

Cyclodextrin therapy in the NPC cat model

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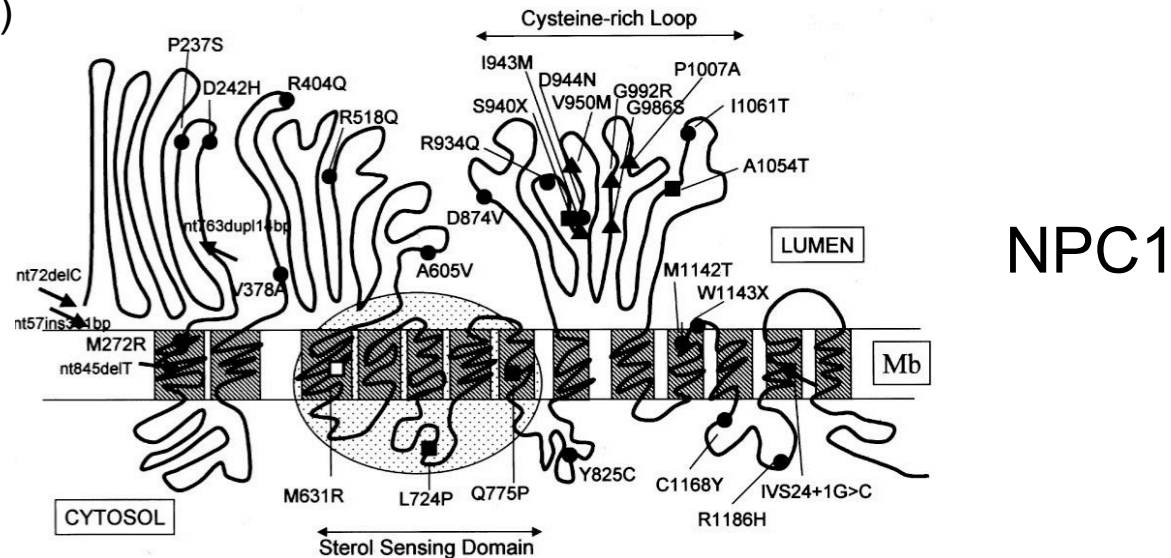
National Niemann-Pick Disease Foundation

Other:

RR02512 (Haskins)

Feline Niemann-Pick type C disease

Feline NPC disease is due to a spontaneously-occurring missense mutation in *NPC1* (C955S; 2864 G-C)



- Abnormalities are similar to those present in juvenile-onset patients:
 - Neurologic, hepatic, and pulmonary disease
 - Unesterified cholesterol and glycosphingolipids accumulate
 - Purkinje cell death, ectopic dendritogenesis and neuroaxonal dystrophy
- NPC disease cats:
 - can be genotyped at birth
 - can begin therapy before or after the onset of clinical evidence of disease
 - can be evaluated for the duration of their lives (median of 24 weeks) using measurements that can also be made in children (blood, CSF, imaging).
 - Have produced 111 affected cats in 7 years (15 cats per year)

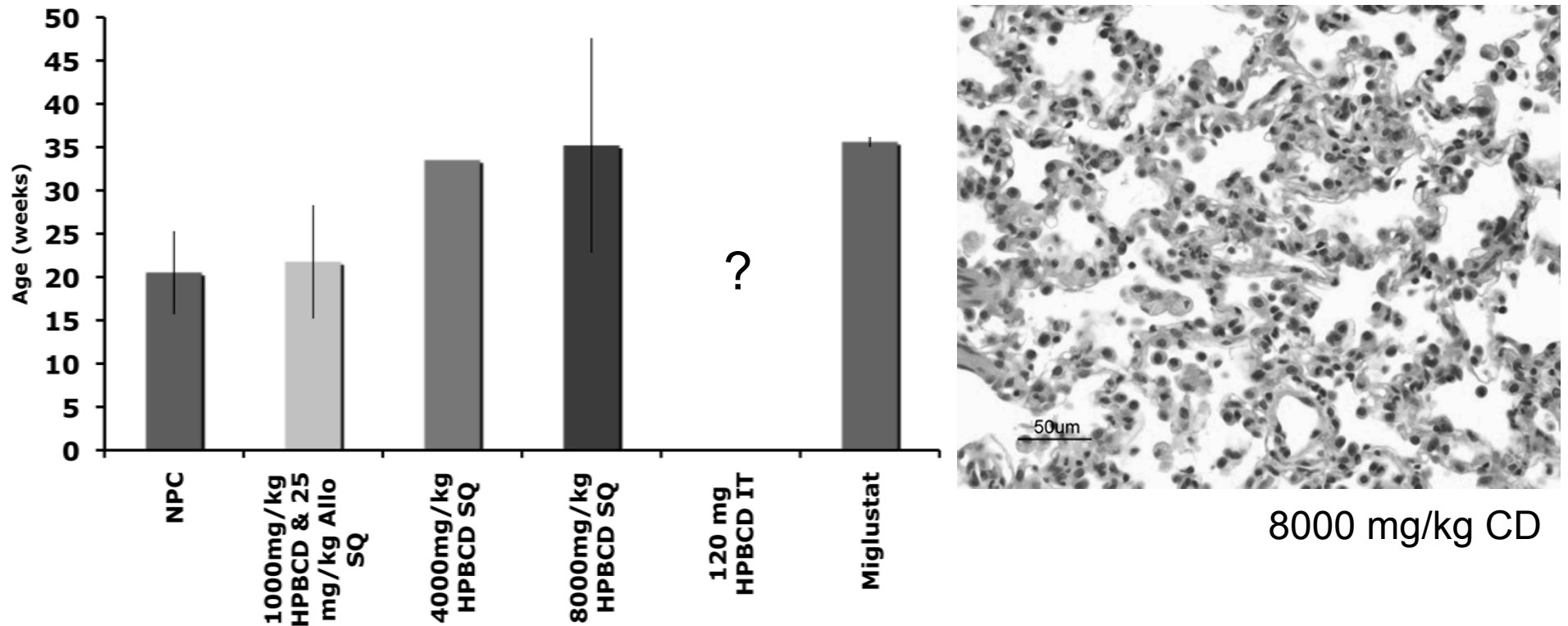
Neurological disease

Progressive neurological dysfunction develops which is indicative of cerebellar/vestibular dysfunction.

