Neurological manifestations in Cystinosis

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Neurological manifestations in Cystinosis

- before cysteamine was available
- despite cysteamine therapy
- potential complications of cysteamine itself or other drugs used in this disorder

Complications before cysteamine was available

- before 1960 every person born with cystinosis died in infancy or < age 10

- before cysteamine, renal transplant improved survival to 2nd/3rd decade

- visual disturbance, corneal and retinal
- muscle weakness
- CNS problems

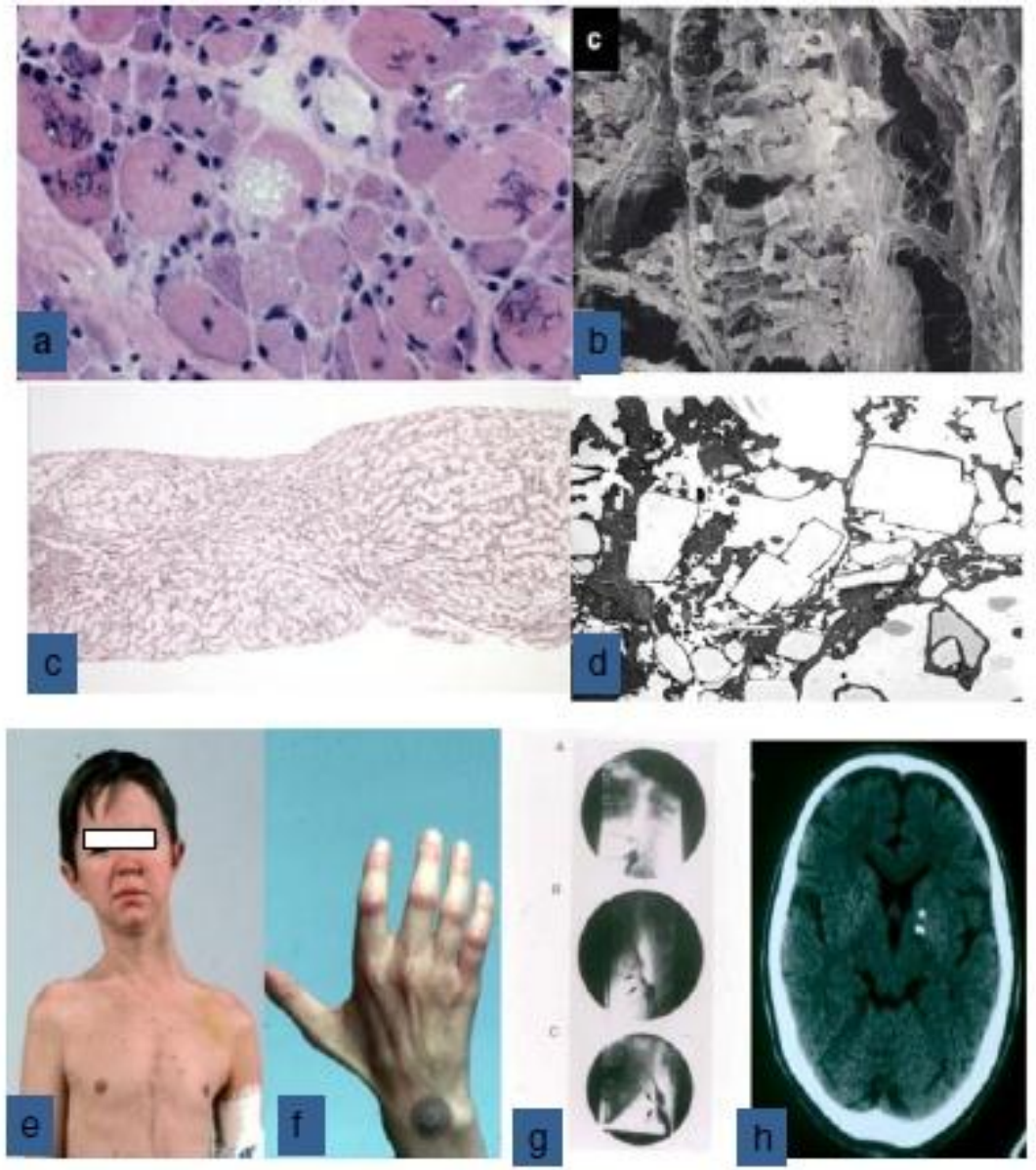
Complications before cysteamine was available

A study in 1993 of 36 patients (11 on cysteamine)

