ANIMAL MODEL OF HUMAN DISEASE

Werdnig–Hoffmann Disease (Infantile Spinal Muscular Atrophy)

Animal Model: Motor Neuron Disease in the Wobbler (wr/wr) Mouse

Contributed by: J. E. Leestma, MD, Department of Pathology, Neurology Laboratory, Northwestern University School of Medicine, 303 East Chicago Avenue, Chicago, IL 60611.

Biologic Features

First reported by Falconer [1] in 1956, the Wobbler mouse arose as a spontaneous autosomal recessive mutation (wr) in inbred C57Bl/Fa mice. The syndrome develops late in gestation but cannot be diagnosed with confidence until about 3 weeks of age. The first signs are progressive weakness leading to contractures in the upper extremities (Figure 1), a tendency for an unusual clasping of the feet when suspended by the tail (Figure 2), an upward-pointing snout, smallness of stature, and a wobbly gait.[2–5] Over several months some animals become more affected than others, and some show a late hindlimb weakness.[6] Less than the expected 25% rate of expression of the *wr* trait is observed in litters, and it is possible that some fetuses die *in utero* or at birth of a more severe form of the disease. Most animals survive to maturity but are troubled with eye infections (inability to groom) and may die suddenly, apparently of infections. The life expectancy is less than that of normal mice, but survival of 6 months of more is not uncommon.[3]

The muscles of mastication, the neck, the shoulder girdle, and the intercostal groups are markedly affected, distal muscles more so than proximal, and show "group" changes typical for neurogenic atrophy (Figure 3).[3–5] The neuropathologic characteristics of the condition consist of vacuolar degeneration (Figure 4), most prominent in the motor neurons of the upper spinal cord and lower brain stem, with variable involvement of cerebellar nuclei, reticular formation, vestibular nuclei, forebrain cortical neurons, olfactory lobe, and dorsal gray of the spinal cord.[2,3] Intramuscular nerves show degeneration with branching of preterminal axons. There is little gliosis or other reaction.[4] Ultrastructural study of neurons reveals dilation and vacuolation of endoplasmic reticulum and Golgi apparatus;

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proliferation of small tubular profiles, which may be smooth ER, proliferation and concentration of cytoplasmic microtubules and filaments, lipid accumulation in vacuoles, and dense lamellar cytoplasmic bodies in some neurons.[3,5]

Abnormalities in the animal other than in the nervous system include reproductive sterility in both males and females.[7,8] Females may not show normal estrus cycles and have small genital tracts, though ovaries may contain follicles. Females along with males show significantly low levels of estrogen (E2) binding activity in liver, along with elevated plasma estradiol levels, indicating a possible defect in tissue responsiveness to estrogen.[7] Male Wobblers have abundant spermatozoa, but few show motility. The sperm tail axonemes have altered geometry of the outer tubular doublets and central pairs of microtubules which may be shared with cilia in the reproductive tract.[8] This altered axoneme may account for the immotility of the sperm. The livers of Wobblers may show vacuolar changes in hepatocytes which have not been extensively studied.[3] There are suggestions of other systemic abnormalities as well.

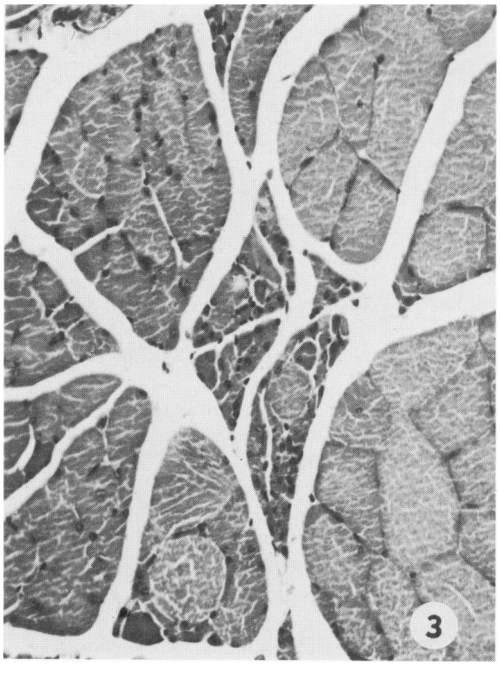
There is no known marker for the *wr* gene, and only animals homozygous for the trait (wr/wr) show any signs of neurologic disease.[2] Heterozygotes appear completely normal and are reproductively competent even though their estrogen binding activity and plasma Estradiol levels are intermediate between controls and Wobblers.[7] This inability to identify carriers by means other than breeding them necessitates a relatively large animal colony in order to provide adequate numbers of Wobblers for study.