Onset of signs	Age in weeks (mean +/- SD)
Tremors and ataxia	6.8 +/- 0.8 weeks
Falling when running	11.8 +/- 1.9 weeks
Falling when walking	15.3 +/- 2.6 weeks
Unable to walk	17.0 +/- 2.1 weeks
Unable to stand	19.0 +/- 3.0 weeks

Subcutaneously administered cyclodextrin

Sigma HP- β -CD-H107 powdered form



Survival time (all cats except 2 (*) were euthanized due to neurological dysfunction - inability to maintain sternal recumbancy)

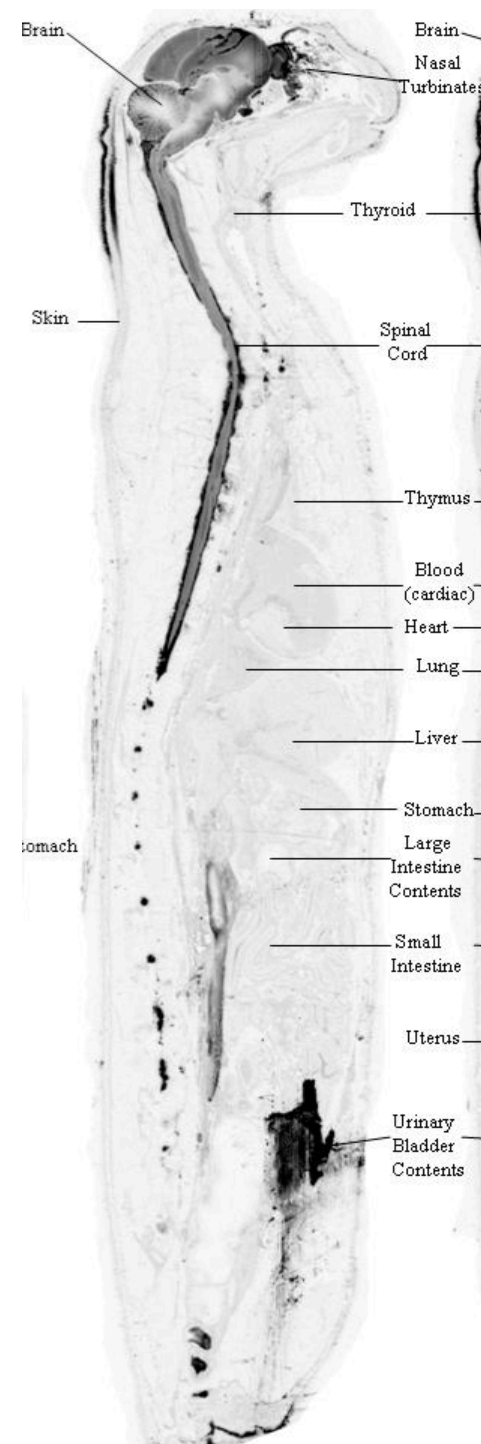
- 4000 mg/kg & 8000 mg/kg HP β CD-treated cats lived longer than untreated cats
 - Two cats treated with 4000 mg/kg SQ lived to 31 and 36 weeks of age
 - Two of five cats treated with 8000 mg/kg SQ lived to 40 and 52 weeks of age
 - Two of five cats treated with 8000 mg/kg died acutely at 21 and 25 weeks of age due to pulmonary disease*

Mean plasma and CSF concentration of HPBCD in normal cats 1 hour after SC injection

