was underreporting of estrogen use in the PDD group because information on ERT was derived from the informants of PDD patients, whereas both controls and PDND patients provided their own risk-factor information. In addition, although age, ethnicity, and education were adjusted for in the analysis, these characteristics may have influenced the subjects' opportunity to obtain ERT or the physicians' decision to offer it. Although age was a covariate in the logistic regression models, the PDD group was significantly older than the PDND and control groups. Some of these limitations could be addressed by conducting a prospective study or a randomized double-blind clinical trial.

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X-linked female band heterotopia–male lissencephaly syndrome

Article abstract—We report a family with band heterotopia in a mother and daughter and lissencephaly in a son (X-linked inheritance pattern). Postmortem examination of the boy revealed classical lissencephaly and, among other findings, simplified and discontinuous inferior olives without inferior olivary heterotopia. The absence of inferior olivary heterotopia may distinguish X-linked lissencephaly from other conditions with classic lissencephaly such as Miller-Dieker syndrome.

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In 1994, Pinard et al.[1] described two families with mothers and daughters with band heterotopia and sons with classical lissencephaly (a total of six people affected). This syndrome was termed "X-linked lissencephaly and subcortical band heterotopia" by Dobyns and Truwit.[2] Classical lissencephaly occurs in several conditions, including isolated lissencephaly sequence and Miller-Dieker syndrome. In addition to the cerebral abnormality, inferior olivary heterotopia are present in all but two reported patients with classical lissencephaly.[3-6] We report an additional family with band heterotopia in a mother and daughter and classical lissencephaly in a son without inferior olivary heterotopia.

Case reports. *Patient 1.* This patient (the mother of Patients 2 and 3) is a 29-year-old woman who developed habitual partial and generalized seizures at the age of 13 years. She has mild mental retardation with visual perceptual and fine motor deficits on neuropsychological evaluation. MRI demonstrated bilaterally symmetric, moderately thick band heterotopia (figure 1).

Patient 2. This patient (the daughter of Patient 1) is a 4-year-old girl born at 42 weeks' gestation with a birth

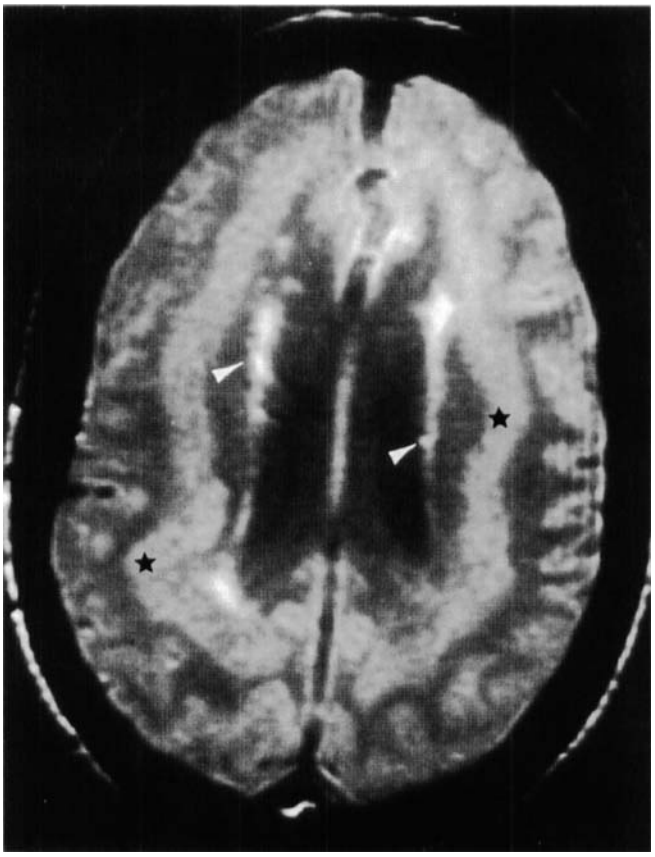

Figure 1. Patient 1 (mother). Bilateral symmetric, moderately thick band heterotopia (black stars) on axial proton density weighted MRI at the level of the bodies of the lateral ventricles. Note that there are also high signal periventricular nodules that are probably age-related vascular abnormalities, but there is a possibility that they are periventricular nodular heterotopia (white arrowheads).

