Wobbly Hedgehog Syndrome in African Pygmy Hedgehogs (*Atelerix* spp.)

Donnasue Graesser, Ph.D.
Terry R. Spraker, DVM, Ph.D., Dipl. ACVP
Priscilla Dressen, DVM
Michael M. Garner, DVM, Dipl. ACVP
James T. Raymond, DVM, MS, Dipl. ACVP
Gordon Terwilliger, BS
Jung Kim, MD
Joseph A. Madri, MD, Ph.D.

Abstract

Wobbly Hedgehog Syndrome (WHS) is a progressive paralysis that occurs in approximately 10% of pet African hedgehogs in North America. Clinical signs of WHS begin with mild ataxia, progress to more severe neurologic signs, and ultimately lead to complete paralysis. The onset of WHS commonly occurs under 2 years of age, but can occur at any age. Progression rate is variable, and the majority of hedgehogs are completely paralyzed by 15 months after the onset of clinical signs. WHS can only be definitively diagnosed by post-mortem examination of tissues from the central nervous system. The characteristic histopathology of WHS is vacuolization of the white matter of the brain and spinal cord, and associated neurogenic muscle atrophy. There is no inflammation of the central nervous system associated with WHS. The etiology of WHS is unknown, but pedigree analysis indicates a familial tendency to the disease.

Keywords: ***Atelerix*****; hedgehogs; wobbly hedgehog syndrome; paralysis; paresis; demyelination**

African pygmy hedgehogs are becoming increasingly popular pets in North America, as well as in South America, Europe, and some Asian countries. Pet African pygmy hedgehogs in North America belong to the genus *Atelerix*, and include central African hedgehogs (*Atelerix albiventris*), Algerian hedgehogs (*Atelerix algirus*), and hybrids of the two species. African hedgehogs have also been utilized as a research species in the United States, because they possess a protein similar to human lipoprotein(a).[1]

Since the mid-1990s, a condition characterized as progressive paralysis or degenerative myelopathy has been observed in pet African hedgehogs.[2-5] This condition has been coined Wobbly Hedgehog Syndrome (WHS).[3-5] A similar disease has been reported in European hedgehogs (*Erinaceus europaeus*).[5,6] We have evaluated the clinical histories and post-mortem histopathology of a large sampling of African hedgehogs with WHS, and a report, we provide an

From the Yale University School of Medicine, Departments of Pathology and Comparative Medicine, New Haven, CT 06510 USA, Colorado State University Veterinary Diagnostic Laboratory, Fort Collins, CO 80523 USA, NorthStar Veterinary Clinic, Fort Collins, CO 80525 USA, and Northwest ZooPath, Monroe, WA 98272 USA.

Address correspondence to: Donnasue Graesser, Hedgehog Welfare Society, PO Box 242, Chaplin, CT 06235. E-mail: donnasue.graesser@aya.yale.edu

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Figure 1. Unilateral exophthalmos, protrusion of one eye, is a common feature of hedgehogs with WHS, occurring in 28% of the cases in this study. Photo courtesy of Teresa Johnson.

overview of the clinical signs and progression of WHS, and a brief description of the pathology underlying the disease.

Clinical Signs and Statistics

In a survey of owners of pet African hedgehogs between the years 2000 and 2005, 10% of hedgehogs (n = 676) were reported to have some degree of progressive paralysis. Detailed clinical histories were obtained for 61 of the animals that demonstrated neurologic signs, and 45 cases were submitted for post-mortem examination. In 5 of these cases, the neurologic signs resulted from unrelated pathology, generally brain tumors. The remaining 40 cases demonstrated similar lesions of the central nervous system (CNS), which are discussed in the Pathology section below. Clinical statistics were derived only from the 40 hedgehogs confirmed to have these characteristic lesions. The study consisted of 22 females and 18 males. There is no statistical evidence for gender bias of WHS.

