Evaluation of cholesterol metabolism in Cerebrotendinous Xanthomatosis

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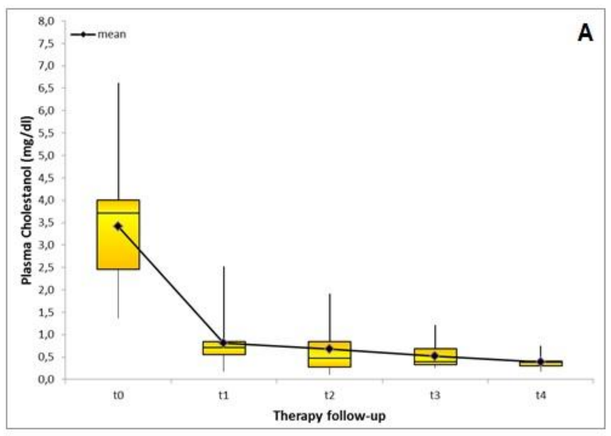
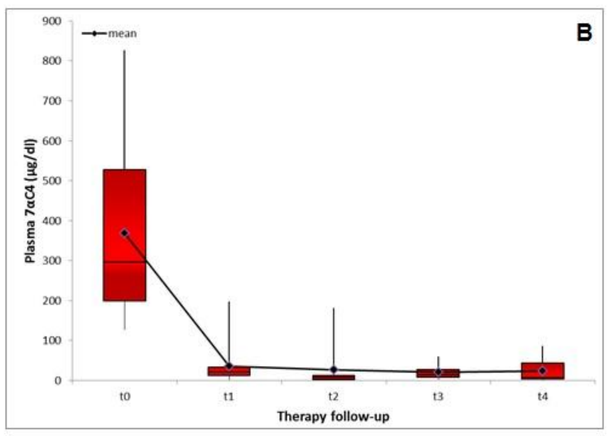
Background: Cerebrotendinous xanthomatosis (CTX) is a treatable bile acid disorder caused by mutations of CYP27A1. The pathogenesis of neurological damage has not been completely explained. Oral chenodeoxycholic acid (CDCA) can lead to clinical stabilization, but in a subgroup of patients the disease progresses despite treatment. In the present study, we aimed at identifying reliable diagnostic and prognostic markers and understanding if differences exist between stable patients and those with progression.

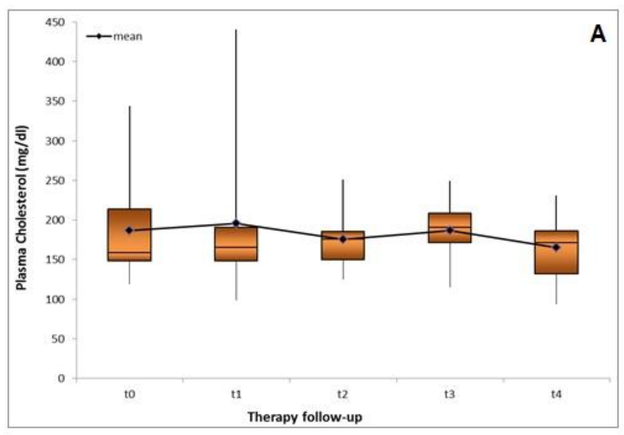
Methods: We enrolled 19 untreated CTX patients and assessed serum profile of bile acids intermediates, oxysterols, cholesterol, lathosterol, and plant sterols. Then we performed a long-term follow up and compared biochemical data with neurological outcome.

