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Landau-Kleffner: an effective non-surgical treatment

The last ARRI reported on a very rare disorder known as Landau-Kleffner syndrome (LKS), which is sometimes mistaken for autism, and which can be treated with a new surgical technique (ARRI 5/1). Now Israeli researchers Pinchas Lerman, Tally Lerman-Sagie and Sara Kivity report that a non-surgical treatment for Landau-Kleffner syndrome (LKS) also appears to be highly effective.

Until recently, only about 20% of children with LKS recovered completely. The remainder either had mild to moderate residual effects, or remained profoundly aphasic. A recently developed surgical technique (ARRI 5/1) offered hope as a successful treatment for LKS children, with Frank Morrell and colleagues seeing dramatic improvement in all of the first four children who underwent the procedure. This surgery—which entails making dozens of tiny horizontal cuts in the brain area where seizures occur—appears to cause no significant impairment of brain function. Despite its success rate, the technique has an obvious drawback: it is highly invasive surgery.

All four children treated with corticosteroid therapy by Lerman and colleagues regained their speech.

Drug therapy a success

Drug therapy, rather than surgery, is the technique Lerman et al. describe in *Developmental Medicine and Child Neurology*. The researchers administered corticosteroids (hormones produced by the adrenal glands) to four children diagnosed with LKS. "In all four cases," they report, "the EEG promptly became normal, with subsequent long-lasting remission of the aphasia and improvement of seizure control." The children have been followed for three to six years, since their therapy ended, and remain free from seizures and language problems. According to the researchers (personal communication), they have treated two other children who also responded well. "It would appear that to permit resumption of language function the epileptic discharges should be curbed," they say, "and this can be achieved by corticosteroids as well as by surgery."

Lerman et al. believe, based on the cases they have treated, that "in order to be effective, corticosteroid treatment should be given early, in adequate doses, and for a sufficient length of time" — probably at least two to three months. (One of the children they treated suffered relapses three different times when corticosteroid dosage was reduced, and improved each time when the dosage was raised.) They also caution that if aphasia has been present for a year or more, treatment may normalize the EEG without affecting the aphasia.

"It is likely," they say, "that prolonged 'bombardment' of the speech centers by epileptic discharges results in aphasia," and that the longer this continues, the more the brain is affected, until recovery is no longer possible.

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Fragile X gene discovery announced

Last fall when Fragile X researchers from around the world met in England, Stephen Warren recalled recently, "[we] decided that none of us knew anything then that we didn't know a year earlier."

It's a safe bet they won't be saying that this year.

In 1991, researchers studying Fragile X — which is the second most common genetic form of retardation, and is strongly linked to autism — are having a hard time keeping up with developments. First, two teams of researchers — Jean-Louis Mandel et al. in France, and Grant Sutherland et al. in Australia — pinpointed the region on the X chromosome where the defective gene responsible for the syndrome was located. Their reports in *Science* were followed on May 31 by the announcement in *Cell* by Warren and colleagues that they had located the gene itself. "We know what we are dealing with for the first time," Warren told *Newsweek*.

Will aid diagnosis

The gene they found appears to provide instructions for a protein made only in brain cells, and researchers will next try to determine where the gene operates in the brain, what its normal function is, and how the defective version of the gene causes Fragile X. What they learn may not only help explain Fragile X syndrome and help lead to eventual treatments and possibly a cure, but also offer insight into how genes affect behavior and brain development.

Researchers will also try to explain why the defective gene — unlike most inherited mutations — is highly unstable. The defect appears to involve a repetition of an amino acid, arginine, in the protein the gene normally makes, but the number of repetitions appears to vary from person to person. Fragile X expert Randi Hagerman speculated in the *Wall Street Journal* that these variations may be the reason why Fragile X can cause such a wide range of symptoms.

Discovery of the Fragile X gene will make diagnosis of the syndrome, and of unaffected carriers, much more accurate. Previously, Fragile X could be diagnosed only by looking for the chromosome abnormality it causes (a constricted area at the tip of the long arm of the X chromosome) — a defect not always seen in unaffected carriers. "Now, however," says Michelle Hoffman, "researchers can almost always detect even obscure Fragile X sites by a direct DNA analysis of the region." David Nelson concurs, "It's the best diagnostic tool you can imagine."

Long DNA fragment found

All of the researchers found that individuals with Fragile X had a longer-than-normal fragment of DNA — the area where a defective "blueprint" apparently causes the arginine sequence to be repeated excessively. According to Hoffman, the fragment size is normal when the male carriers transmit it to their daughters (who also are nonaffected carriers), but "in the affected children of those daughters, the Fragile X sites show an astonishing size increase . . . sometimes containing more than twenty times as much genetic material as in the [nonaffected] mothers."

Researchers have long puzzled over the unusual inheritance pattern of Fragile X. Normally X-linked disorders affect all males inheriting a defective gene, because they have only one X chromosome (while females have a second X with a normal gene which can compensate for the defective one). But up to half of males with the

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