allows for considerable postnatal reorganization of the microanatomy of the brain. While the general program of low density of synapses at birth, high density during the toddler years, and pruning to adult levels during late childhood must be under genetic instruction, the choice of which half of the billions of synapses are retained and which half are lost cannot be dictated by the 50,000 genes expressed in the human brain. It is much more likely that synapse retention and loss is determined by the quantity and quality of activity in a particular connection.\textsuperscript{23} This, in turn, is influenced by environmental factors including not only sensory and motor stimulation but the adverse effects of toxins.

Lead is known to disrupt several biochemical events linked to neurotransmitter release that could alter the efficiency of developmental pruning of synaptic connections. By blocking voltage-sensitive calcium channels on the plasma membrane of presynaptic nerve endings, lead may reduce stimulated nerve impulses,\textsuperscript{24} especially in brain regions that accumulate high levels of the toxicant. In addition, lead either mobilizes internal calcium or acts as a calcium agonist within the nerve terminal.\textsuperscript{25} A physiological outcome of this action of lead is the enhanced release of background levels of neurotransmitters. The combination of a decrease in signal driven neurotransmitter release with an increase in the spontaneous release of neurotransmitters means that the stimulus to noise ratios may decrease as lead accumulates in the developing brain. In turn, the processes of synaptic pruning may become less precise leaving a cortical architecture with a normal synaptic density but not necessarily the most efficient connections. If this is the response to lead, the microanatomy of the brain might be altered for years after the toxic exposure.

Protein kinases are enzymes that phosphorylate proteins. In the brain, these kinases appear to alter neurotransmitter release, control the responsiveness of neurotransmitter receptors, regulate ion flux, and trigger gene activation involved in memory formation.\textsuperscript{26} The calcium second messenger systems are major activators of protein kinases in brain, and there is evidence that low levels of lead directly interact and inappropriately stimulate several brain protein kinases.\textsuperscript{27,28} Such an activation at a critical developmental stage could also adversely influence synapse formation, retention, and pruning.

We have proposed that interference with selective pruning rather than more overt neuronal loss underlies the more subtle effects of lead poisoning.\textsuperscript{29} Unlike hypoxia where motor deficits are usually more prominent than intellectual or behavioral changes, low-level lead toxicity appears to alter attention, memory, and problem-solving more than muscle tone and coordination. This argues for a different kind of lesion than the selective sponal loss of neurons provoked by hypoxia or hypoglycemia. The deficiency appears to be more than a physiologic imbalance because it does not improve with time and lowering of blood lead levels. Although proof is lacking, the temporal association between exposure to lead in toddlers with dynamic changes in synapse organization provides the right system at the right developmental stage to explain the lasting changes in neurobehavioral function described in exposed children.

The exact steps by which lead alters neuron function are unknown. In fact, lead may have its primary toxic action in the endothelial cells and astrocytes that control the fluid environment of the brain and provide the hormone and trophic factors that nurture the neurons and their synapses. Abnormal neuronal function and synaptic anatomy could thus be an indirect effect of lead on the support systems of the brain rather than a direct action of lead at the synapse. If this were the case, the more subtle
neurobehavioral deficits of low-level lead exposure would have a similar pathophysiology as the high-level acute encephalopathy.

Although it now seems proven beyond a reasonable doubt that lead is a developmental neurotoxin at very low blood levels, the effect on IQ is small—about five points in the blood lead range under concern. Many other maternal, familial, social, and environmental factors produce similar or greater variations in IQ. Figure 3 shows that even though the changes in IQ are small, when considered from a population perspective, they cause a shift in outcomes so that the lead-exposed population is considered overrepresented at the lower end of cognitive scales and underrepresented at the higher end, which may contribute to the underachievement of the exposed group of children. In-city poor make up the majority of the exposed. Furthermore, while IQ measurements may be the most quantitative and convincing indicator of a lead effect, the behavioral and attentional deficits may actually underlie more of the school failures and poor social adjustments common to the lead-exposed population. These factors should be weighed as social policy is formulated on the large expense of making older homes free of lead.

The medical approach to the treatment of lead poisoning cannot avoid these social issues because the success of chelator and adjunct therapy is contingent upon finding safe, lead-free housing. To prescribe chelators while the child remains in a lead-contaminated home is probably worse than no drug treatment at all. Too often, the choice of the family is living in a lead paint-free project that is rampant with drug abuse and crime to a safer affordable home with unsafe exposure to environmental lead. This dilemma is as important as biochemical mechanisms and medical treatments in coming to terms with lead poisoning in children.

REFERENCES