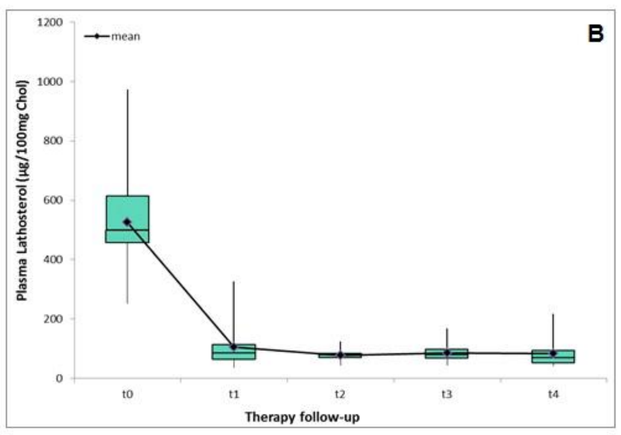
Results: We observed increase of cholestanol, 7α-hydroxy-4-cholesten-3-one (7αC4), lathosterol, and plant sterols, whereas 27-hydroxycholesterol (27-OHC) was extremely low or absent. CDCA treatment at a daily dose of 750 mg normalized all biochemical parameters except for 7αC4 which persisted slightly higher than normal in most patients, and 27-OHC which was not modified by therapy. Biochemical evaluation did not reveal significant differences between stable and worsening patients.

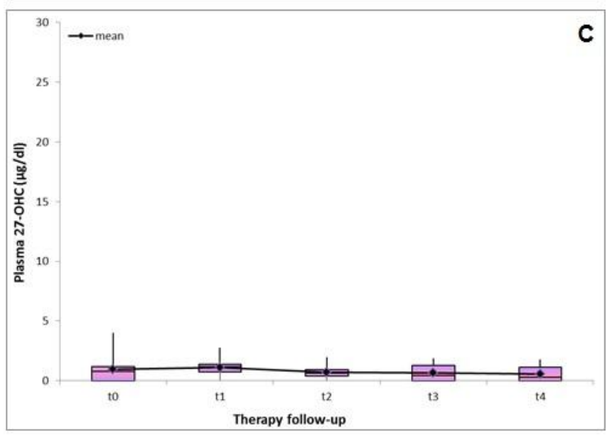
Demographic info				Clinical picture and disability scores							*CYP27A1* gene analysis	
Fm	Pt	S	Age	Catar	Xant	Cogn impair	Psych disturb	Spast	Ataxia	RS/EDSS	First mutation	Second mutation
a	1CP	M	43	yes	yes	yes	no	yes	yes	3/6 (=)	c.646 G>C	c.646 G>C
b	2CG	M	21	yes	yes	yes	yes	no	no	1/ 3 (=)	c.752 C>A	c.1263+5 G>T
	3CR	F	18	yes	yes	no	yes	no	no	0/2 (=)	c.752 C>A	c.1263+5 G>T
c	4DGS	M	30	yes	yes	yes	no	yes	yes	2/4 (=)	c.776 A>G	c.776 A>G
d	5DL	F	34	yes	no	yes	no	yes	yes	3/5 (↑)	c.1263+1 G>A	c.1263+1 G>A
	6DL	M	36	no	yes	yes	no	yes	yes	3/7 (↑)	c.1263+1 G>A	c.1263+1 G>A
e	7FG	M	45	yes	yes	yes	yes	yes	yes	3/5 (↑)	c.752 C>A	c.752 C>A
f	8FP	M	37	yes	yes	yes	no	yes	yes	3/4 (↑)	c.1184+1 G>A	c.1184+1 G>A
g	9GL	M	25	yes	yes	no	no	no	no	1/1.5 (=)	c.863 delA	c.1183 C>T
	10GM	M	13	no	no	no	no	no	no	0/0 (=)	c.863 delA	c.1183 C>T
h	11IS	M	31	yes	yes	yes	yes	yes	yes	2/3 (=)	c.647-1 G>T	c.1183 C>T
i	12PC	F	33	yes	no	yes	no	yes	no	2/3 (↑)	c.752 C>A	c.752 C>A
j	13RS	F	54	no	yes	no	yes	yes	no	2/3.5 (=)	c.646 G>C	c.1538 G>A
k	14RA	F	31	yes	yes	yes	yes	yes	yes	2/3.5 (=)	c.1263+81_1596+?del	c.1263+81_1596+?del
l	15RM	F	22	yes	yes	no	yes	no	no	0/2 (=)	c.1183 C>T	c.646 G>C
m	16SD	M	32	yes	yes	yes	yes	yes	yes	2/3.5 (↑)	c.1184+1 G>A	c.1184+1 G>A
n	17SR	F	36	yes	yes	yes	no	yes	no	3/3.5 (=)	c.646 G>C	c.1184+1 G>A
	18SV	M	29	yes	yes	yes	yes	yes	no	2/3.5 (↑)	c.646 G>C	c.1184+1 G>A
o	19VS	F	48	yes	no	yes	no	no	no	1/1.5 (=)	c.1016 C>T	c.1016 C>T

