

Tumor/treatment-related hypothalamic obesity requires multidisciplinary care strategies – a German claims data analysis

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Background

- Severe, persistent obesity (hypothalamic obesity, TTR-HO) may follow treatment for sellar/suprasellar tumors involving the hypothalamus
- Rapid, severe weight gain usually starts during the first months after treatment and leads quickly to morbid obesity

Objective

Patient characterization and improved understanding of treatment pathways

Provide characterization of treatment pathways by analyzing resource utilization, follow-up

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Results II

- See a general practitioner 12.27 GP visits and 20.45 specialist visits (Table 2).
- 22% consult for diabetes insipidus in Q1, increased to 57% in Q4. Over 80% consult in follow-up period.
- 27% of patients consult for hypopituitarism in Q1, increased to 54% in Q4.
- 100% of patients under 20 years of age consulted for hypopituitarism. 85% of patients 20 to 60 years of age and only 60% of patients over 60 years of age.

Table 1. Frequency of HO- and non-HO-related hospitalization among patients with TTR-HO (n=37)

	Post observational period											
Outcome	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Y1	Y2		
ns												
Mean number per patient with TTR-HO	0.92	0.73	0.54	0.36	0.30	0.36	0.19	0.30	2.54	1.13		
related to the index hospita	alization							•				
Mean number per patient with TTR-HO	0.30	0.27	0.24	0.14	0.14	0.14	0.05	0.03	0.95	0.35		
Percent of all hospitalizations, %	32%	37%	45%	38%	45%	38%	29%	9%	37%	31%		
Percent of all hospitalizations, %	18%	20%	22%	40%	0%	0%	0%	0%	23%	0%		
	Outcome IS Mean number per patient with TTR-HO related to the index hospitalizations, % Percent of all hospitalizations, %	OutcomeQ1nsMean number per patient with TTR-HO0.92related to the index hospitalization Mean number per patient with TTR-HO0.30Percent of all hospitalizations, %32%Percent of all hospitalizations, %18%	OutcomeQ1Q2nsMean number per patient with TTR-HO0.920.73related to the index hospitalizationMean number per patient with TTR-HO0.300.27Percent of all hospitalizations, %32%37%Percent of all hospitalizations, %18%20%	OutcomeQ1Q2Q3nsMean number per patient with TTR-HO0.920.730.54related to the index hospitalizationMean number per patient with TTR-HO0.300.270.24Percent of all hospitalizations, %32%37%45%Percent of all hospitalizations, %18%20%22%	OutcomeQ1Q2Q3Q4nsMean number per patient with TTR-HO0.920.730.540.36related to the index hospitalizationMean number per patient with TTR-HO0.300.270.240.14Percent of all hospitalizations, %32%37%45%38%Percent of all hospitalizations, %18%20%22%40%	OutcomeQ1Q2Q3Q4Q5nsMean number per patient with TTR-HO0.920.730.540.360.30related to the index hospitalizationMean number per patient with TTR-HO0.300.270.240.140.14Percent of all hospitalizations, %32%37%45%38%45%Percent of all hospitalizations, %18%20%22%40%0%	Outcome Q1 Q2 Q3 Q4 Q5 Q6 ns Mean number per patient with TTR-HO 0.92 0.73 0.54 0.36 0.30 0.36 related to the index hospitalization 0.30 0.27 0.24 0.14 0.14 0.14 Mean number per patient with TTR-HO 0.30 0.27 0.24 0.14 0.14 0.14 Percent of all hospitalizations, % 32% 37% 45% 38% 45% 38% Percent of all hospitalizations, % 18% 20% 22% 40% 0% 0%	OutcomeQ1Q2Q3Q4Q5Q6Q7IsMean number per patient with TTR-HO0.920.730.540.360.300.360.19related to the index hospitalizationMean number per patient with TTR-HO0.300.270.240.140.140.140.05Percent of all hospitalizations, %32%37%45%38%45%38%29%Percent of all hospitalizations, %18%20%22%40%0%0%0%	Outcome Q1 Q2 Q3 Q4 Q5 Q6 Q7 Q8 Is Mean number per patient with TTR-HO 0.92 0.73 0.54 0.36 0.30 0.36 0.19 0.30 related to the index hospitalization Mean number per patient with TTR-HO 0.30 0.27 0.24 0.14 0.14 0.14 0.05 0.03 Percent of all hospitalizations, % 32% 37% 45% 38% 45% 38% 29% 9% Percent of all hospitalizations, % 18% 20% 22% 40% 0% 0% 0% 0%	Outcome Q1 Q2 Q3 Q4 Q5 Q6 Q7 Q8 Y1 Is Mean number per patient with TTR-HO 0.92 0.73 0.54 0.36 0.30 0.36 0.19 0.30 2.54 related to the index hospitalization Mean number per patient with TTR-HO 0.30 0.27 0.24 0.14 0.14 0.14 0.05 0.03 0.95 Percent of all hospitalizations, % 32% 37% 45% 38% 45% 38% 29% 9% 37% Percent of all hospitalizations, % 18% 20% 22% 40% 0% 0% 0% 0% 23%		

Methods

Study Design

Retrospective rolling-cohort design based on a representative German claims database (n=5.24 million) from 2010-2021 with one-year washout and two years follow-up