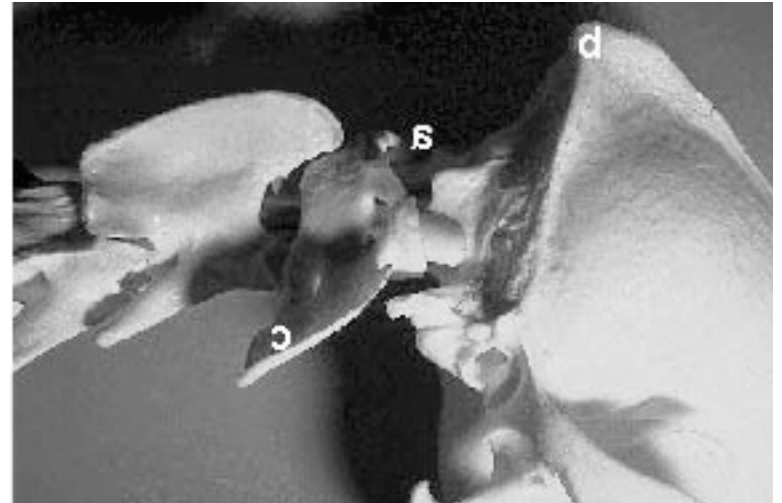
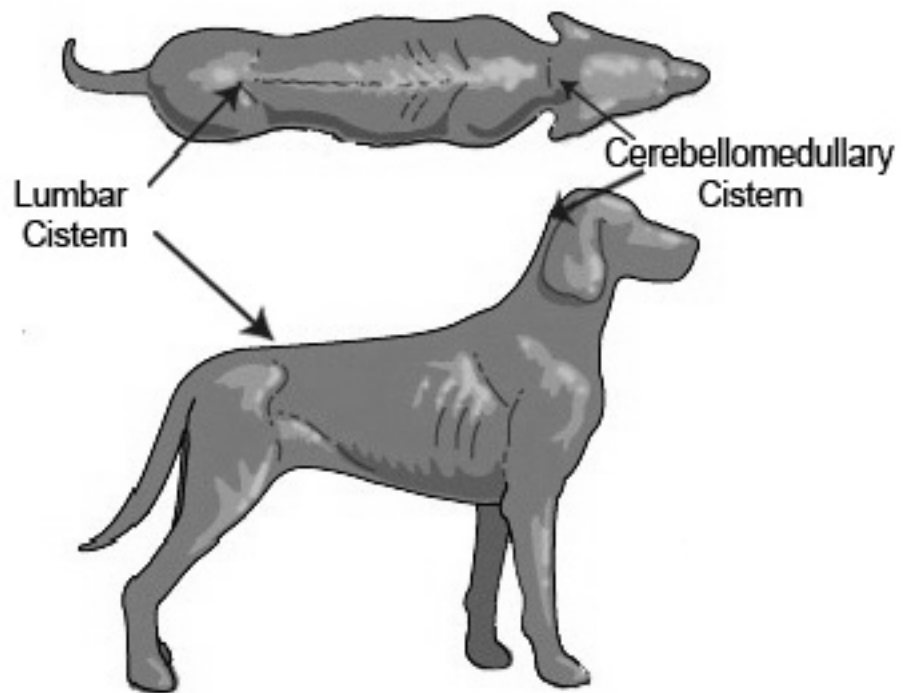
Dose (mg/kg)	Concentration ($\mu\text{g/mL}$)		Plasma/CSF Ratio
	Plasma	CSF	
1000	547	$<5.00^1$	>109
4000	2570	19.45	132
8000	3485	21.2	164

Pharmacokinetic parameters for HPBCD in plasma and CSF of normal cats following a single 120 mg IT dose of HPBCD

PK Parameters	Units	Plasma	CSF
C_{max}	($\mu\text{g/mL}$)	125.4	11645
T_{max}	(h)	0.25	0.25
$\text{AUC}_{0-24\text{h}}$	($\mu\text{g}\cdot\text{h/mL}$)	173	20300
$\text{AUC}_{0-\text{inf}}$	($\mu\text{g}\cdot\text{h/mL}$)	215	20400
CL/F	(mL/h)	557	5.89
$T_{1/2}$	(h)	1.77	3.93
V_z/F	(mL)	1420	33.3



