THAOS®

Spring/Summer 2011

Issue 6

News Update

Inside this issue:

***New* THAOS Scientific Board Members**

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THE FIRST TWO THAOS MANUSCRIPTS TO BE SUBMITTED THIS SUMMER:

THAOS Baseline Data
&
THAOS Methods

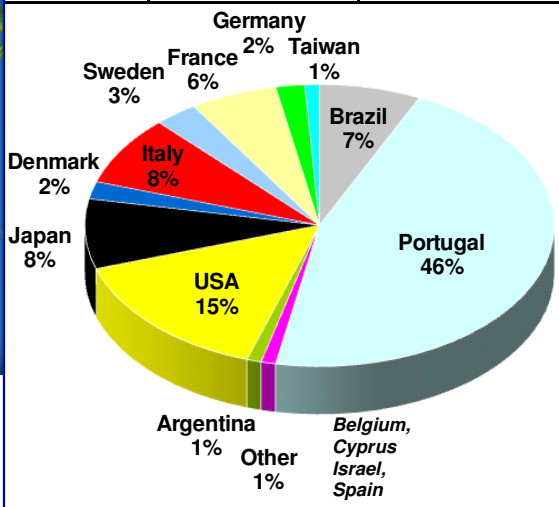
Welcome to the Spring/Summer edition of the THAOS newsletter. THAOS continues to expand in sites, enrollment, and countries thanks to your great efforts. As you will see in this newsletter, the amount of data are rapidly growing and the clinical picture of this international population is coming into focus. You will read on Page 4 of the many changes that have been made to the database, some of which have been site requests for ease of data entry. The Scientific Board has expanded to include three new members (see below), and an Executive Committee of elected Board members is currently being formed to further focus on and strengthen the scientific output. THAOS continues to have a presence at Scientific meetings (see Page 4) with abstracts accepted and oral presentations being granted. Now may be a good time to consider analyzing some aspects of the THAOS data for presentation at a national or international meeting!!

Teresa Coelho, Chair, THAOS Scientific Board

Current Enrollment Status

	Oct 2010	May 2011
# sites	38	45
# countries	17	19
# subjects	693	952
# subjects with mutations	603	854
# subjects with Wild-type TTR	67	92
# mutations	38	40
# mutations with 10 subjects or more	8	8
# subjects with follow-up data	58	297

45 THAOS Sites in 19 Countries



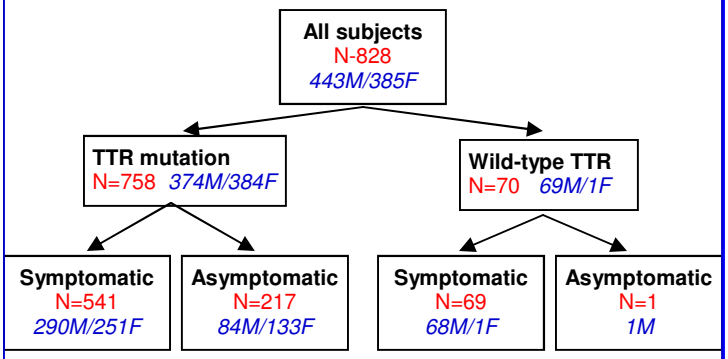
Since the Fall newsletter in October, enrollment increased by a third, active sites by 7, and countries by 2. The majority (46%) of THAOS subjects come from Portugal, followed by the USA (15%).

TOP ENROLLING SITES:
Teresa Coelho, Porto, Portugal *358*
Isabel Conceiçao, Lisbon, Portugal *80*
Márcia W. Cruz, Rio de Janeiro, Brazil *61*

ANALYSIS of BASELINE DATA for 828 SUBJECTS

Of the 828 subjects (443M/385F) with analyzable data, 758 subjects (92%) had mutations and a median age of 42 years. Of the 70 Wild-type TTR subjects, almost all (98.6%) were male with a median age of 76.1 years. Of the 758 subjects with mutations, 71.4 % were symptomatic with an age at onset of 38.2 years, while 98.6% of Wild-type TTR subjects were symptomatic with age at onset of 71.6 years.

Data tables run: 20April2011



	Wild-type TTR	TTR Mutation
No. of Subjects	70	758
Age at THAOS entry, yrs*	76.1	42.0
Males, %	98.6	49.3
Symptomatic, %	98.6	71.4
Age at onset, yrs*	71.6	38.2
Disease duration, yrs*	3.4	4.3

**Median*

Most Common Mutations (40 mutations in 758 subjects)

	Male	Female	Total	% of Subjects with Mutation	Cumulative %
Val30Met	248	311	559	73.7	73.7
Val122Ile	23	8	31	4.1	77.8
Leu111Met	10	7	17	2.2	80.0
Glu89Gln	6	11	17	2.2	82.2
Thr60Ala	6	7	13	1.7	83.9
Ser77Tyr	9	4	13	1.7	85.6