22% blind or severe visual impairment
86% hypothyroid
30% distal myopathy
58% dysphagia
22% cerebral calcification

Gahl JAMA 1993

Fig. 2 Late complications of cystinosis **a**) vacuoles in the muscle cells, **b**) cystine crystals in the hand muscles, **c**) hepatic nodular hyperplasia, **d**) bone marrow cystine crystals. **e**) adult patient with trunk muscle wasting, **f**) hand muscle atrophy **g**) barium swallowing study : Pooling in valleculae and pyriform sinuses **h**) cerebral calcifications



Pediatr Nephrol 2013 Gahl W

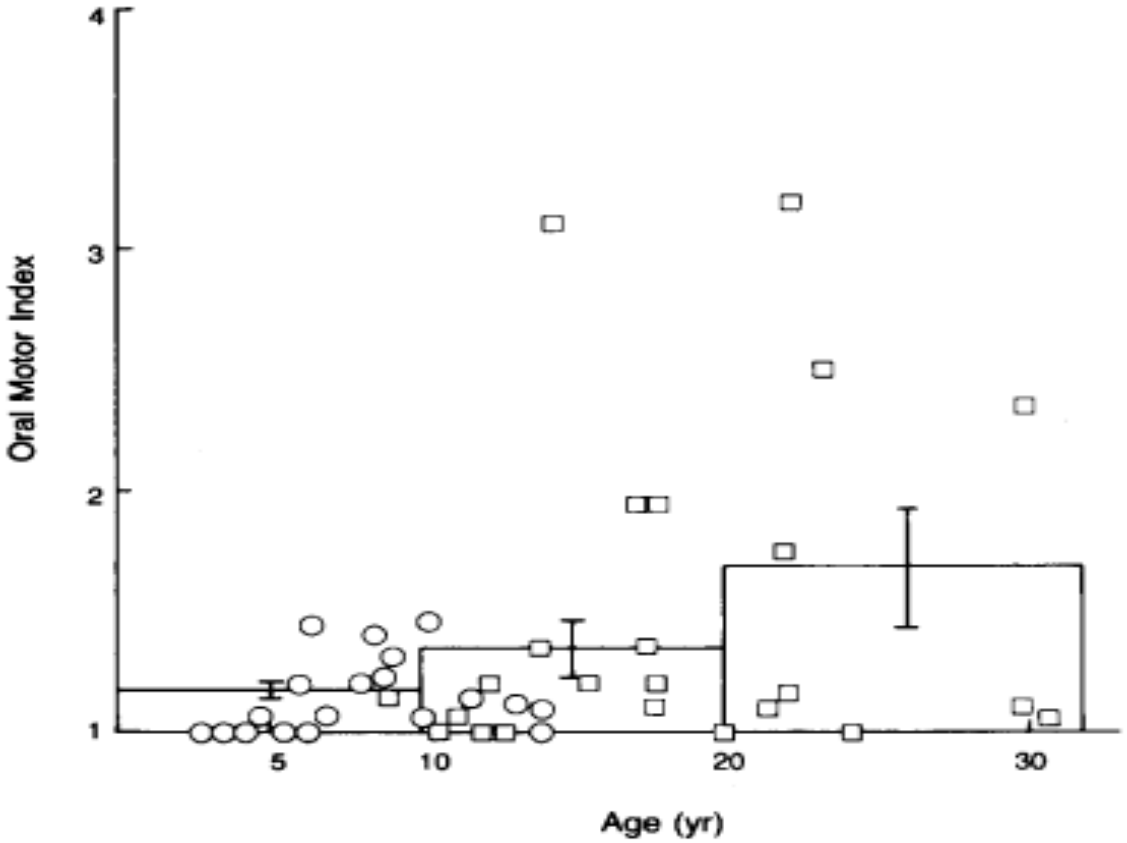


Figure 1. Oral Motor Index as a Function of Age in Patients with Nephropathic Cystinosis.

The oral motor index is plotted as a function of age at the time of examination in 43 patients. Circles represent patients who had not undergone renal transplantation, and squares those who had. The higher the oral motor index, the greater the oral motor dysfunction. The horizontal lines indicate mean values, and the vertical bars the standard error for the age groups 0 to 10, 11 to 20, and 21 to 31 years.