Cerebrospinal fluid collection in dogs and cats



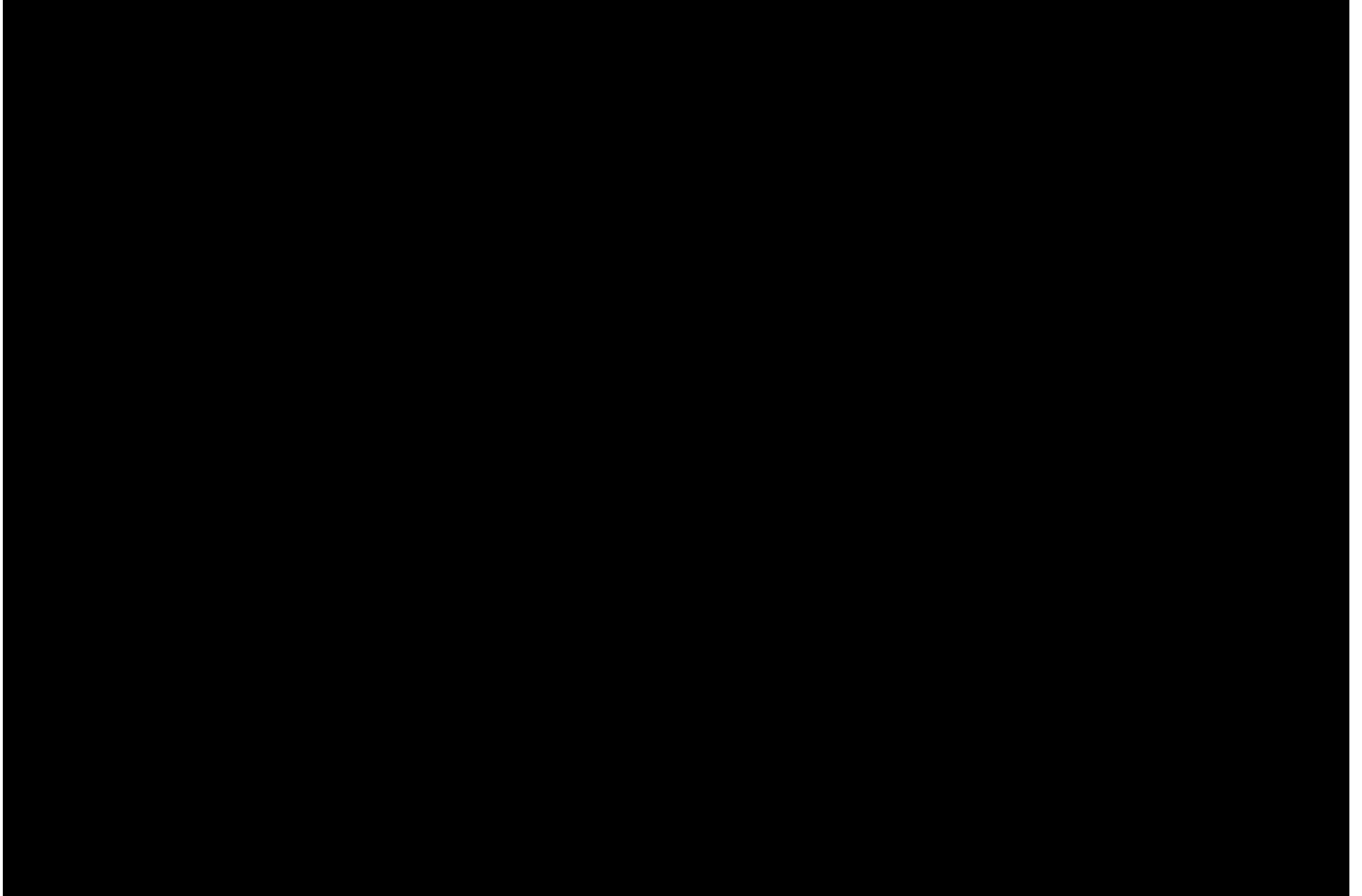
Treatment groups

Group	Genotype	Route	Dose	Dose per ml of CSF (~ 4 ml in adult)	Dosing interval	Animal number	
						M	F
1	Unaffected	-	-		-	>50	>50
2	NPC	-	-		-	30	23
3	NPC	IT	3 mg	0.75mg/ml	14 days	1	2
4	NPC	IT	7.5 mg	1.9mg/ml	14 days	1	2
5	NPC	IT	15 mg	3.75mg/ml	14 days	2	1
6	NPC	IT	30 mg	7.5 mg/ml	14 days	0	3
7	NPC	IT	60 mg	15 mg/ml	14 days	2	1
8	NPC	IT	120 mg	30 mg/ml	14 days	0	5
9	NPC	IT; SQ	120 mg; 1000 mg/ kg BW	30 mg/ml	7 days; 14 days	5	3
10	NPC	IT	120 mg late	30 mg/ml	14 days	3	2

IT-Sigma HP- β -CD-C0926 cell-culture tested form
20% solution Groups 1-6, 10; 3% solution Groups 7-9

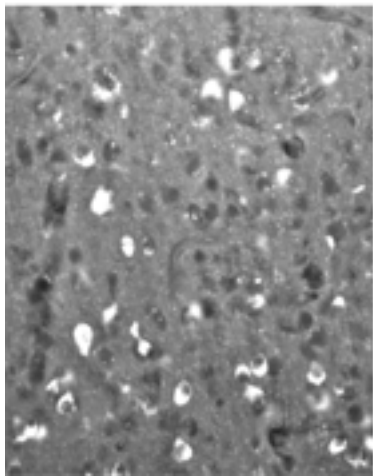
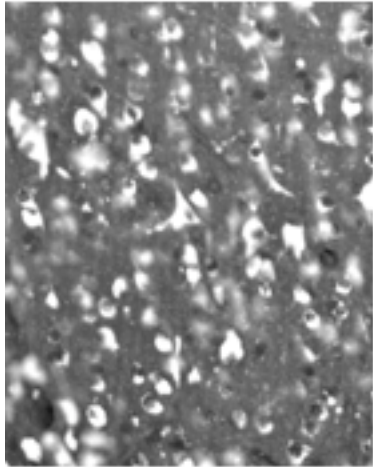
SC-Sigma HP- β -CD-H107 powdered form
20% solution

120 mg IT cyclodextrin started at 3 weeks of age results in clinically normal NPC cats at 24 weeks of age

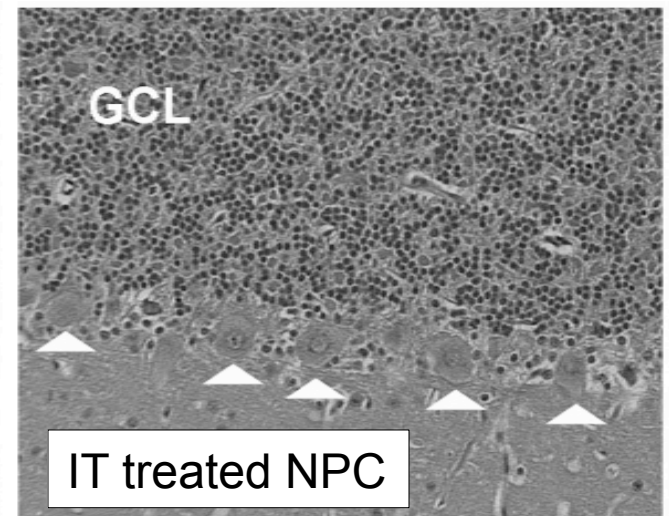
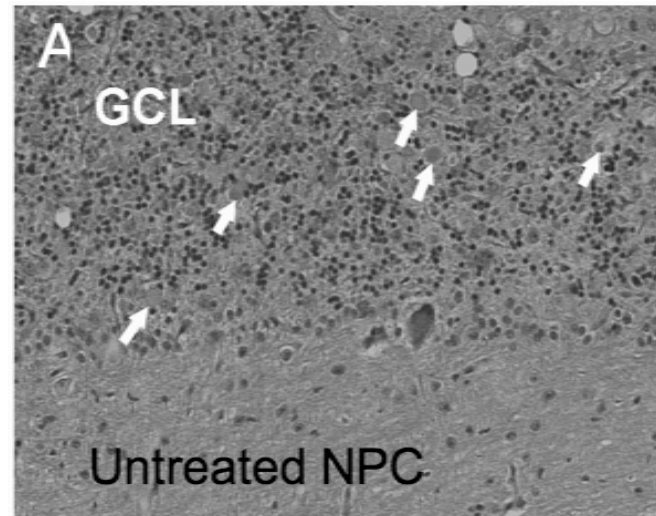


Purkinje cell numbers, cholesterol, gangliosides, and sphingosine normalize in IT treated cats

NPC UNTREATED



IT HPBCD



What happens if cats are treated after signs have begun?