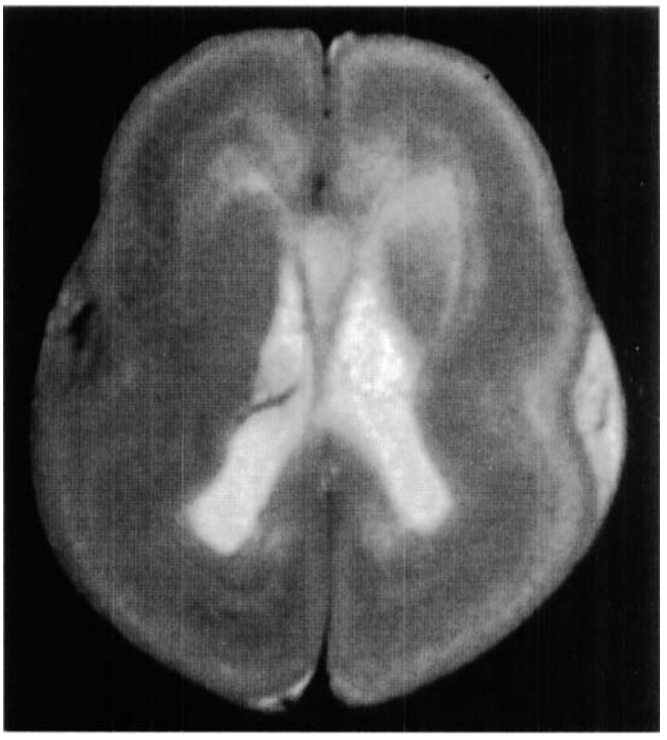

Figure 2. Patient 3 (son). Lissencephaly on axial T2-weighted MRI at the level of the bodies of the lateral ventricles. There is complete absence of gyration (agyria) except for a small indentation in the region of the Sylvian fissure.

weight of 6 lbs. 14 oz. There were no neonatal problems, but developmental milestones were delayed. At 30 months she had a staring episode, but no other seizures have occurred. MRI revealed bilaterally symmetric thick band heterotopia with the band divided into two layers in the lower aspect of the cerebral hemispheres.

Patient 3. This patient (the son of Patient 1) was born in 1993 and died at the age of 2 years. Gestation was 41.5 weeks, and he weighed 9 lbs. at birth. Pregnancy was complicated by gestational diabetes and treatment of the mother with carbamazepine. The mother had a generalized seizure 1 month before delivery. He developed initially focal, but then generalized seizures at the age of 36 hours. EEGs demonstrated multifocal seizures. Chromosomal studies were normal, including fluorescent in situ hybridization using a cosmid probe for the Miller-Dieker syndrome critical region on chromosome 17 (Dr. Mary C. Phelan, Greenwood Genetic Center, Greenwood, SC). During his life he had frequent seizures and was severely developmentally delayed, with microcephaly and spastic quadriparesis. MRI revealed lissencephaly (figure 2) that was confirmed by postmortem examination.

Pathologic findings in Patient 3. The brain weighed 603 grams at postmortem examination. The surface of the brain was agyric. The cortical plate was thick (up to 2 cm) with thinned white matter and corpus callosum, as well as enlarged ventricles. The temporal lobes were less affected. The claustrum was not identified grossly.

On microscopic examination the occipital and parietal neocortices were divided into four poorly formed layers, which from exterior to interior were an outer molecular layer, a thin cellular layer mainly composed of irregularly distributed large pyramidal neurons, a comparably thin pauci-cellular layer without myelinated fibers, and a thick unlayered heterotopic field of pyramidal neurons. The deeper portion of the broad heterotopic field was transected in some areas by a bundle of myelinated fibers that ran parallel to the ventricular surface. Some less heavily stained myelinated axons lay exterior to the bundle and ran perpendicular or tangential to the surface in small clusters. The other areas of the cerebral cortex lacked any semblance of a laminar organization. The frontal cortex was more unlayered, with a less apparent pauci-cellular layer and a more haphazard admixture of myelinated fibers and nests of heterotopic neurons in the deeper portions of the heterotopic field. Some large heterotopic clusters were also found in the white matter underlying a thinner cortex. Periventricular heterotopia were not seen. The ependyma was focally disrupted in all areas examined with astrocytic overgrowth and subventricular ependymal rosettes. The claustrum was small and dysplastic. There was diffuse gliosis in the cerebral cortex and basal ganglia.

