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MUCOPOLYSACCHARIDOSIS II (MPS II) IN A FREE-LIVING KAKA (*NESTOR MERIDIONALIS*) IN NEW ZEALAND

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ABSTRACT: A lysosomal storage disease, identified as a mucopolysaccharidosis (MPS), was diagnosed in a free-living Kaka (*Nestor meridionalis*), an endemic New Zealand parrot, which exhibited weakness, incoordination, and seizures. Histopathology showed typical colloid-like cytoplasmic inclusions in Purkinje cells and many other neurons throughout the brain. Electron microscopy revealed that storage bodies contained a variety of linear, curved, or circular membranous profiles and electron-dense bodies. Because the bird came from a small isolated population of Kaka in the northern South Island, a genetic cause was deemed likely. Tandem mass spectrometry revealed increased levels of heparan sulfate-derived disaccharides in the brain and liver compared with tissues from controls. Enzymatic assays documented low levels of iduronate-2-sulfatase activity, which causes a lysosomal storage disorder called MPS type II or Hunter syndrome. A captive breeding program is currently in progress, and the possibility of detecting carriers of this disorder warrants further investigation.

Key words: Enzymology, Hunter syndrome, lysosomal storage disease, mass spectrometry, mucopolysaccharidosis II, parrot, ultrastructure.

INTRODUCTION

More than 70 inherited lysosomal storage diseases (LSDs) of human beings are known (Mehta and Winchester 2012; Alroy and Lyons 2014; Platt et al. 2018), many of which have also been described in mammals (Hopwood et al. 2004; Alroy and Lyons 2014), but relatively fewer in birds. These include a putative metachromatic dystrophy in Hawaiian Geese (*Branta sandvicensis*; Wight 1976); glycogen storage disease type II in Japanese Quail (*Coturnix coturnix japonica*; Matsui et al. 1983; Kunita et al. 1998); mucopolysaccharidosis (MPS) IIIB in farmed Emu (*Dromaius novaehollandiae*; Kim et al. 1996; Aronovich et al. 2001); an LSD in hummingbirds (*Calypte costae*; Proudfoot et al. 2000), resembling a form of MPS; and GM2 gangliosidosis in a Greater Flamingo (*Phoenicopterus ruber*; Zeng et al. 2008). A form of neuronal ceroid-lipofuscinosis has been diagnosed on histologic grounds in a Mallard (*Anas platyrhynchos*; Evans et al. 2012) and in a Peach-faced Lovebird (*Agapornis roseicollis*; Reece and MacWhirter 1998), but the types have not been specified further.

With the exception of MPS II (Hunter syndrome), glycogen storage disease Type IIb (Danon disease) and α-galactosidase A deficiency (Fabry disease), which are X-linked, LSDs are inherited as autosomal recessive traits (Greiner-Tollersrud and Berg 2013; Platt et al. 2018). Occasional disorders of lysosomal catabolism caused by toxic agents may mimic those that are inherited, for example swainsonine intoxication after ingestion of *Swainsona* spp. plants and other genera by grazing animals (Alroy and Lyons 2014; Cook et al. 2014), in which the toxic principle resides in endophyte fungi. An LSD of Humboldt Penguins (*Spheniscus humboldti*) resembling a sphingolipidosis was probably caused by chloroquine intoxication administered to control avian malaria (Wünschmann et al. 2006).

Most LSDs are generalized systemic diseases but have their greatest clinical effect via compromised central nervous function. Al-

though individually rare, clusters of a particular disease occasionally occur because of inbreeding or founder effect (Jolly et al. 2016). An LSD in a Kaka (*Nestor meridionalis*), an endangered New Zealand parrot, was reported in 2017 (Hunter et al. 2017). Detailed investigation of tissues from the affected bird has identified the disease as a MPS type II that is likely to be inherited. Although Kaka are endangered, recovery is occurring in selected areas by breeding in habitats in which predators have been controlled. South Island Kaka are also at risk from competition for food resources from introduced wasps (*Vespula* spp.) and brush-tailed possums (*Trichosurus vulpecula*; Beggs and Wilson 1991).