NEJM 1990 Sonies BC

Complications before cysteamine was available

1982 – 19y hemiparesis and dysarthria,
50% had encephalopathy

1987 – confusion, memory loss and cerebral atrophy

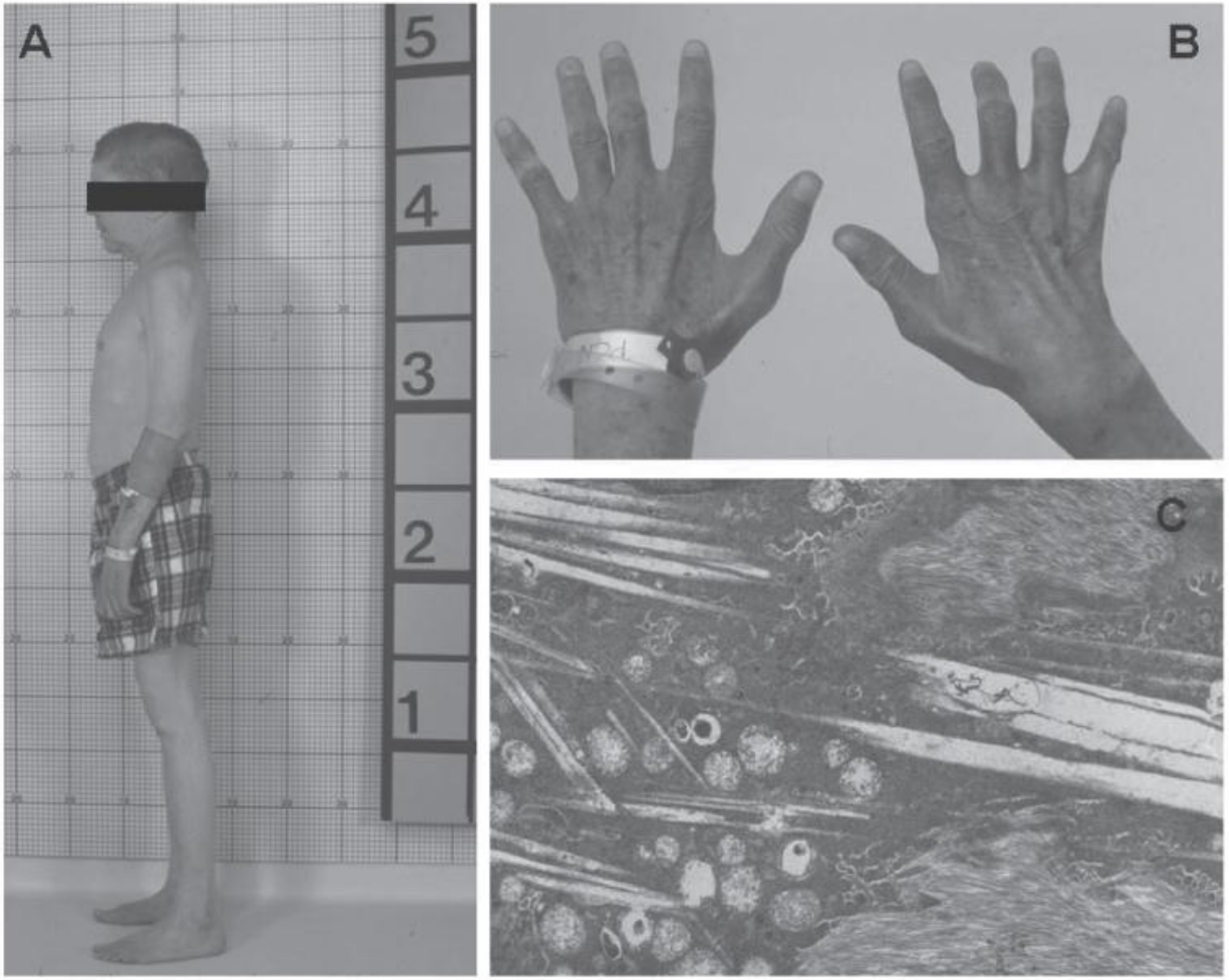
1988 – severe vacuolar myopathy in a 20y
progressed from hands to difficulty sitting up
cystine crystals confirmed on biopsy

1989 – mental retardation, epilepsy, tremor pyramidal syndrome

Neurological complications despite cysteamine

Cysteamine available since 1976 but FDA approval 1994

A 38y female was followed in one study
Age 6 – presented with renal problems
Age 13 – dialysis
Age 14 – renal transplant
Age 23 – poor concentration/coordination
Age 29 – sleepy, MRI head – atrophy
CYSTEAMINE started
Age 32 – distal myopathy, encephalopathy improved



A. Short stature and generalized muscle wasting are evident in a 39-year-old man with cystinosis. B. Marked atrophy of the interosseous muscles of the hands is seen in the same patient. C. Electron microscopy of a postmortem specimen revealed shard-like crystals in the cornea of a 22-year-old patient.