Demographics for Val30Met Subjects in Various Countries

	BR	PT	JP	SE
No. of Subjects	55	384	54	18
M/F ratio	1.1	0.7	0.9	1.6
Age at THAOS entry, yrs*	37.3	35.0	48.0	61.7
Symptomatic, N (%)	44 (80%)	238 (62%)	52(96%)	15 (83%)
Age at onset, yrs*	30.4	32.3	39.8	51.4
Disease duration, yrs*	5.7	3.5	5.7	5.2

**Median*

The six most common mutations cover 85.6% of subjects with TTR mutations. Val30Met is the most common of the TTR mutations. Of the 559 subjects with Val30Met, 511 (91.4%) are clustered in 4 countries. Age at onset varies within the same mutation depending on geographic location.

Family History in Subjects with TTR Mutations

	Symptomatic Males N=279	Symptomatic Females N=247	Asymptomatic Males N=81	Asymptomatic Females N=132	Asymptomatic All	P-value
Family History	**75.6%**	**92.7%**	88.9%	99.2%	95.3%	**<.001**
Father	42.7%	48.5%	59.7%	51.9%	**54.7%**	**<0.01**
Mother	49.3%	45.9%	33.3%	43.5%	**39.9%**	
Other	8.0%	5.7%	7.0	4.6%	5.4%	

Family history was reported for 92.7% of symptomatic females vs. 75.6% of males (p-value <0.001). Family history of affected father and mother was similar between symptomatic males and females. However, 54.7% of asymptomatic subjects reported family history of affected father vs. 39.9% from the mother (p-value <0.01)

Biopsies and Transplants (Symptomatic Subjects)

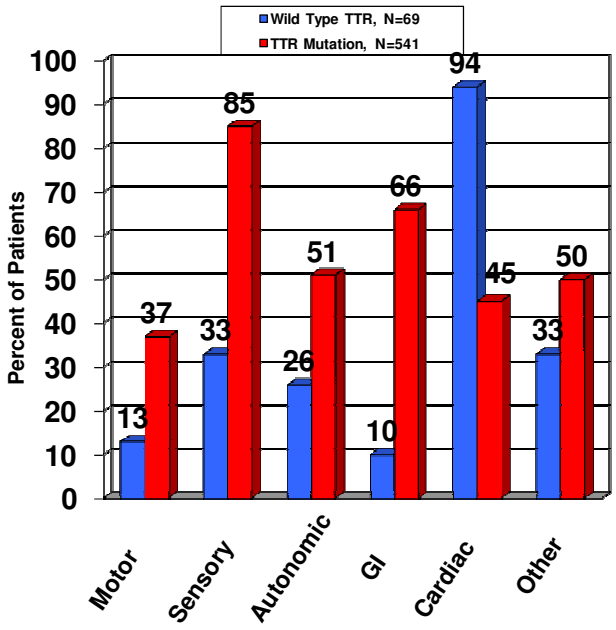
	Mutations N = 526	Wild-type TTR N = 67
# Pts with Biopsies	348 (66.2%)	64 (95.5%)
# Biopsies Performed	424	79
# Pts with + amyloid	299	63*
		** reported + TTR amyloid*
Most Common Biopsies		
Salivary Gland	38.4%	0.0%
Abdominal Fat Pad	14.6%	6.3%
Cardiac	11.3%	79.7%
	N = 541	**N = 69**
# Pts with Transplants	144 (26.6%)	5(7.2%)
Liver only	126	0
Heart only	5	4
Kidney only	1	0
# Pts with 2 Transplants	11	1
# Pts with 3 Transplants	1	0

66.2% of subjects with mutations had biopsies compared with 95.5% of subjects with Wild-type TTR. The salivary gland was the most common biopsy tissue for subjects with mutations. 26.6 % of subjects with mutations had transplants.