24 week old untreated
NPC cat



42 week old NPC cat in which 120
mg IT administered at 16 weeks of
age
(late treatment group; Group 10)

What is the lowest dose of cyclodextrin that results in clinical improvement?

3mg IT (0.75 mg/ml)



7.5 mg IT (1.9 mg/ml)



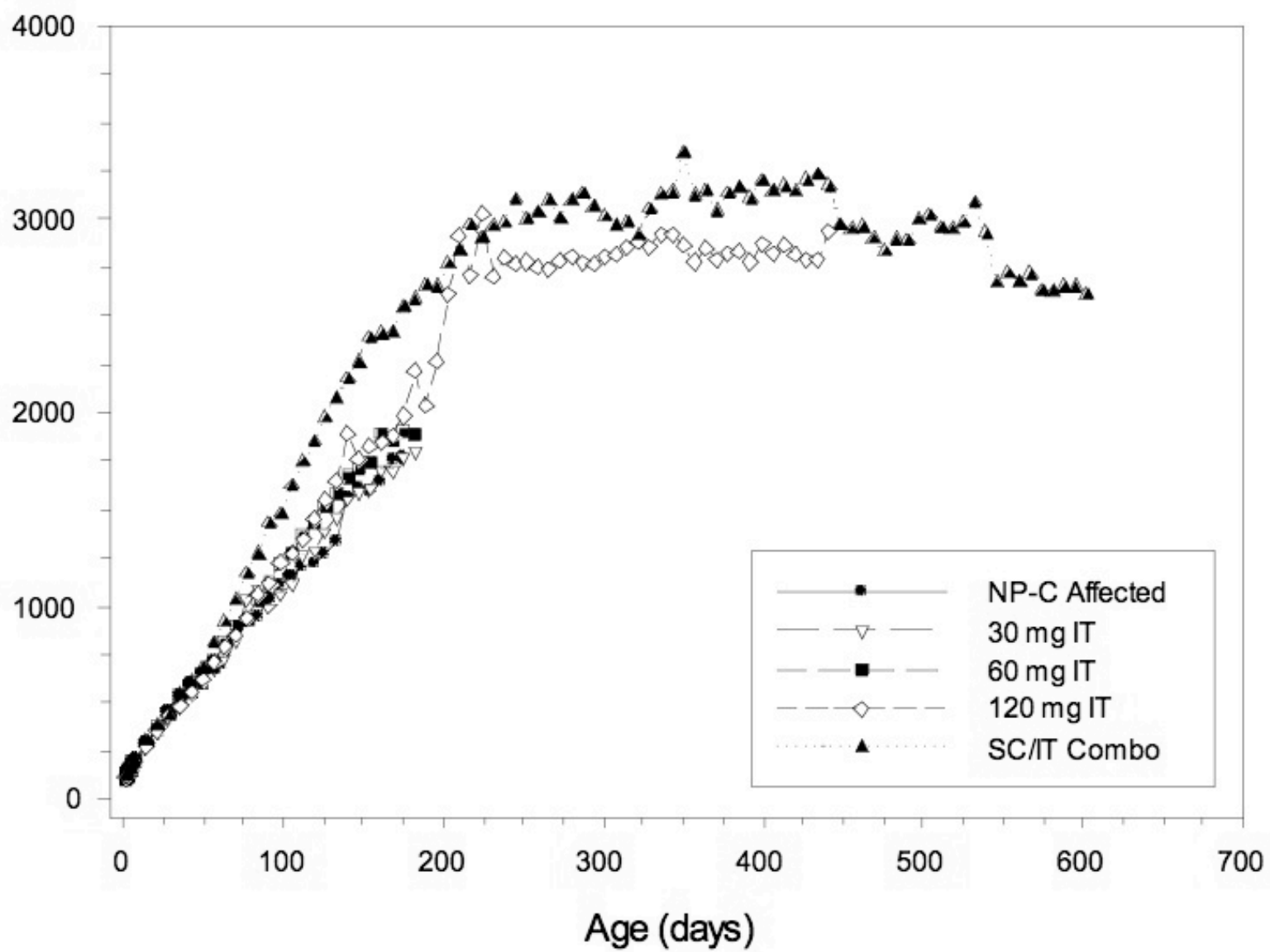
24 week old NPC cats in which IT treatment began at 3 weeks of age

How do the cats treated with 120 mg IT do long term?