MATERIALS AND METHODS

Histopathology and electron microscopy

At postmortem examination, tissues were fixed in 10% formalin and submitted to Wildbase at Massey University for histopathology. They were processed into paraffin, and sections were stained by H&E, periodic acid–Schiff reaction, and Luxol fast blue. Brain and liver were also processed into epoxy resin and thick sections stained with toluidine blue. Thin sections were stained with lead citrate and uranyl acetate for electron microscopy.

Tandem mass spectrometry

A further set of frozen tissues, brain from the affected Kaka, brain and liver from an unaffected (control) Kaka, and brain and liver from a normal Cockatiel (*Nymphicus hollandicus*), were available. On thawing, they were homogenized in 20 mM Tris and 0.5 M NaCl pH 7.2, and total protein content was determined with a microbicinchoninic protein assay kit (Thermo Fisher Scientific, Rockford, Illinois, USA) per the manufacturer's instructions.

Tissue homogenates (100 μg total protein equivalent) were exposed to butanolic or methanolic acid to derive disaccharides. Previously published methods (Trim et al. 2014, 2015; He et al. 2019) were used in a slightly modified form. Briefly, samples were placed in glass tubes and freeze-dried overnight. To one set of samples, 50 μL 2,2-dimethoxypropane was added followed by 1,000 μL of butanolic HCl (3 M). Another set of samples were exposed to 50 μL 2,2-dimethoxypropane followed by 1000 μL of methanolic HCl (1.25 M). The tubes were sealed and incubated at 100 C for 2 h (butanolysis) or 65 C for 2.5 h (methanolysis). After incubation, the samples were dried under N_2 for 1 h at 45 C and reconstituted in deuterated internal standard (IS) and mixed for 30 min on an orbital shaker (Ratek Instruments, Boronia, Victoria, Australia). The solution was centrifuged for 15 min at 17,900 × G on a Biofuge Pico (Heraeus, Hanau, Germany). The supernatant was placed into a 96-well microtiter plate and kept at 6 C in an Acquity UPLC sample manager (Waters Corporation, Milford, Massachusetts, USA) until analyzed.

All mass spectrometry was performed with an API 4000 Qtrap mass spectrometer (AB/Sciex, Concord, Ontario, Canada). Liquid chromatographic separation before mass spectrometry analysis was by means of an Acquity UPLC (Waters Corporation) equipped with a 2.1-mm ID × 50-mm BEH C18 (1.7 μm particle) analytic column (P/N 186002350). A binary solvent system was used with solvent A consisting of water with 0.1% formic acid and solvent B consisting of acetonitrile with 0.1% formic acid. A 2-μL injection of sample was loaded on the column at a flow rate of 350 μL/min with 99% solvent A. Chromatographic separation was performed with the gradient in Supplementary Material Table 1.

Data were acquired in multiple reaction monitoring mode. Methanolysis multiple reaction monitoring transitions were monitored for 50 ms each; they were *m/z* 390.200 to 162.100 methanolysis IS, *m/z* 384.200 to 162.077 methanolysis heparan sulfate (HS), and *m/z* 426.200 to 236.100 chondroitin sulfate/dermatan sulfate (DS). For the butanolysis products, *m/z* 468.245 to 162.077 (butanolysis HS), and *m/z* 477.300 to 162.077 (disaccharide IS) were each monitored for 50 ms. Peak areas were calculated by Analyst 1.6.2 (AB/Sciex). Disaccharide peak area counts were ratioed to IS counts (methanolysis). After butanolysis, disaccharide concentration was calculated with reference to a standard curve (prepared with GlcN-α1-6-dibutylated–GlcUA). Data were expressed as micrograms per milligram (μg/mg) total protein.

Enzymology

To determine the activity of iduronate-2-sulfatase (IDS), 4-methylumbelliferyl substrates were used: Toronto Research Chemicals M334715; iduronidase (1 μg/mL) from R&D Systems [Minneapolis, Minnesota, USA], 4119-GH-010; Voznyi et al. 2001), *N*-sulfoglucosamine sulfohydrolase (Biosynth Carbosynth [Berkshire, UK] EM06602; Hocquemiller et al. 2020), *N*-acetyl-α-glucosaminidase (NAGLU; Marsh and Fensom 1985; Calbiochem [San Diego, California, USA] 474500), heparan-α-glucosaminide *N*-acetyltransferase (HGSNAT; Moscerdam [Berkshire, UK] EM31025), *N*-acetylglucosamine-6-

TABLE 1. Activity of various lysosomal enzymes in tissue homogenates from Kaka (*Nestor meridionalis*) affected with and not affected with mucopolysaccharidosis (MPS) II and a control (Cockatiel, *Nymphicus hollandicus*) on 4-methylumbelliferyl substrates.