One of the earliest indicators of WHS in hedgehogs is the inability to close the hood. On examination, hedgehogs with WHS first present with mild ataxia, frequently described as lack of coordination, becoming off balance, stumbling, tripping, or wobbling. In early stages of WHS, the clinical signs are usually relapsing and remitting. Over several months, the signs become progressively more severe and may include falling consistently to one side, tremors, exophthalmos (Fig 1), scoliosis, seizures, muscle atrophy, self-mutilation, and difficulty regulating body temperature. In 70% of the cases in this study, the paralysis was ascending from hindlimbs to forelimbs. Two hedgehogs had no clinical signs, but were included in this study based on the appearance of characteristic histopathologic lesions. A synopsis of the primary clinical signs of WHS is presented in Table 1. To better appreciate the appearance and movement of a hedgehog with WHS, a video clip can be viewed at the following web site: http://www.wobblyhedgehog.org.

The progression of WHS is generally accompanied by severe weight loss. However, in most cases, there is no apparent loss of appetite until the terminal stages of the disease, when most hedgehogs become dysphagic (Table 1). Unless there is other complicating pathology leading to the death of the hedgehog, the end result of WHS is tetraplegia with muscle atrophy (Fig 2). Many owners choose euthanasia when the hedgehog becomes significantly immobile and quality of life is compromised. However, some owners choose supportive care and hand-feeding (Fig 3). A hedgehog that has progressed to tetraplegia, but is not yet dysphagic, can live for several months with supportive care.

WHS occurs most frequently in hedgehogs under 2 years of age, but can present at any age (Fig 4). The average age for onset of clinical signs of WHS in this study was 18.5 months (range, 1-36 months). In 60% of cases, the hedgehog was immobile within 9 months after the onset of ataxia (Fig 5). In 90% of cases, immobility occurred by 15 months after the onset of ataxia. There was no correlation between age at onset and progression rate. We also surveyed

Table 1. Occurrence of Clinical Signs in Hedgehogs with Wobbly Hedgehog Syndrome

Clinical sign	Frequency (n = 40)	Percentage
Lack of coordination	38	95%
Significant weight loss	35	88%
Dysphagia in late disease	31	78%
Falling to one side	28	70%
Paralysis was ascending	28	70%
Tremors	26	65%
Unilateral exophthalmos	11	28%
Curvature of spinal column	9	22%
Seizures	8	20%
Self-mutilation or aggression	4	10%
No neurologic signs	2	5%

All cases included in this table were determined to have characteristic WHS histologic lesions in the CNS by post-mortem examination.

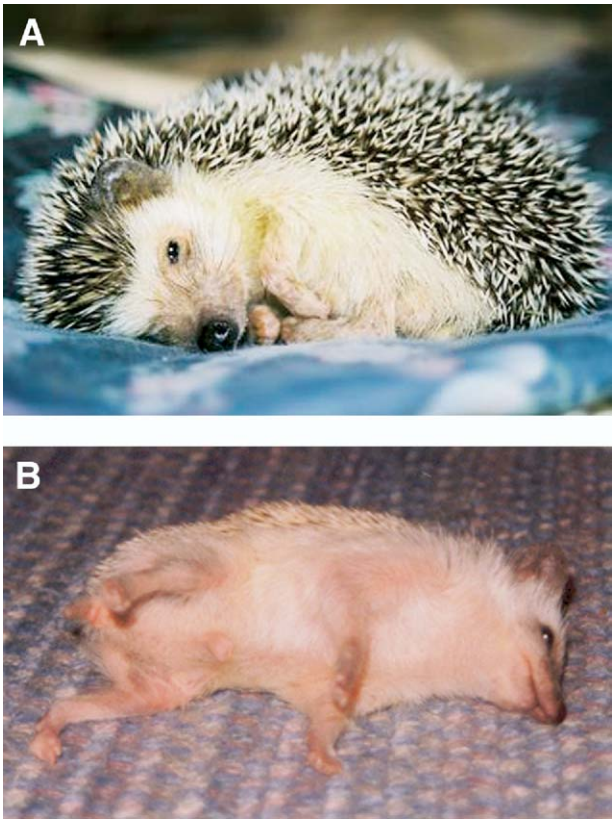

Figure 2. Hedgehogs in final stages of WHS. (A and B) Each of these hedgehogs has suffered from the progressive paralysis associated with WHS over several months, and demonstrates many clinical signs typical of the final stages of the disease including tetraplegia, muscle atrophy, and obvious emaciation. Photos courtesy of Donna Pate and Laura Ledet.