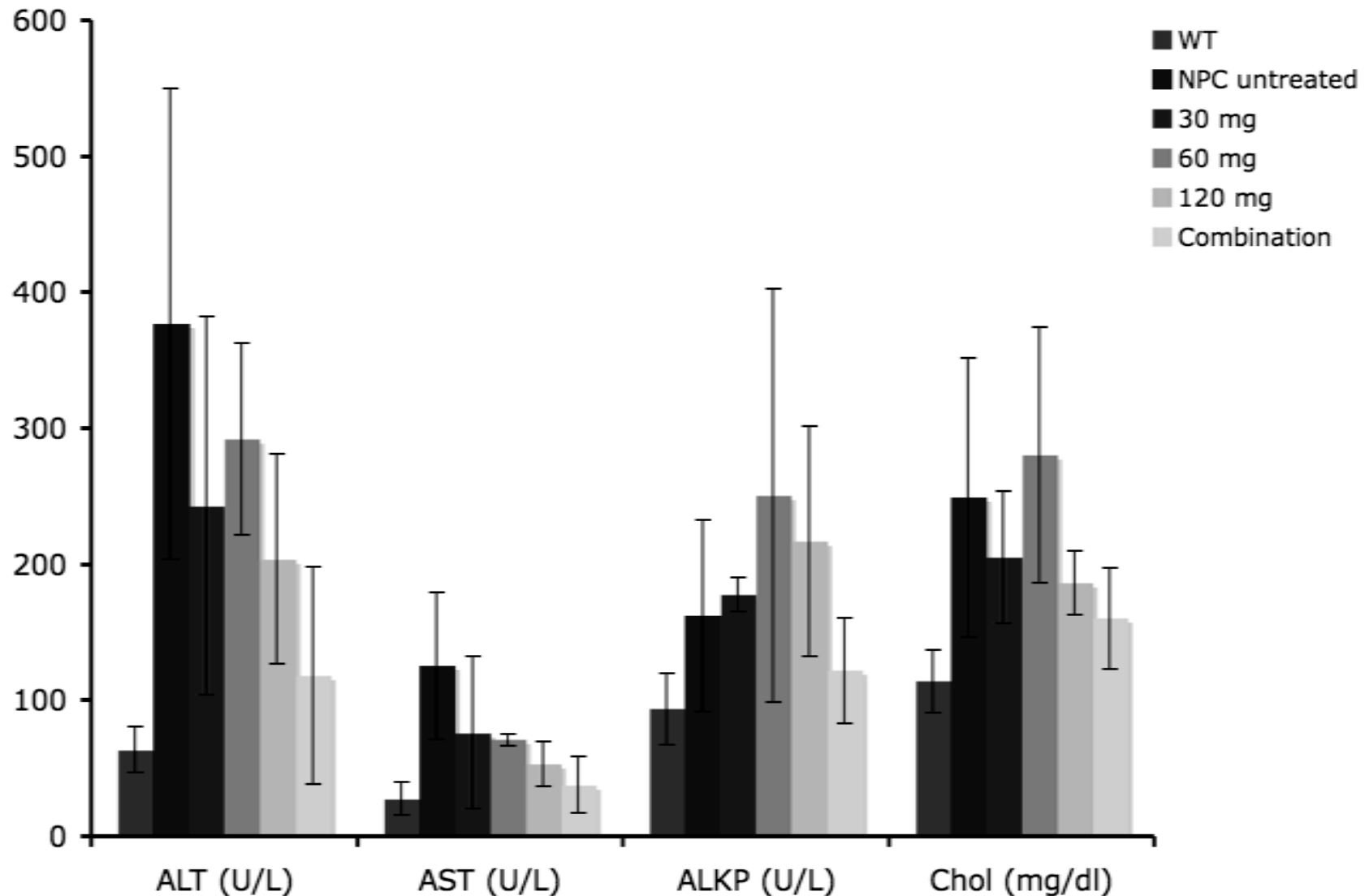


68 week old NPC cat treated with 120 mg IT and 1000 mg/kg SC

Mean Body Weight (g)