		Enzyme activity (pmol/min per mg)				
Disease	Enzyme[a]	Affected Kaka liver	Control Kaka liver	Control Cockatiel liver	Affected Kaka brain	Control Cockatiel brain
MPS IIIA	SGSH	7	31	18	5	8
MPS IIIB	NAGLU	331	259	42	48	34
MPS IIIC	HGSNAT	0.03	0.07	0.33	2.10	0.98
MPS IIID	GNS	3.03	2.80	1.91	2.16	1.13
MPS VII	GUSB	3816.3	6163.6	5757.0	1726.1	599.0
MPS II	IDS	0.15	3438.1	131.7	0.085	57.0

[a] SGSH = *N*-sulfoglucosamine sulfohydrolase; NAGLU = *N*-acetyl-α-glucosaminidase; HGSNAT = heparan-α-glucosaminide *N*-acetyltransferase; GNS = *N*-acetylglucosamine-6-sulfatase; GUSB = β-glucuronidase; IDS = iduronate-2-sulfatase.

sulfatase (GNS; Toronto Research Chemicals [North York, Ontario, Canada] M334955), and β-glucuronidase (Sigma [St. Louis, Missouri, USA] M9130). Manufacturer-provided methods were used to examine the activity of HGSNAT and GNS. All data were reported as picomoles per minute per milligram (pmol/min per mg), and fluorescent counts were read on a Victor3 plate reader (PerkinElmer Inc., Waltham, Massachusetts, USA) with emission and excitation filters of 355 and 460 nm.

RESULTS

Clinical signs and history

A juvenile male Kaka was found weak and lethargic in a carpark of Nelson Lakes National Park, New Zealand. It was easily caught and taken to Natureland Zoo, Nelson, where it was given a course of antibiotics and antifungal drugs before being referred to the Wellington Zoo for further treatment. On arrival, the bird was semicomatose but improved with intravenous fluids. Radiographs showed an enlarged liver; blood biochemistry showed normal liver function but raised potassium levels. Although it began eating, clinical signs did not improve, and seizures became noticeable. Supportive therapy was discontinued, and the bird was euthanatized on welfare grounds.

Gross pathology

At postmortem examination, the body was in poor nutritional condition. The liver was enlarged, pale, and friable with rounded edges. Fluid in the pericardial sac was mildly increased in volume.

Histopathology

Many neurons throughout the brain, but particularly Purkinje cells (Fig. 1a), roof nuclei, and nuclei of the brainstem, were either vacuolated or contained fine, granular, pale material distending the cytoplasm and displacing Nissl substance. In epoxy resin and toluidine blue–stained sections, the Purkinje cells contained pale blue–gray colloid-like inclusions in the cytosol up to 2–3 μm in diameter, but with poor contrast, that remained in the section postprocessing. Some neurons in the brainstem contained very small

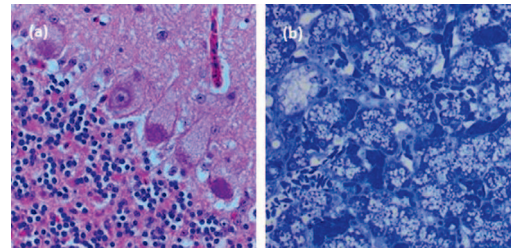

FIGURE 1. Histopathology of the Kaka (*Nestor meridionalis*) with mucopolysaccharidosis II. (a) Purkinje cells in the cerebellum showing foamy cytoplasm slightly distending the cell bodies. H&E. Bar=50 μm. (b) Liver showing highly vacuolated hepatocytes and endothelial cells. Epoxy resin section. Toluidine blue. Bar=50 μm.