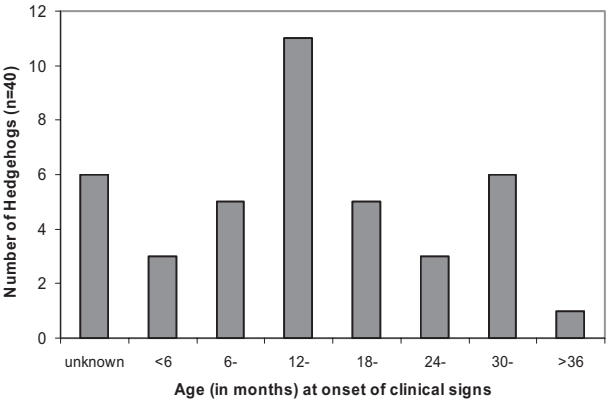

Figure 4. Age at onset of clinical signs of WHS. Thirty-four of the hedgehogs in this study had a known birth date. Most commonly, clinical signs of WHS first appeared before 2 years of age. WHS may occur in older hedgehogs as well.

owners of hedgehogs with WHS for information on dietary regimens, treatments, and supportive therapies, and have not demonstrated any correlation between these variables and progression rate.

Pathology

Although the clinical signs described above are typical of hedgehogs with WHS, currently, definitive diagnosis of WHS can only be made by post-mortem histopathologic examination of the CNS. Other reported causes of progressive paralysis in hedgehogs have included various brain tumors, intervertebral disc disease, and hepatic encephalopathy. Following is a description of the characteristic pathology of WHS.

Figure 3. Supportive care of hedgehog with WHS. This hedgehog is immobilized because of WHS, yet she is able to eat and drink with assistance. With hand-feeding and supportive care, hedgehogs with WHS can survive for many months. Photo courtesy of Sarah Shore.

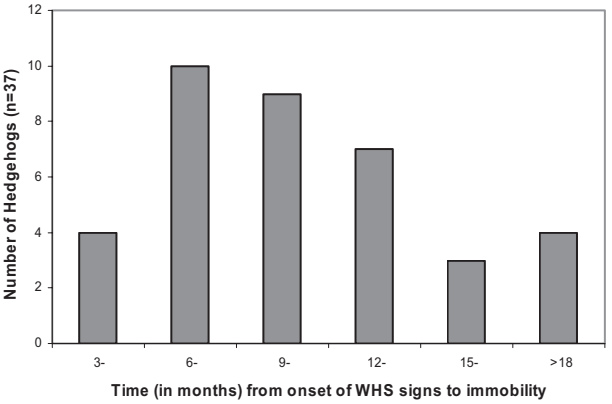

Figure 5. Progression to immobility in WHS. Thirty-seven of the hedgehogs in this study progressed to significant paralysis. (Two hedgehogs had typical WHS lesions, but no clinical signs. In 1 case, death due to lymphosarcoma preceded full progression of WHS). This graph indicates the time of progression from onset of clinical signs to immobility of the hedgehog.

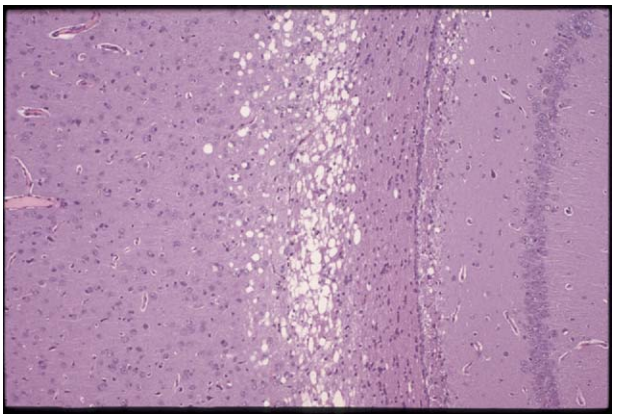

Figure 6. Cerebrum of a hedgehog with WHS. Hematoxylin and eosin stain of a thin section of cerebrum from a hedgehog with WHS. Note the extensive spongiosis of the white matter tracts of the corona radiata. (20 × magnification)