HIGHLIGHTS

Symptoms

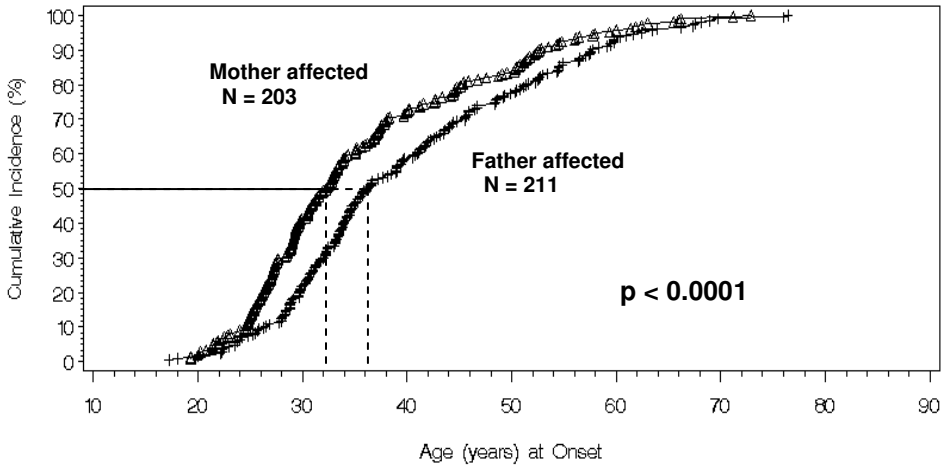
Percent of subjects with symptoms



	Wild-type-TTR N = 69	TTR Mutation N = 541
Motor Neuropathy	**9 (13%)**	**202 (37%)**
Walking Disability	4 (6%)	157 (29%)
Muscle Weakness	7 (10.1)	179 (33%)
Sensory	**23(33%)**	**462 (85%)**
Neuro Pain/Parasthesia	11 (16%)	385 (71%)
Numbness	14 (20%)	299 (55%)
GI	**7 (10%)**	**355 (66%)**
Unintentional Wgt Loss	1 (1%)	172 (32%)
Diarrhea/Constipation	2 (3%)	163 (30%)
Autonomic	**18 (26%)**	**276 (51%)**
Dizziness	11 (16%)	153 (28%)
Urinary Retention	0 (0%)	123 (23%)
Cardiac	**65 (94%)**	**243 (45%)**
Rhythm Disturbance	35 (51%)	121 (22%)
Heart Failure	59 (86%)	96 (17%)
Other	**23 (33%)**	**270 (50%)**
Genitourinary	2 (3%)	90 (17%)
Renal Impairment	8 (12%)	41 (8%)

Nearly all subjects with mutations (85%) and a third (33%) of Wild-type TTR subjects reported sensory neuropathy symptoms. Most (94%) Wild-type TTR subjects reported cardiac symptoms vs nearly half (45%) of subjects with mutations. The most frequent symptoms of subjects with mutations are neuropathic pain/parasthesia (71%), muscle weakness (33%), unintentional weight loss (32%), diarrhea/constipation (30%), and walking disability (29%). Most frequent symptoms for Wild-type TTR subjects are heart failure (86%), rhythm disturbance (51%), numbness (20%), neuropathic pain/parasthesia and dizziness (16%).

ONSET OF DISEASE: Dependence of Parental Inheritance



Overall, subjects (N = 203) who inherit the disease from their mother, experience a significantly lower age at onset (p< 0.001) when compared to subjects (N = 211) who inherit the disease from their father.

Database Updates: Version 1.05

- If mutation is chosen at registration, only mutation will be available under zygocity on TTR screen
- Additional mutations have been added to the drop down menu on TTR screen
- Question added on TTR screen "When was the diagnosis of ATTR made (mm/yyyy)"
- Question added on TTR screen "Were there any misdiagnoses before the proper diagnosis was made?" If yes (drop down menu contains list of misdiagnoses), please choose all that apply and include date (mm/yyyy)
- 'Unknown' has been added to Yes/No categories in Medical History
- Carpal tunnel syndrome and erectile dysfunction (males only) have been added to medical history
- Reverse order in tree view. General Exam is now listed before General Assessment as visit date must be entered before general assessment will be pre-populated
- General Assessment will be pre-populated at every visit, not just first follow-up visit.
- Start and stop dates are added for walking disability to reflect when patient progresses from one stage to another
- F3 function key is now available for chemistry, ECG and Echo screens.
- Lab units entered by site will be carried forward at the next visit
- Guidelines for SSR and Nerve Conduction studies has been added to the NCS screen
- DCFs generated in database will be sent to each user at a site.

THAOS Presentations

Scientific Meetings:*

American Academy of Neurology (AAN), April 9—16, 2011, Honolulu, HI - abstract accepted

European Neurology Society (ENS), May 28-31, 2011, Lisbon, Portugal—abstract accepted for oral presentation

Peripheral Nerve Society (PNS), June 25-29, Potomac, MD, abstract accepted

European Federation of Neurological Societies (EFNS), September 10-13, Budapest, Hungary– poster presentation with discussion

American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM), September 14-17, San Francisco, CA—abstract accepted

Heart Failure Society of America (HFSA), September 18—21, Boston, MA—abstract submitted

World Muscle Society, October 18—22, Algarve, Portugal—abstract submitted

**Abstracts from prior meetings can be viewed via the Investigator's portal on the THAOS Website (www.thaos.net)*

The THAOS newsletter is published two times per year, and its message is to inform the THAOS community what data are in the database and what is needed for THAOS to be successful. The data you see is a snapshot of what is in the database. The Scientific Board has also analyzed the data by age at onset (≤50 yrs vs ≥50 yrs), symptomology, mutation, verified diagnosis (variant with positive amyloid; Wild-Type TTR with positive TTR amyloid), gender, and age >65 yrs. The Board encourages participants to submit proposals for further analyses for meeting presentations and/or publications.

Remember

to

Schedule Follow-Up Visits for Your Patients!!!!