Serum chemistry analysis at 24 weeks of age

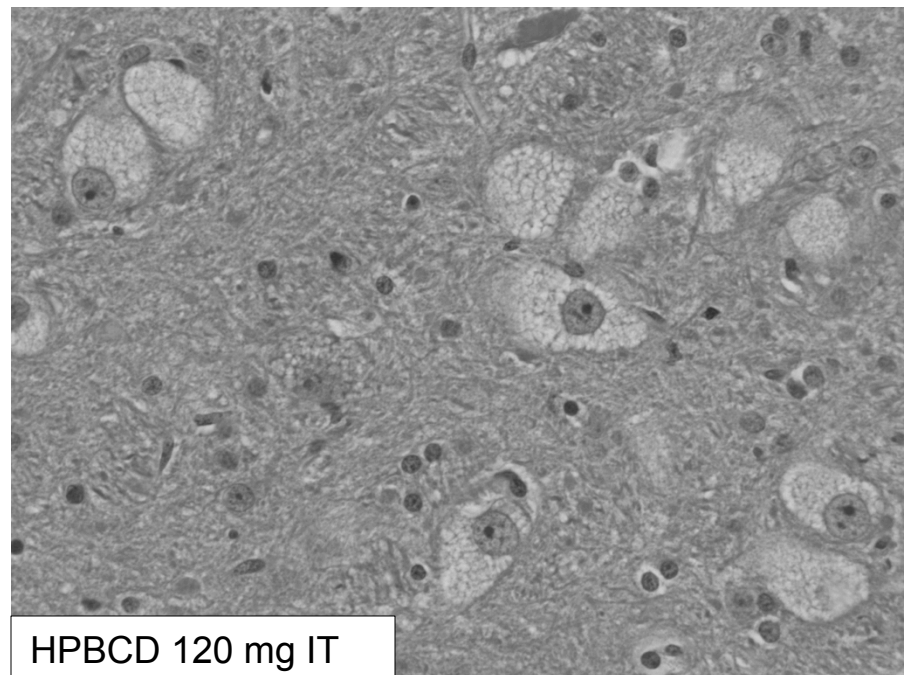
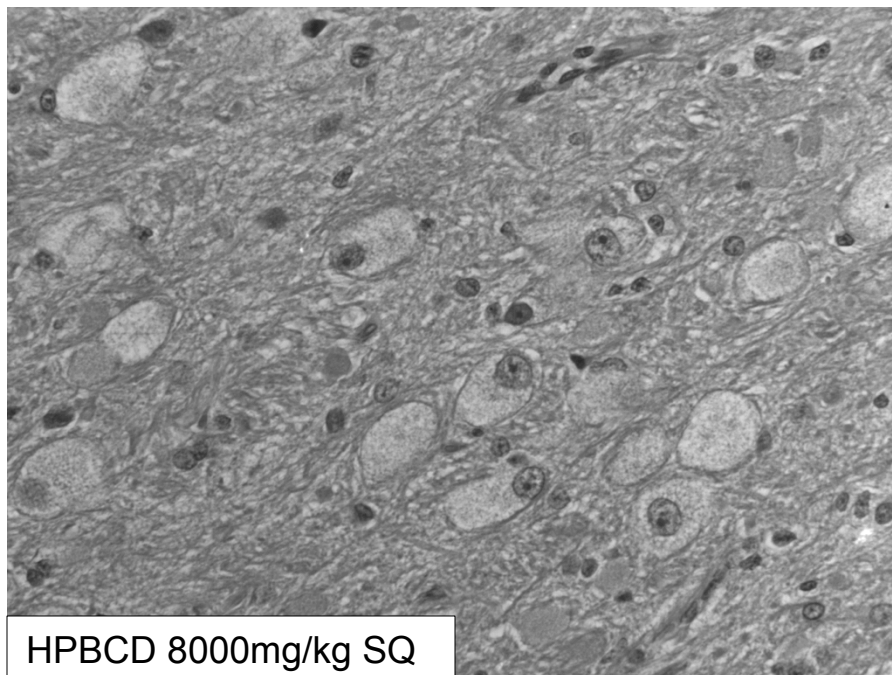
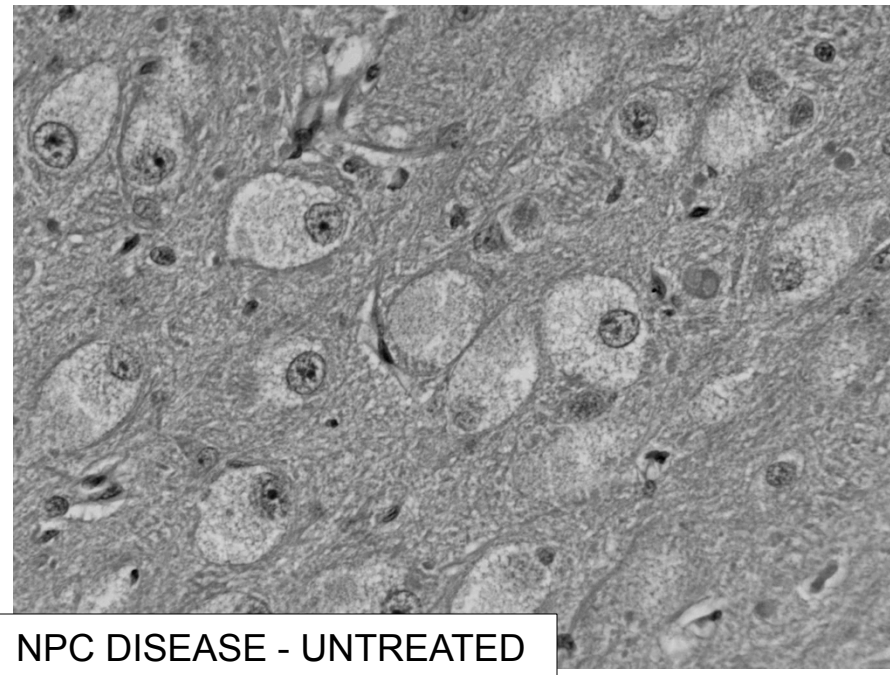
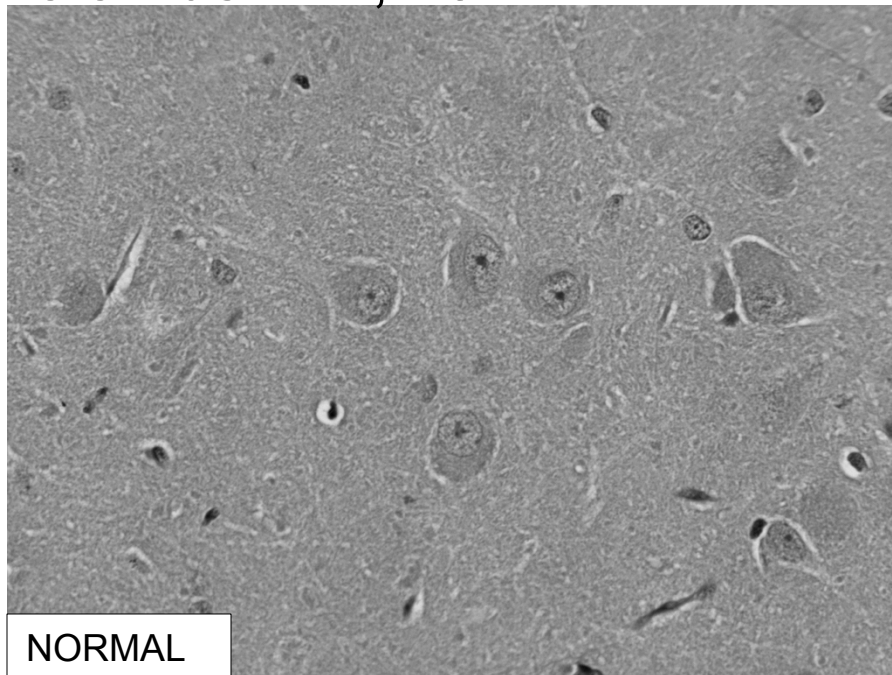


Cats receiving both SC and IT cyclodextrin showed liver enzyme values indistinguishable from WT cats.