Ann Intern Med 2007 Gahl W

Nijmegen group studied 10 adults (19-36y)
7 on cysteamine, 3 not

Table 1. Clinical characteristics of adult cystinosis patients

Patient no.	Age	Sex	Height (cm)	Age at start of dialysis	Age at renal transplants	Most recent creatinine value (μmol/l)	Professional status	Visual acuity	Thyroid function	Glycaemia	Neurological and muscle dysfunction
1	19	F	161	18	–	600	health care studies	decreased	normal	normal	no
2	21	F	160.1	10	12/14	160	shop assistant	normal	normal	normal	sw/dys
3	21	M	158.5	12	14	100	low profes-sional studies	normal	normal	*	no
4	23	F	150	11	12	79	secretary	*	normal	normal	no
5	24	M	150	7	7/9/19	58	does not work	decreased	decreased	**IDDM type 1	epilepsy
6	25	M	168.8	17	19	655	does not work	normal	decreased	*	no
7	29	M	163	13	16	800	driver	normal	*	normal	no
8	30	M	175.0	not started	–	571	mechanic	*	normal	normal	no
9	33	F	154.7	11	22	96	nurse	decreased	*	normal	no
10	36	M	166	22	19/25	120	does not work	decreased	decreased	normal	sw/dys, dyspnoea

sw/dys. swallow dysfunction; *not controlled/unknown; **IDDM, insulin-dependent diabetes mellitus.

Nephrol Dial Transplant 2002 Geelen JM

Neurological complication	Bethesda study 1993 N=36	Nijmegen study 2002 N=10
Visual loss/ blindness	22%**	40%
CNS disorder	22%	10%
Dysphagia	58%	20%*

Nijmegen study conclusions

To reduce complications

- improving compliance with therapy was pivotal
- a reliable/consistent way of measuring cystine was essential
- multidisciplinary approach is necessary

Neurological complications despite cysteamine

Bethesda study 2007 (Ann Intern Med)

100 patients (18-45y)
From 1985-2006
92% transplanted
39 had long term cysteamine