The fourth ventricle was enlarged. There was diffuse cerebellar atrophy with decreased density of granular and Purkinje cells as well as gliosis. The dentate nucleus had a simplified configuration and decreased neuronal density.

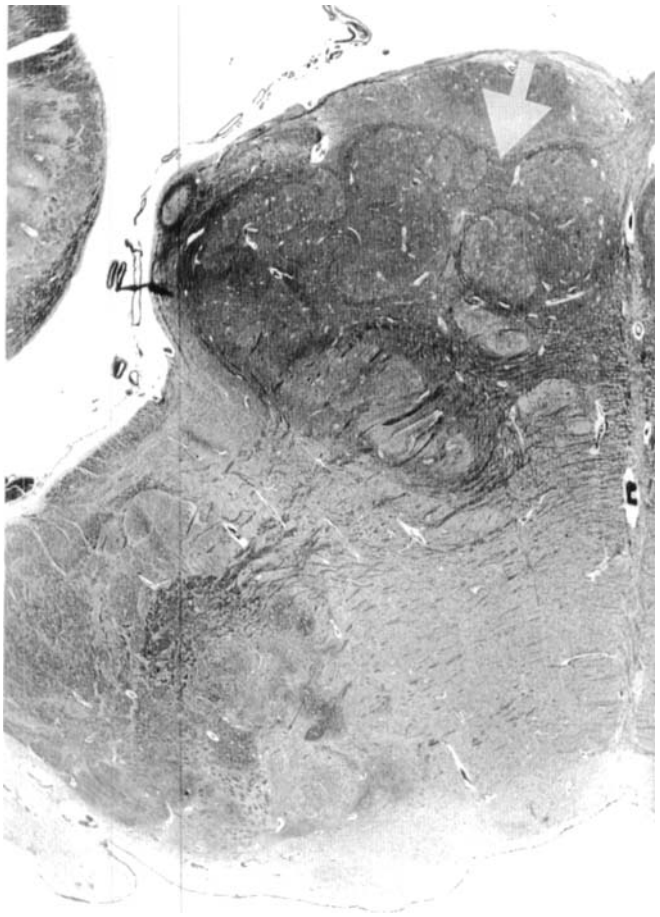

Figure 3. Cross section of the medulla. The inferior olivary nucleus is dysplastic but is located in its normal anatomic position. A discontinuity in the inferior olive is indicated by the arrow. No inferior olivary heterotopia are present. Magnification ×12.5, before 25% reduction.

There were heterotopic Purkinje cells in the cerebellar white matter.

The medullary (inferior) olives were dysplastic with decreased undulations and interruptions in their structural continuity (figure 3). No olivary heterotopia were present.

No abnormalities of the dura, sinuses, leptomeninges, veins, arteries, spinal cord, or pituitary gland were present.

Discussion. In 1994 Pinard et al.[1] described two families with bilaterally symmetric band heterotopia in females and lissencephaly in males diagnosed by MRI. Genetic linkage studies in our family, the two families of Pinard et al., and another unpublished family with female band heterotopia-male lissencephaly reveal that this syndrome is linked to an abnormality within Xq21.3-24.[7]

The term "lissencephaly" (agyria-pachygyria syndrome) includes a variety of conditions that have widespread absence of normal cortical gyration. The lissencephalies have been classified into two major groups based on the appearance of the cortex and the presence or absence of other malformations and dysplasias.[2,4] Classical lissencephaly (previously type 1) is characterized, in its most severe expression, by the formation of four broad cortical layers with a thin white-matter layer. Miller-Dieker syndrome, Norman-Roberts syndrome, isolated cases of sporadic lissencephaly (ILS), and familial lissencephaly are classical lissencephalies.

Patient 3 had classical lissencephaly with a thick four-layered cortex and thin white matter without obstructive hydrocephalus. In Patient 3, however, no deletion was present in chromosome 17p, the location of the genetic abnormality in Miller-Dieker syndrome.