Gross Observations

The average range of animals submitted for post-mortem examination was between 200 and 300 g. Hedgehogs were usually emaciated with varying degrees of skeletal muscle atrophy of the limbs and spinal column. Occasionally, abrasions to the toes of the paws could be seen. These abrasions were most likely the result of the animal dragging its limbs because of loss of full range of motion and inability to fully extend the limbs.

Slightly enlarged and pale livers were common. Many animals had a roughened, pitted surface to the cortex of the kidneys. Pale triangular lesions could often be visualized within the renal cortex. Gross lesions were not observed in the brain, spinal cord, heart, lungs, digestive system, endocrine system or reproductive system except when nonrelated tumors were present.

Histopathology

Forty-five hedgehogs presumed to have WHS were submitted for post-mortem histopathologic examination. No evidence of WHS was found in 5 of these hedgehogs: 1 hedgehog was diagnosed with fibroblastic meningioma; 3 with astrocytomas; and 1 with severe hepatic lipidosis and hepatic encephalopathy.

The remaining 40 animals were observed to have similar histologic lesions in the CNS. The majority of these hedgehogs were in the terminal phase of WHS, although some were euthanized in earlier stages of the disease. Six (15%) of these hedgehogs had unrelated tumors in addition to WHS. Two (5%) of the hedgehogs had no clinical signs and were submitted to the study based on a family history of progressive neurologic signs. Their cause of death was unrelated to WHS, yet they possessed CNS lesions compatible with early WHS. The following is an overview of the histologic lesions characteristic of WHS.

The primary histologic lesion in hedgehogs with WHS is vacuolization of the white matter tracts of the cerebrum, cerebellum, and brain stem (Fig 6). The lesion also occurs in the white matter tracts throughout the spinal cord (Fig 7). There appears to be a loss of myelin first, then secondary degeneration and loss of the axon, followed by neuronal degeneration. The affected regions are quite extensive, especially in the corona radiata of the cerebrum and the white matter of the cerebellum, brain stem, and spinal cord. There is also a degeneration and loss of lower motor neurons of the ventral horns of the spinal cord. Demyelination is also found in the ventral rootlets, but is not a feature in the dorsal rootlets and spinal ganglia or peripheral ganglia. There is little to no evidence of peripheral neuropathy. Inflammation is not a feature in the brain or spinal cord in hedgehogs with WHS, except mild astrocytosis in the brain.

The primary lesion found in skeletal muscle is neurogenic atrophy of myocytes, without inflammation. These myocytes are eosinophilic and triangular.

Hepatic and renal pathology is also seen in some of the hedgehogs with WHS. Mild to severe hepatic lipidosis is present in 20% of the cases. There is no inflammation associated with these areas of centrilobular fatty degeneration. Also common are multiple areas of renal cortical infarction. These are wedge-shaped regions in the cortex that are characterized by tubular degeneration and moderate infiltration of lymphocytes and plasma cells within the

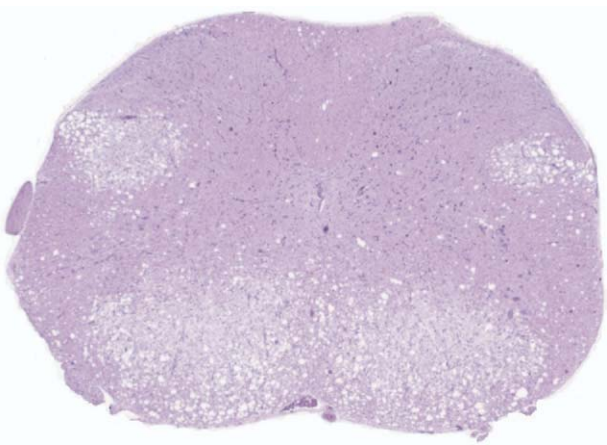

Figure 7. Spinal cord of a hedgehog with WHS. Hematoxylin and eosin stain of a thin section of spinal cord from a hedgehog with WHS. Note the extensive areas of demyelination in the lower medial tracts and the lateral central tracts. (4 × magnification)