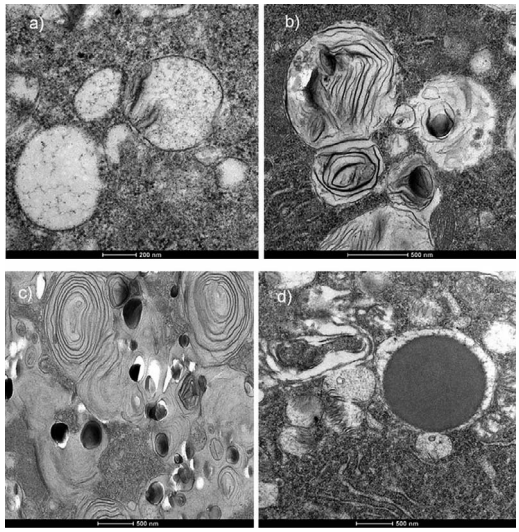

FIGURE 2. Electron micrographs of the brain of the Kaka (*Nestor meridionalis*) with mucopolysaccharidosis II. (a) Brainstem neurons showing membrane-bound vesicles with only a small amount of amorphous material and a similar vesicle with some electron-dense laminar membranous profiles. Bar=200 nm. (b) A brainstem neuron showing a variety of laminar, curved, and circular membranous profiles. Bar=500 nm. (c) A cerebellar Purkinje cell showing large gel-like inclusions (up to 2–3 μm in diameter) containing a variety of rounded membranous profiles and electron-dense bodies. The latter have been slightly torn from the gel-like material, resulting in artifactual spaces. (d) A round granular inclusion in a brainstem neuron resembling a polyglucosan body distinct from those shown in Purkinje cells in panel (a). Bar=500 nm.

basophilic staining granules, often within a surrounding paler area in the cytosol. Other vacuolated cells included macrophages, perivascular macrophages, astrocytes, and endothelial cells. Spheroids were noted in cerebellar white matter, in roof nuclei, and in some brainstem nuclei. Hepatocytes and Kupffer cells were also highly vacuolated (Fig. 1b).

Electron microscopy

In neurons, storage material had accumulated in bilayer, membrane-bound cytosomes. Some contained only a small amount of amorphous material (Fig. 2a). More frequently, they contained a variety of membranous profiles or dense bodies. Membranous profiles were either linear or curved, with some in concentric circles (Fig. 2b, c). Cytosomes in Purkinje cells were much larger than elsewhere and more complex. Various curved and circular profiles and dense bodies occurred within a larger matrix of poorly staining colloid-like material (Fig. 2d). The dense bodies were often displaced by the microtome knife, creating artifactual space. When viewed in the correct plane, the large complex cytosomes were also membrane bound. Round, dense, granular bodies, mostly filling a membrane-bound cytosome, were distinct from those earlier and less commonly observed (Fig. 2d).

Mass spectroscopy

Heparan sulfate–derived disaccharides prepared by the butanolysis method were measured in the affected Kaka brain and liver and compared with levels in a control Kaka liver and a Cockatiel brain (Fig. 3). These showed an elevation of HS disaccharide in the affected Kaka tissues relative to controls. Disaccharides prepared by the methanolysis method showed a similar relative elevation of HS plus a modest increase in DS (Fig. 3a) within the affected Kaka's liver. Chondroitin sulfate levels did not change.

Enzymology

The activity of various lysosomal enzymes associated with HS catabolism show that this disorder is associated with deficient activity of IDS (Table 1). In human patients, this is associated with MPS II (Hunter syndrome).

DISCUSSION

Histopathology and ultrastructural findings in this Kaka, that presented with a neurologic disease, were indicative of a lysosomal storage disease and more particularly a MPS. The round cytosomes depicted in Figure 2d resemble polyglucosan bodies (Jolly et al. 2002), and it is suggested that they are composed of complex sugars derived from aggregations of the linear repeating disaccharide units in the same manner as those in