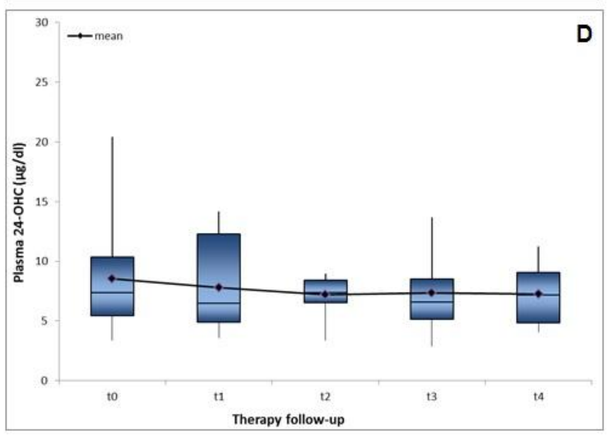


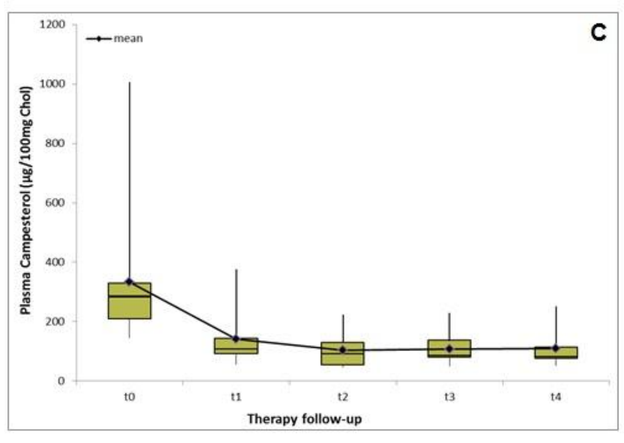


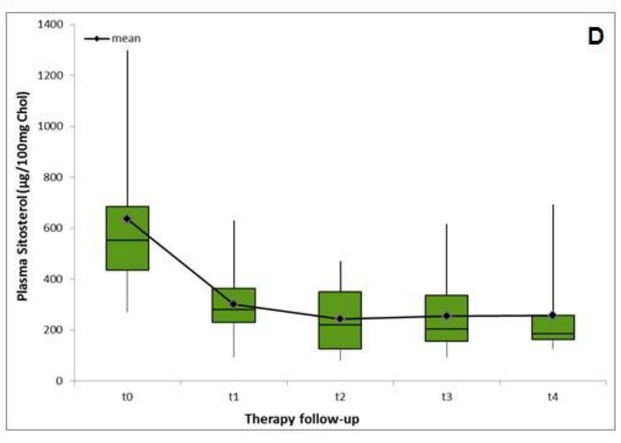












Discussion: Cholestanol and 7αC4 represent important markers for CTX diagnosis and monitoring of treatment. Treatment with CDCA should aim at normalizing serum 7αC4 as well as cholestanol, since 7αC4 closely mirrors 7α-hydroxylation rate and is strictly correlated with brain damage. Assessment of serum 27-OHC is a very good tool for biochemical diagnosis at any stage of disease. Lathosterol and plant sterols should be considered as additional markers for diagnosis and monitoring of therapy. Further studies including assessment of bile acid intermediates in cerebrospinal fluid are needed in patients who show clinical progression. Our metabolic evaluation allowed to clarify the diagnostic role of the various biochemical parameters and to better assess the effects of CDCA treatment on cholesterol metabolism.