Questions in feline model

- What happens if cats are treated IT after signs have begun?
 - Neurological signs of disease stop progressing
 - For how long?
- What is the lowest dose of cyclodextrin IT that results in the most substantial neurological benefit (based on short-term clinical evaluation)?
 - 15 mg and higher (≥ 3.75 mg/ml)
- What dose results in no alterations to hearing threshold?
 - 7.5 mg (≤ 1.9 mg/ml)
- How do the cats treated with 120 mg IT do long term?
 - They develop signs of neurological disease localized to other parts of the nervous system (ie. brainstem)
 - Liver enzymes continue to rise
 - Pulmonary disease?
 - Peripheral nerve disease?

Thalamus- HE, 40x



Why do neurological signs develop in older treated cats?

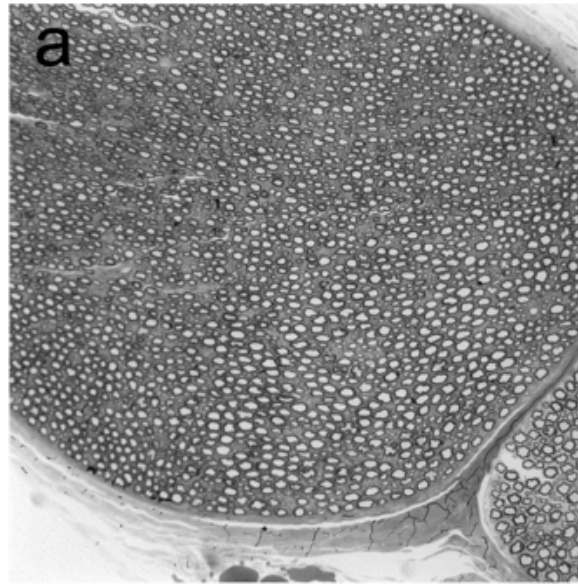
- Brainstem may not be treated as effectively as cerebellum
 - Cerebellomedullary cistern delivery may not allow cyclodextrin to reach all brainstem nuclei
 - Cyclodextrin may not effect all neurons equally
- Cyclodextrin may be less effective with time

Questions in feline model

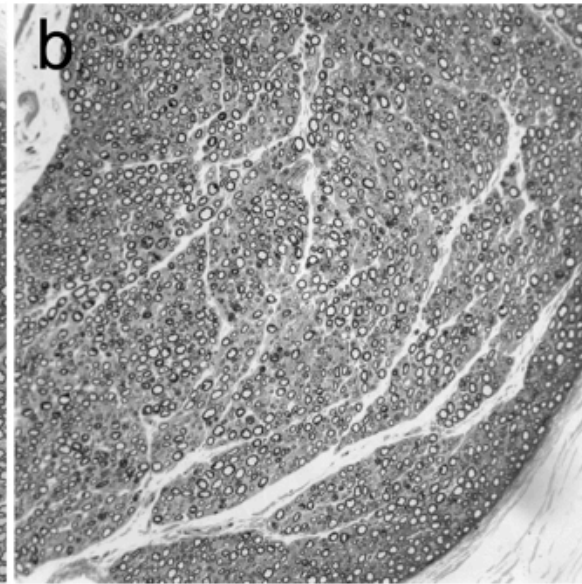
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NPC cats show thin myelin sheaths and nerve fibers containing membranous debris and lipid

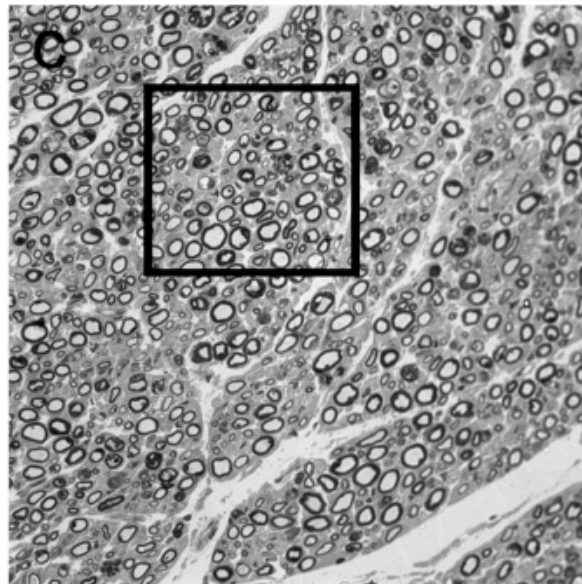
Ulnar nerve



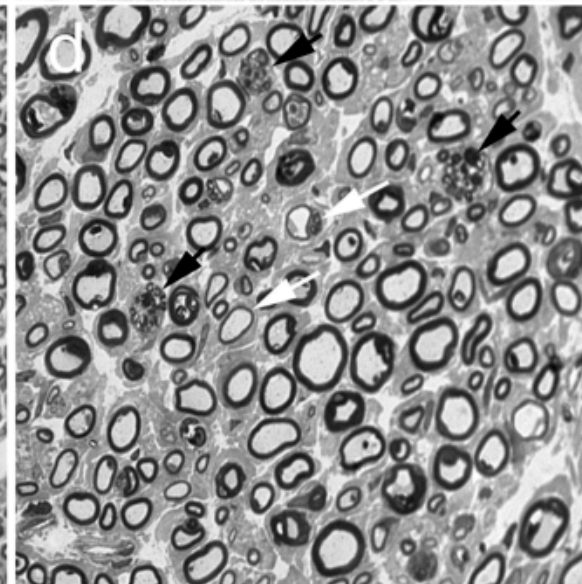
Wild type



NPC



NPC



NPC

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