Comparison With Human Disease

Bearing in mind the divergence of opinion regarding classification of human infantile motor neuron disease (spinal muscular atrophy),[9] the condition of the Wobbler mouse appears to bear a close resemblance to Werdnig–Hoffmann disease. The similarities are: autosomal recessive inheritance, early age of onset, variable degrees of severity and progression of development, involvement of the shoulder girdle with "jug handle" deformity, and severe intercostal and neck muscle involvement. Dissimilarities include: minor involvement in the lower extremities, vacuolar degeneration in neurons seen only in rare instances in man,[10] and the presence of systemic disease in the Wobbler. The model has been described in the past as an analog of ALS but by most measures more closely resembles Werdnig–Hoffmann disease.

Usefulness of the Model

Most models of motor neuron disease are in large animals and have never been critically studied due to inherent difficulties in working with



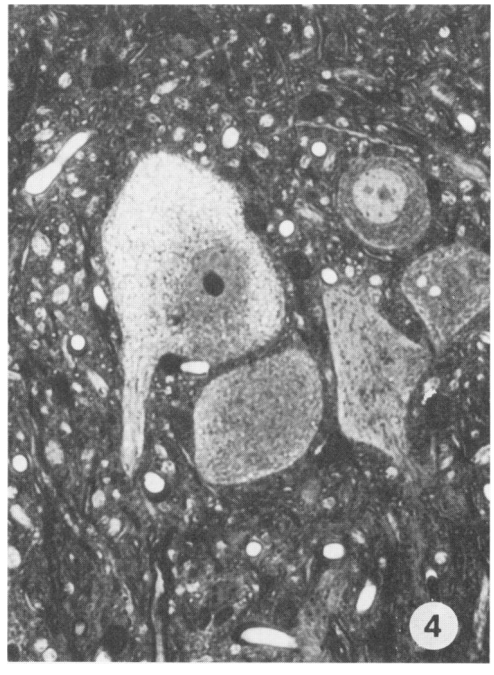


Figure 1—A moderately affected Wobbler mouse showing the typical contracted "jug handle" deformity of the forelimbs and atrophy of the lower extremities. **Figure 2**—The Wobbler mouse displaying its characteristic clasping position of the lower extremities and feet when suspended by the tail. The forelimbs are atrophic and contracted. **Figure 3**—Typical "group" atrophy in an affected muscle from the lower extremity of a Wobbler mouse. (H&E, X200) **Figure 4**—Lumbar anterior horn from a Wobbler mouse illustrating a swollen, vacuolated motor neuron with chromatolysis. Less pronounced and subtle vacuolation can be seen in smaller neighboring neurons. (Embedded, 1-mμ section, stained with toluidine blue, X520)

them or scarcity of breeding stock.[3] The Wobbler mouse is probably as convenient a model as exists for many aspects of hereditary motor neuron disease in spite of the problems in colony management.

The Wobbler offers an opportunity to study the genetics of infantile motor neuron disease, the pathogenesis and developmental pathology of the lesion, and the curious associated non-neurologic disease in the animal. It is this latter aspect that may be most exciting, for if a unifying pathobiologic hypothesis for the disease in this animal can be formulated, it might afford a greater experimental usefulness of human material and stimulate new ideas about this neurologic degenerative disease.

Availability

Presently there are seven colonies of Wobbler mice in existence in the United States and at least three in Europe. Colonies are presently known to exist at Northwestern University (Pathology); University of Chicago (Neurology); Medical College of West Virginia (Pathology); New England Medical Center (Neurology); the National Institutes of Health (Animal Resources); and Albany Medical College (Neurology). The animals are not commercially available, though most colonies have a surplus of genetically indeterminant animals that can usually be provided for test breeding and colony development. Recent breeding experiments in several laboratories indicate that productivity and success in breeding may be increased by outcrossing the current animal which carries the *wr* gene, the C57Bl mouse, with other strains.

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