THAOS®

Spring 2010

News Update

Issue 4

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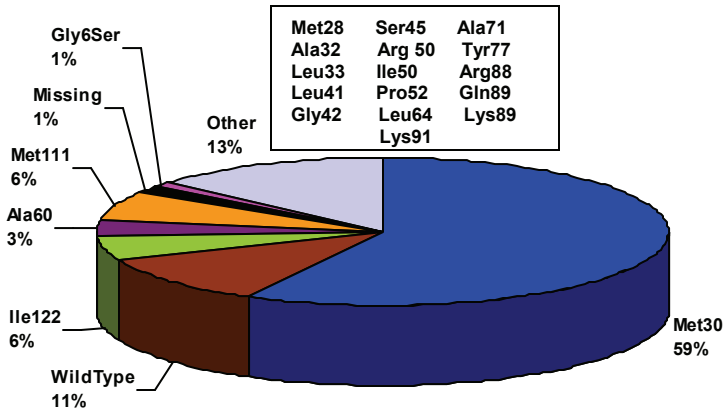
2010 THAOS Posters

Welcome to the fourth issue of the THAOS newsletter! THAOS continues to expand with 34 activated sites in 14 countries and an enrollment of 377 patients (18 May 2010). We would like to thank each of you for your continued efforts in identifying and enrolling patients. A special thanks to our three highest enrolling sites: Teresa Coelho from Porto, Portugal with 135 patients, Isabel Conceição from Lisbon, Portugal, with 35 patients, and Márcia Waddington Cruz from Brazil with 28 patients. Congratulations are in order for all our THAOS sites because on March 10 with 259 patients in the database, we were able to extract signed data for 238 patients. That is a compliance rate of 92%!!! The first three pages of this newsletter summarize the analyses of these data. Page 4 highlights other THAOS news. Because of its importance, we repeated the section, *Minimum Dataset for Evaluation*, from the last issue. We encourage all centers to enter complete clinic visit data, using these guidelines as the minimal dataset for evaluation of all genotypes, including asymptomatic carriers. – *Teresa Coelho, Chair, THAOS Scientific Board*

Baseline Data for 238 Patients

	TTR Mutation	Wild Type
Total Number of patients with analyzable data	208	27
Age (median), years	45.2	76.7
Asymptomatic, %	29.8	0.0
Males, %	53.4	96.3
Age at onset, mean years	42.6 (n=129)	75.7 (n=12)
Disease Duration, mean years	4.6 (n=129)	2.4
Ethnicity		
Caucasian, %	76.9	85.2
African descent, %	7.2	7.4
American Hispanic, %	0.0	3.7
Latino American	1.4	0.0
Asian	11.5	3.7
Other	2.9	0.0

Genotype



Of the 238 patients with analyzable data, 208 patients (87%) had mutations and a median age of 45.2 years. Almost all Wild Type patients (96.3%) were male with a median age of 76.7. The majority of patients were Caucasian. Of the 208 patients with mutations, almost 30% were asymptomatic. 21 mutations were identified with 59% presenting with Val30Met.

ANALYSIS of BASELINE DATA: THAOS Progress

V30M Patients in Different Countries

	Portugal	Brazil	Japan	Sweden
Number	79	23	19	17
M/F	29/50	12/11	11/8	10/7
Age at Entry, yrs	35.5	38.7	65.9	62.2
Age at onset, yrs	31.9	31.5	57.6	52.4
Duration, yrs	2.5	6.9	5.4	5.9
Asymptomatic, (%)	46	26	0	0

Symptomatic V30M and Non-V30M

	V30M	Non-V30M
Number of pts	90	41
Age, yrs	44.2	61.1
Age at onset, yrs	37.5	52.4
Duration, yrs	5.2	3.7

V30M is the most common of the TTR mutations. Of the 143 patients with V30M, 138 (96.5%) are clustered in 4 countries. Age of onset varies within the same mutation depending on geographic location and differs when comparing mutations.

Family History of Patients with Mutations

	Positive	%
Pts with Family History	**164**	**78.8**
Father	79	48.2
Mother	73	44.5
Father+mother	2	1.2
Other	3	1.8
Unknown	7	4.3
Pts with No Family History	**33**	**16.0**
Unknown Family History	**8**	**3.8**
Information Missing	**3**	**1.4**
	208	**100.0**

Family history was recorded for 164 pts (78.8%) with inheritance evenly distributed between mother and father.