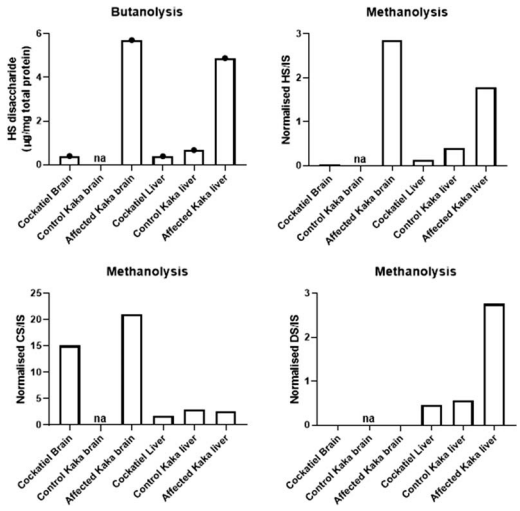

FIGURE 3. Quantitation of stored glycosaminoglycans in the brain and liver of the Kaka (*Nestor meridionalis*) with mucopolysaccharidosis II compared with levels in a control Kaka and Cockatiel (*Nymphicus hollandicus*) determined by acid alcoholysis, liquid chromatographic–tandem mass spectrometry analysis. (a) Heparan sulfate (HS)–derived disaccharide concentration by butanolysis. na = not available. Levels of HS are increased in the affected Kaka liver and brain (c.f. control tissues). Graphs show the relative abundance of (b) HS, (c) chondroitin sulfate (CS), and (d) dermatan sulfate (DS)–derived disaccharides by methanolysis. Note that HS is increased in affected Kaka liver and brain (b), and DS is elevated in affected Kaka liver (d), whereas CS levels are unchanged in the affected Kaka liver (c).

polyglucosan bodies, which accumulate glycogen.

A MPS was confirmed by mass spectrometry, which showed an elevation in HS disaccharides in the affected Kaka liver and brain relative to control samples. No normal Kaka brain was available, so that from a normal Cockatiel was used. Additionally, by the methanolysis method, a five times increase in DS disaccharides was measured in affected liver relative to that in the control liver, which narrowed the probable diagnosis to MPS I, MPS II, and MPS VII; MPS IIIA, B, C, and D were also considered a possibility, because small elevated amounts of DS may also be recorded in some of these diseases by the methanolysis method (Lamanna et al. 2011); this has also been noted by two of the authors (P.J.T. and M.F.S.). The absence of bone lesions made MPS I unlikely, because they are more prominent in that disorder. Enzymology showed deficient activity of IDS, but not of the other enzymes assayed. The disease in this Kaka is thus equivalent to MPS II (Hunter syndrome) in humans. This is the first recorded case of MPS II in birds. It is also rare in animals, with only a single case recorded in a Labrador retriever dog (Wilkerson et al. 1998), although genetically engineered mouse models have been created. In humans, inheritance is X-linked, as it was in the dog, so the disease is mainly found in males. Birds have different sex-determining chromosomes that do not share the same genes as mammalian X and Y chromosomes; hence, inheritance is potentially autosomal.

Kaka are an endangered species and rare in some habitats, with an underrepresentation of females, even in healthy populations (Greene and Fraser 1998), because Kaka are cavity nesters and spend more than 10 wk in the nest before the chicks fledge. As such, both females and chicks are particularly prone to predation by introduced mammals such as stoats (*Mustela erminea*), cats, and brushtailed possums, now ubiquitous throughout New Zealand. Cavity nesting has also been shown to be the key trait associated with range contraction in New Zealand's endemic forest birds (Parlato et al. 2015), resulting in isolated pockets of birds, which could increase the likelihood of in-breeding, a key feature in the epidemiology of genetic diseases of animals (Jolly et al. 2016). Studies on breeding behavior in isolated populations such as Kaka have shown no evidence of inbreeding avoidance (Jamieson et al. 2009), but there is no evidence to suggest the Kaka in the northern region of the South Island have lower genetic diversity than elsewhere in the country (Dussex et al. 2015). Levels of genetic diversity in Kaka from this region are in fact greater than those reported in Kea (*Nestor notabilis*) by Dussex et al. (2014) and in Kakapo (*Strigops habroptilus*) by Bergner et al. (2014). Furthermore, Kaka are adept flyers and may cross the Cook Strait to mix with North Island populations, and vice versa.

Although an inherited LSD is unlikely to be a threat to large, healthy, wild populations, the small population base and relative smaller number of females, particularly in the north of the South Island, makes such a disease a potential problem. To help overcome this problem, captive breeding programs are in place to breed birds for release into the wild (Anonymous 2020).

Because sexual dimorphism based on bill and body size is not always easily measured, feathers are regularly collected for sex determination, so heterozygote testing of DNA from feather quills collected for sex determination would be feasible if the mutation could be found.

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SUPPLEMENTARY MATERIAL

Supplementary material for this article is online at http://dx.doi.org/10.7589/JWD-D-20-00173.

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