Except for the absence of the inferior olivary heterotopia, the neuropathologic lesions in our Patient 3 are indistinguishable from those in isolated lissencephaly sequence (ILS) and Miller-Dieker syndrome.[4] However, inferior olivary heterotopia, located along the migratory track of these nuclei, are consistently described in Miller-Dieker syndrome[3,4] and ILS.[3,8,9] The appearance of the inferior olives in our patient is somewhat reminiscent of Zellweger syndrome (although in this peroxisomal disorder the brain is characterized by pachymicrogyria not lissencephaly).[3]

The only other pathologic data available from a patient with probable X-linked lissencephaly are from one of three brothers with lissencephaly described by Pavone et al.[6] The lesions in their case are nearly identical to those in our Patient 3. The major features are the agyria and pachygyria, a thick four-layered or poorly organized cortex, claustral agenesis, Purkinje cell heterotopia, and dysplasia of the inferior olives. As in our Patient 3, no inferior olivary heterotopia were present in the patient of Pavone et al.

The only other patient with classical lissencephaly without inferior olivary heterotopia that we could find was Case 1 reported by Norman et al.[8] This patient was the product of consanguineous parents and had several distinct facial abnormalities. This syndrome has been termed "Norman-Roberts syndrome."[4]

In the available familial cases of female band heterotopia-male lissencephaly, the daughters are more severely affected than are the mothers both clinically and on MRI. This phenomenon may be explained by either anticipation or variable mosaics. Anticipation refers to progressive worsening of a disorder in subsequent generations and is related to the number of trinucleotide repeats in several conditions.[10] Alternatively, variable mosaics of the inactivated X chromosome may account for the differing severities, and the worsening through generations may be coincidental.

Because females with band heterotopia may have seizures, cognitive impairment, or be neurologically normal, the mothers of male children with lissencephaly, but without the chromosome 17p abnormality, should be studied with MRI to determine if they have band heterotopia. Conversely, identification of band heterotopia in a female raises the possibility that closely related females may also be affected with band heterotopia and that male offspring may

have lissencephaly and die in utero or early in life. Females with band heterotopia should be counseled about the risk of having a male child with lissencephaly and female children with band heterotopia.

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Gabapentin does not interact with a contraceptive regimen of norethindrone acetate and ethinyl estradiol

Article abstract—Anticonvulsants that induce hepatic metabolism increase clearance of oral contraceptive hormones and thereby cause contraceptive failure. Gabapentin is not metabolized in humans and has little liability for causing metabolic-based drug-drug interactions. In healthy women receiving 2.5 mg norethindrone acetate and 50 μg ethinyl estradiol daily for three consecutive menstrual cycles, concurrent gabapentin administration did not alter the steady-state pharmacokinetics of either hormone. Thus, gabapentin is unlikely to cause contraceptive failure.

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Drugs that induce cytochrome P4503A4 (CYP3A4) are known to increase the metabolism of synthetic estrogens and progestogens commonly used in oral contraceptive regimens and thereby can cause drug-drug interactions leading to contraceptive failure.[1] Such interactions have been reported for a significant number of antiepileptic drugs, including carbamazepine, oxcarbazepine, phenobarbital, ethosuximide, primidone, felbamate, phenytoin, topiramate, and zonisamide.[2-4] In contrast, gabapentin, a GABA-analog anticonvulsant effective in the treatment of partial seizures with and without secondary generalization, is not metabolized in humans, does not cause hepatic enzyme induction, and appears to have little liability for causing drug-drug interactions.[5]

The objectives of this study were (1) to determine whether concurrent administration of gabapentin would alter the pharmacokinetics of norethindrone acetate and ethinyl estradiol and (2) to compare the pharmacokinetics of gabapentin during concomitant administration of norethindrone acetate and ethinyl estradiol with historical data.

Methods. This was a nonblind, multiple-dose, crossover, pharmacokinetic study conducted in healthy, nonsmoking women of any race who were aged 18 to 50 years, weighed at least 50 kg, and were not pregnant or lactating. Planned enrollment was 12 subjects. Participants granted written informed consent before study participation and underwent screening and follow-up evaluations, including physical examinations, ECGs, and clinical laboratory tests.

Drug treatments were 2.5 mg norethindrone acetate and 50 μg ethinyl estradiol daily for 21 days of three consecutive menstrual cycles, and gabapentin, 400 mg every 8 hours, on days 16 through 22 of the last cycle. In cycles 2 and 3, the first dose of oral contraceptive was taken 7 days after the last dose of the previous cycle.

Serial blood samples were obtained immediately before and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 30, 36, and 48 hours after the oral contraceptive dose on day 21 of menstrual cycles 2 and 3. Samples were immediately cen-