Myopathy decreased if on cysteamine >20yrs

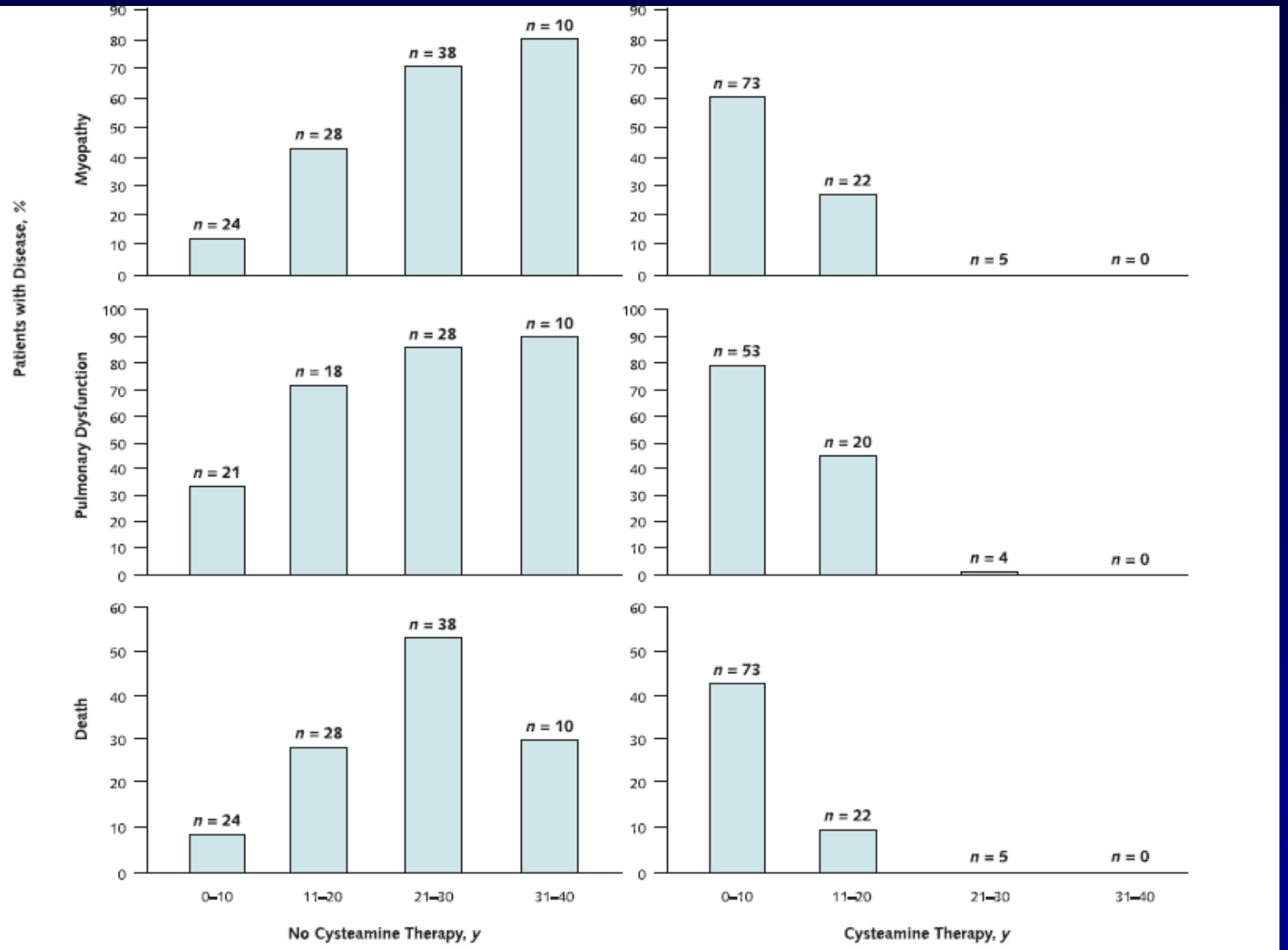
Respiratory muscle weakness (FVC) better if on cysteamine >10y (86% v 54%)

Table 1. **Patient Characteristics**

Characteristic	Patients, *n/n* (%)*
Received a transplant	92/100 (92)
Hypothyroidism	75/100 (75)
Hypogonadism (in men)	39/53 (74)
Pulmonary dysfunction†	53/77 (69)
Swallowing abnormality	58/97 (60)
Myopathy	50/100 (50)
Hypercholesterolemia‡	31/94 (33)
Retinopathy	32/100 (32)
Vascular calcifications	16/52 (31)
Diabetes mellitus requiring insulin therapy	24/100 (24)
Cerebral calcifications	21/95 (22)
Deceased	33/100 (33)

* Not all patients were evaluated for every characteristic.
† Mean values for FVC, FEV_1, total lung capacity, and diffusing capacity for carbon monoxide were less than 80% of predicted values.
‡ Total serum cholesterol level ≥5.2 mmol/L (≥200 mg/dL).

Ann Intern Med 2007 Gahl W



One hundred adults with cystinosis received cysteamine for a certain period of time and then did not receive cysteamine for a defined period of time, and each patient had or did not have a specific complication at the time of admission. Duration of cysteamine therapy was grouped in 10-year increments. The frequencies of diabetes, myopathy, pulmonary dysfunction, and death increased with time off cysteamine therapy and decreased with time on cysteamine therapy.