interstitial tissues. Glomerulosclerosis is often present within the areas of infarction. These hepatic and renal lesions are not found in all hedgehogs with WHS. They may be an incidental finding, because similar lesions are occasionally present in hedgehogs without WHS pathology.

Treatment

Numerous treatments for WHS have been attempted with little or no success. The most commonly reported therapies were supplementation with vitamin E, selenium, vitamin B, and/or calcionate syrup. Oral predisone was often prescribed. Antibiotics, including trimethoprim sulfa, Amoxi-Drop Liquid (Pfizer Animal Health, New York), and Baytril (Bayer, Animal Health Division, Shawnee, KS), were sometimes prescribed to treat concurrent infections. In addition, many hedgehogs have been treated with homeopathic remedies, acupuncture, and physical therapy regimens. Some of these treatments appeared to ameliorate the clinical signs temporarily or slow the progression of paralysis. However, because WHS is a relapsing and remitting disease during early stages and progression of the disease is variable, evaluation of the success of treatments is not possible without controlled studies. No treatment has been shown to stop the progression of paralysis.

Avonex (interferon beta-1a, Biogen Idec, Cambridge, MA) therapy was attempted in 1 case. Beginning 2 weeks after onset of ataxia, Avonex was dosed at weekly intervals (300,000 u/dose) concurrently with depomedrol (20 mg/mL, 0.02 mL) and dexamethasone (2.0 mg/mL, 0.03 mL) for a total of 12 treatments. Despite this treatment, progressive signs appeared within 2 weeks, and the hedgehog was severely debilitated by 12 weeks.

Discussion

WHS is a common cause of progressive paralysis in the pet African pygmy hedgehog population in North America. Other less common causes of progressive paralysis in hedgehogs include brain tumors, degenerative disc disease, and other encephalopathies. WHS can only be definitively diagnosed by post-mortem histologic examination of CNS tissues. The primary histopathology associated with WHS is vacuole formation in white matter areas of the brain and spinal cord, with associated neurogenic atrophy of muscle.

The next most common pathology finding in hedgehogs with WHS is hepatic lipidosis. There appear to be some nutritional complications to the disease, given that the hedgehogs are generally emaciated. Hepatic lipidosis in WHS hedgehogs may be similar to that of emaciated cats and other animals in a starvation state.[7] However, it is also a common finding in African hedgehogs without WHS,[8] so hepatic lipidosis in WHS cases may also be the result of a species-specific predisposition.

The etiology of WHS is unknown. Potential etiologies for diseases affecting the white matter of the CNS fall into 2 general categories: acquired disorders and demyelinating (or dysmyelinating) diseases of genetic/hereditary background.[9] Histopathology and study of disease patterns in the hedgehog population provide some insight into possible causes of WHS.

Acquired disorders of the CNS white matter include infectious diseases such as canine distemper virus[10] and progressive multifocal leukoencephalopathy, a human disease that is caused by infection of oligodendrocytes by JC virus.[11] Autoimmune diseases such as multiple sclerosis in humans[12,13] are also categorized as acquired disorders. WHS is often incorrectly compared with multiple sclerosis; however, autoimmune inflammation is not observed in the CNS tissues of hedgehogs with WHS. Electrolyte imbalances may lead to demyelination, as in a condition known as central pontine myelinolysis in humans.[14] Central pontine myelinolysis is caused by prolonged hyponatremia followed by rapid sodium correction, and has also been reported to occur in dogs.[15,16] Primary demyelination may also occur in response to dietary deficiency, exposure to toxins, or brain ischemia.