Biopsies

	Wild Type N=27	Mutations N=208
# Pts with Biopsies	27 (100%)	113 (54.3%)
# Biopsies Performed	32	147
# Pts with + amyloid	27 (100%)	97*/113 (85.8%)
# Pts with + TTR*	27 (100%)	46*/97 (47.2%)
Type of Biopsies	N = 32	N = 147
Cardiac	26 (81.3%)	26 (17.7%)
Abdom Fat Pad	2 (6.3%)	40 (27.2%)
Salivary Gland	0	20 (13.6%)
Nerve	0	18 (12.2%)
Other	4 (12.4%)	43 (29.3%)

*Y/N answer, not indicated if 'N' is a negative finding or not done

Transplants

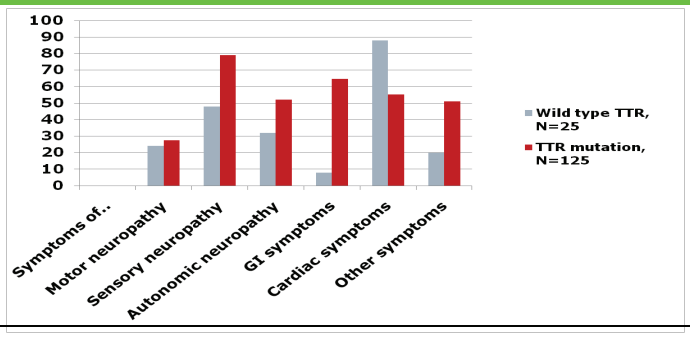
47 (19.7%) patients received a total of 52 transplants
- **43 liver**
- **8 heart**
- **1 kidney**

Multiple transplants among the 52 transplants
- **4 liver + heart**
- **1 liver + kidney + heart**

Symptomatic patients with liver transplants (LT)

	Wild Type	V30M	NonV30M
Total N	**27**	**90**	**41**
# Pts with LT	**0 (0%)**	**28 (31.1%)**	**10 (24.3%)**

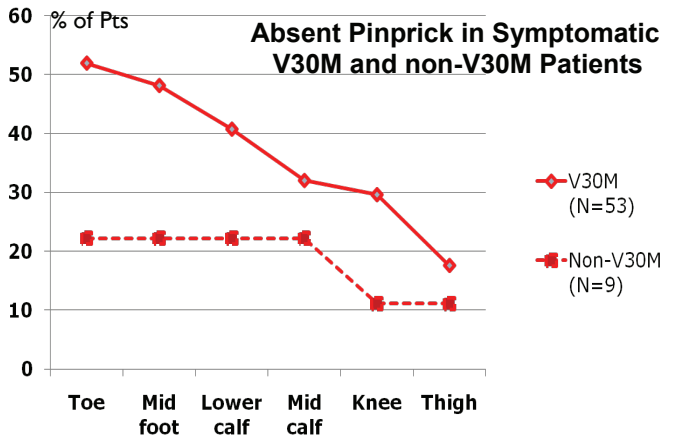
Symptoms in Symptomatic Patients

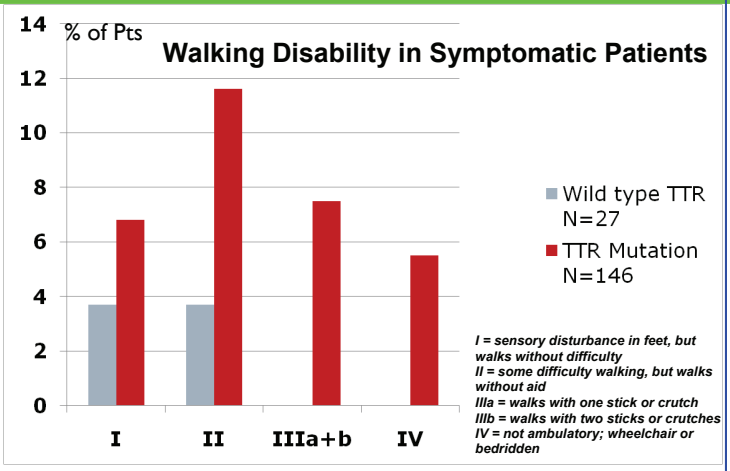


None of the wild type patients had a liver transplant while 29% of the symptomatic patients with mutations did. Nearly all the wild type (88%) patients had cardiac symptoms, but more than half of the patients with TTR mutations (55%) also reported cardiac symptoms. Sensory neuropathy was observed in patients with TTR mutations (79%) as well as those with wild type TTR (48%)

ANALYSIS of BASELINE DATA: THAOS Progress

Neuropathy Data

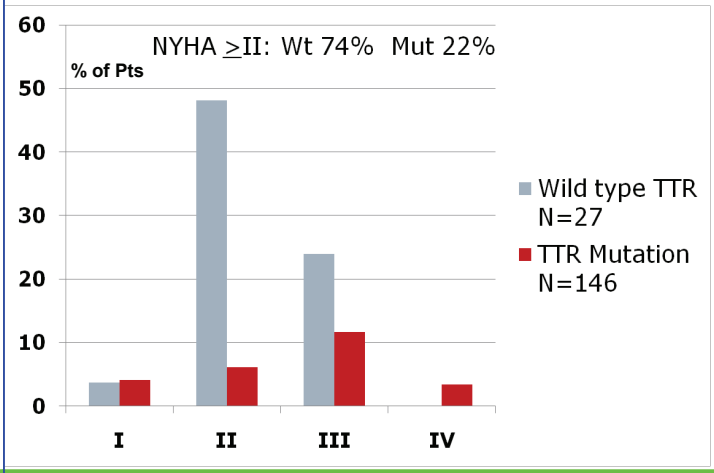




Small fiber sensory neuropathy was more common distally than proximally. A larger percentage of symptomatic V30M patients had absent pinprick sensation when compared to non-V30M patients. Patients with mutations had more severe motor impairment as demonstrated by ambulatory difficulties than patients with wild type TTR.