Ann Intern Med 2007 Gahl W

Neurological complications despite cysteamine

Cognitive dysfunction

Mild learning difficulty
Visuospatial problems

No clear benefit from Cysteamine

- cystine accumulation
- microvascular disease
- B-B barrier breakdown

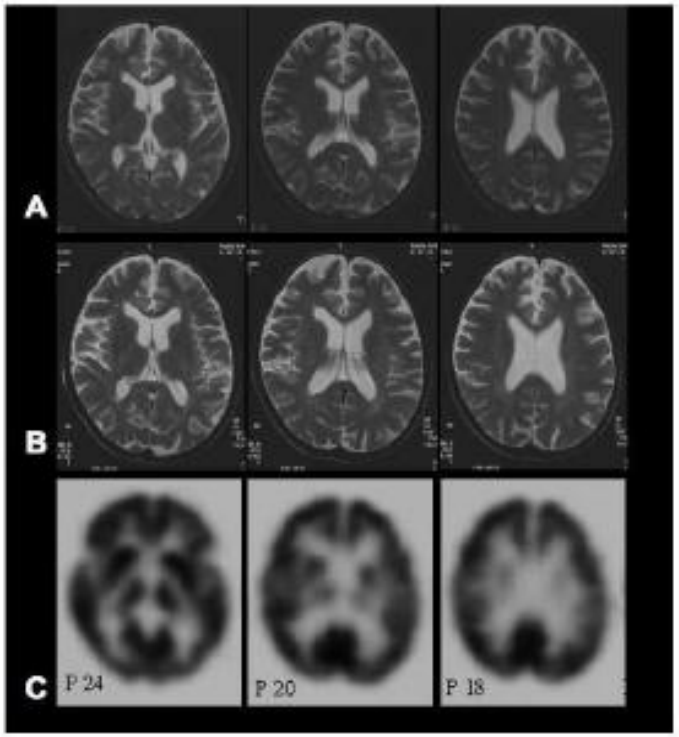


Figure 1
Imaging studies. (A) Initial magnetic resonance imaging revealed signs of cerebral atrophy with a prominent inter-hemispheral fissure at the age of 23 years. (B) The second magnetic resonance imaging 11 years later did not reveal any progression of cerebral atrophy nor any other signs of cystinosis-associated encephalopathy. (C) Positron emission tomography at the age of 34 years demonstrated normal cortical glucose utilisation without signs of encephalopathy.

Journal Medical Case Reports 2008
Muller M

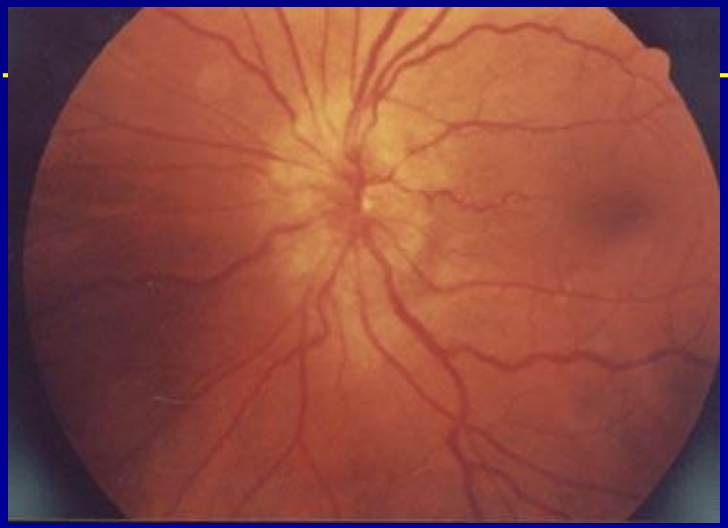
Neurological complications despite cysteamine

Atherosclerosis/Stroke

Case reports only plus vessel calcification

Small, non-invasive study of 13 patients showed no difference with controls (J Inherit Metab Dis 2011)

Benign intracranial hypertension (BIH)



- Headaches worse first thing in the morning
- Occasional shutting down of vision

Neurological complications of cysteamine and other drugs used in cystinosis

Cysteamine

Ataxia
Encephalopathy
Seizures
Lupus-like, APS
Copper deficiency
?Inflammatory myelopathy

Neurological complications of cysteamine and other drugs used in cystinosis

Immunosuppressive agents

- steroids
- tacrolimus
- cyclosporin

Neurological complications of cysteamine and other drugs used in cystinosis

Other drugs

Statins – muscle damage secondary to vitamin D deficiency +/- coenzyme Q10

PPI/metformin – B12 deficiency

Some neurological complications of cystinosis do not respond to cyteamine

e.g. the distal myopathy, **WHY?**

Other mechanisms at work

- autophagy
- increased oxidative stress/mitochondrial dysfunction

Neurological complications of cystinosis Conclusions

- Cysteamine has dramatically reduced mortality and morbidity in cystinosis
- It clearly delays the onset of renal dysfunction, encephalopathy and dysphagia
- Myopathy and cognitive disorders and possibly cerebrovascular disease do not respond so well to treatment

Neurological complications of cystinosis

- Disease mechanisms other than cystine accumulation need to be considered including oxidative stress and secondary mitochondrial dysfunction

- In addition to Vitamin D supplementation, copper, carnitine and antioxidant therapies should be considered

- A multi-disciplinary approach should be adopted with particular attention given to neuromuscular respiratory disorders and risk of aspiration