Other demyelinating diseases of the CNS are due to inherited factors such as enzyme defects in numerous metabolic pathways (for example, Canavan's disease).[17] Mutations in the gene encoding the proteolipid protein component of myelin cause dysmyelinating diseases such as Pelizaeus-Merzbacher disease in humans,[18] shaking pup in dogs,[19,20] and similar dysmyelinating diseases in other animal models.[21]

Some insight into the possible etiology of WHS is gained from studies of disease cluster patterns. There are no reports of transmission of WHS between unrelated hedgehogs sharing living quarters, or in the same household. Even in relatively large breeding facilities, reported WHS cases are restricted to defined family lineages (Fig 8). The hedgehogs in this example pedigree were all separated from their mothers and littermates at weaning, were distributed geographically throughout the United States, were up to 34 months of age when

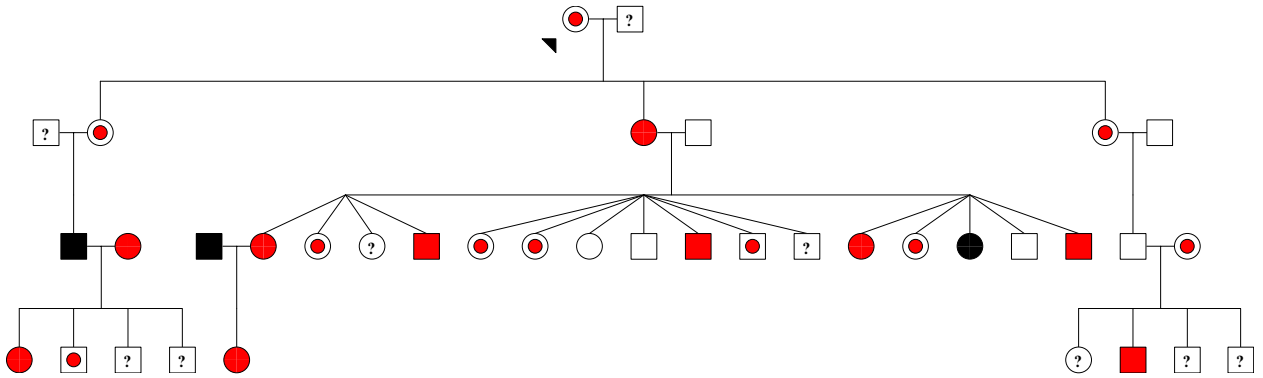

Figure 8. Pedigree of a family lineage with WHS. This pedigree demonstrates the familial tendency of WHS. The hedgehogs in this pedigree were reported to the study from diverse geographic locations throughout the United States. WHS was not reported to occur in unrelated hedgehogs living in the same household, or sharing cages with these hedgehogs. Females in the pedigree are represented by circle symbols; males are represented by square symbols. The presence or absence of WHS signs and lesions is indicated as follows: filled red symbols = progressive paralysis, WHS lesions present in CNS; partially-filled red symbols = progressive paralysis, histopathology not available; filled black symobls = no clinical signs, WHS lesions absent in CNS; open square = no clinical signs, histopathology not available; question mark = no information available.

they first showed obvious signs of the disease, and are all deceased. The lack of transmission of WHS between unrelated hedgehogs, and the tendency of WHS to occur in family lines, strongly suggests an inherited component to the disease.

Although no evidence of an infectious agent has been observed, the familial tendency of WHS does not rule out a transmissible component to the disease. It is possible that the familial pattern is a result of an inherited susceptibility to an infectious agent, possibly via genes encoding viral receptors. It is also possible that vertical transmission of an infectious agent mimics an inherited trait. If so, the incubation period for the agent is lengthy, because symptoms of the disease may take up to 3 years post-weaning to appear. In any case, breeding of hedgehogs with presumed WHS, or those closely related to hedgehogs diagnosed with WHS, is not recommended.

Further studies will aim to more fully describe the pathology of WHS, to elucidate the etiology of WHS, to analyze the hereditary pattern of disease, and to investigate treatment options.

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