Cardiac Data

Heart Failure in Symptomatic Patients (NYHA Class)



ECG Findings

	Wild Type TTR	TTR Mutations
Abnormal ECG	20/20 (100%)	48/113 (42.5%)
Rhythm Abnormality	14/20 (70%)	14/47 (29.8%)

While more patients with wild type TTR had symptoms of heart failure than those with TTR mutations, heart failure was reported in these patients as well. Abnormal ECGs were observed in 42.5% of patients with TTR mutations, and all patients with wild type TTR. The principle abnormalities were atrial fibrillation, conduction abnormalities, and paced rhythms.

Health-Related Quality of Life

EQ-5D Index in Symptomatic Patients with Mutations

Age group	EQ-5D index *mean (SD)*		Difference	P-value
	THAOS	Controls (US)*		
18-34 (N=15)	0.77 (0.206)	0.92 (0.217)	-0.15	0.0075
35-49 (N=16)	0.62 (0.256)	0.88 (0.221)	-0.16	<0.0001
50-64 (N=14)	0.58 (0.272)	0.84 (0.275)	-0.26	0.0004
65+ (N=13	0.63 (0.256)	0.79 (0.24)	-0.16	0.0164

* 6,000-12,000 subjects per age group
PW Sullivan et al, *Med Care*:2005;43:736-749

EQ-5D in Various Disease States

Disease	Age, yrs	N	EQ-5D index
THAOS patients with symptoms	**69-64**	**14**	**0.58**
Diabetes	60	2,854	0.758
Stroke	67	995	0.694
Emphysema	66	597	0.68
Breast Cancer	64	236	0.81
Rheumatoid arthritis	59	235	0.661
General US population	**50-64**	**8,275**	**0.838**

EQ-5D index scores were calculated for 55 symptomatic patients with mutations. Different age groups in THAOS were compared to Controls (US) and to patients with other chronic diseases. These data demonstrate that symptomatic patients with ATTR report worse quality of life than controls as well as patients with other chronic diseases.

THAOS Database May 2010 - Key Updates

- An automatic email will be sent to users at each site when a patient has been in the system for one year—a reminder for a follow-up visit.
- Enrolled Patient Screen to include columns for unsolved Data Clarification Forms (DCFs) and number of sections that are unsigned.
- Users will have the ability to delete an examination and/or change the examination date (exception is "baseline" visit date).
- Password will no longer be needed to open printable documents.
- Worksheets to be updated to meet new requirements in new version.
- TTR Data-Biopsy to request evaluation method for precursor protein.
- Family History to include a request on how many generations of ATTR are known.
- General Assessment
  Screen to be disabled for retrospective & baseline visits.
  First Follow up visit will be pre-populated from medical history for any ongoing event.
- Transplant History
  Transplant-related complications section revised.
- Neurologic Assessment
  New screen to ask if HRDB/TILT/QST/IENF tests were completed (this screen only requests that you enter the date when tests were done).
  Nerve Conduction Screen to include Sympathetic Skin Response.

Minimal Dataset for Evaluation

THAOS, a natural history database, is following subjects over a ten-year period. Although the protocol does not require any specific tests or procedures to be performed, the value of the database lies in the completeness and careful recording of all data obtained from the clinic visit. The following is the recommended minimal dataset for each patient enrolled in THAOS, regardless of genotype or phenotype, including asymptomatic carriers:

- Registration
- TTR data
- Family History
- Medical History (general assessment on follow-up)
- Physical Examination
- Serum albumin levels
- Electrocardiogram
- Serum NT-ProBNP or BNP levels (if abnormal, then echocardiogram would be recommended)
- Pinprick, touch and vibration of great toe (both sides); ankle and patellar reflexes; muscle strength of toes and ankles (if abnormal, then either perform full neurologic examination or refer to neurology for evaluation).

Yearly follow-up is recommended, with re-evaluation of the minimal assessments at the least. It is requested that complete clinic visit evaluation data along with Quality of Life are entered into THAOS.

THAOS Reminders

Patient Follow-up—Remember to enter annual follow-up data for all enrolled patients!!!!

Amendment 2 —Remember to send IRB/EC approvals, approved ICFs and Protocol Signature Page

Continuing Review— Remember to send IRB/EC approvals and approved ICFs

Baseline Visit— Complete Medical History section at Baseline visit. Do NOT complete General Assessment section. Refer to Schedule of Assessments in your THAOS Study Manual for sections to be completed during baseline, follow up, and retrospective visits

Payments for clinic visits — only complete visits with signed data will be paid. Payments will be forwarded in May and early June.

Any questions? Contact bwhite@foldrx.com

Our Next Goal

500 patients

By October 1, 2010