Inclusion Criteria

- Prevalent tumor diagnosis and incident tumorrelated surgery or radiotherapy* (n=3,976).
- HO identified by incident obesity diagnosis and validated by incident diabetes insipidus and desmopressin prescription

Exclusion Criteria

Patients with a history of Prader-Willi syndrome (ICD-10-GM Q87.1) excluded

Outcomes

- Inpatient stays and ICU admissions
- Outpatient physician contacts per specialty group
- Inpatient and outpatient diagnoses
- Rx prescriptions

Outcome Measures

- Share of patients with diagnosis

Prescription Medications

Outpatient Physician Visits

- 5.5 average prescriptions per patient per
- quarter, average of 22.1 unique medications over the follow-up period -ന്
 - (Table 4).
 - 68% had neuroendocrine replacement therapy in Q1
 - 19% had combinations of three neuroendocrine therapies (Figure 1)
 - Y1: 100% had a neuroendocrine replacement therapy and 89% were on a combination of 3+ more therapies at some point
 - Y2: 68% of patients were on combination of 3+ therapies in at least one quarter
 - In both years, 25% were on 4+ therapies for neuroendocrine deficits at some point

Discussion

- Highly complex treatment and need for close multidisciplinary collaboration
- Multiple inpatient and outpatient consultations
- Patients hospitalized for oncological follow-up and for management of comorbidities
- Complex polytherapies common
- Treating neuroendocrine deficiencies contributes to comorbidities and weight gain

Table 2. Outpatient contacts (mean per patient) with specialist groups within the two years following TTR-HO-associated index hospitalization (n = 37)

	Post-observational period										
Specialist group	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Y1	Y2	Total
General Practitioner	1.59	1.84	1.62	1.54	1.54	1.22	1.46	1.46	6.59	5.68	12.27
Endocrinology/Diabetology	0.38	0.38	0.32	0.35	0.27	0.27	0.22	0.32	1.43	1.08	2.51
Ophthalmology	0.49	0.19	0.35	0.35	0.27	0.22	0.16	0.24	1.38	0.89	2.27
Gynecology	0.16	0.27	0.22	0.24	0.38	0.24	0.27	0.30	0.89	1.19	2.08
Neurosurgery	0.24	0.11	0.14	0.08	0.08	0.03	0.03	0.14	0.57	0.28	0.85
Neurology	0.08	0.16	0.19	0.14	0.08	0.16	0.08	0.14	0.57	0.46	1.03
Radiology	0.22	0.05	0.22	0.05	0.19	0.05	0.05	0.16	0.54	0.45	0.99
Oncology/Haematology	0.00	0.03	0,00	0.00	0.00	0.00	0.00	0.00	0.03	0.00	0.03
Other	1.16	1.52	1.18	1.25	1.43	1.19	1.52	1.48	5.11	5.62	10.73

Table 3. Share of patients with TTR-HO with the most frequent outpatient diagnoses documented within the two years following TTR-HO-associated index hospitalization (n = 37)

			Post-observational period								
	Top-10 diagnoses (ICD-10-GM)	Index	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Total
Oncological	Benign neoplasm: Pituitary gland (D35.2)	46%	51%	49%	46%	49%	46%	41%	43%	46%	59%
	Neoplasm of uncertain or unknown behavior: Pituitary gland (D44.3)	35%	32%	32%	32%	0%	24%	22%	27%	19%	54%
	Neoplasm of uncertain or unknown behavior: Brain, unspecified (D43.2)	22%	19%	0%	24%	22%	19%	14%	14%	0%	43%
	Neoplasm of uncertain or unknown behavior: Craniopharyngeal duct (D44.4)	22%	19%	27%	24%	27%	24%	24%	24%	22%	32%
	Hypopituitarism (E23.0)	27%	32%	41%	49%	54%	54%	46%	59%	46%	84%
Neuro-	Diabetes insipidus/AVP-D (E23.2)	22%	41%	46%	59%	57%	62%	51%	49%	46%	81%
endocrine	Hypothyroidism, unspecified (E03.9)	0%	0%	22%	24%	16%	22%	19%	22%	22%	38%
Other	Obesity, unspecified: Degree or extent of obesity unspecified (E66.99)	27%	24%	30%	32%	22%	30%	27%	32%	24%	49%
	Essential hypertension, unspecified: Without indication of hypertensive crisis (I10.90)	24%	19%	27%	35%	27%	27%	22%	27%	22%	43%
	Visual field defects (H53.4)	24%	22%	0%	0%	0%	0%	0%	16%	0%	38%
Abbreviation: a	rginine vasopressin deficiency; AVP-E)									

- Average interactions per patient
- Share of patients receiving prescriptions and defined daily doses (DDD) per therapy
- Shares patients with specific therapies and therapy combinations

Results I

- **Inpatient Visits**

• Hospitalized on average 3.68 times in the 2-year follow-up period; 37% of hospitalizations in the first year and 31% in the second year are due to TTR-HO (Table 1).

In the follow-up period, patients with TTR-HO are hospitalized 3.68 times on average

On average, patients see a general practitioner 12.27 times and various specialists 20.45 times.

The need for complex neuroendocrine therapy develops quickly. Most patients have 2-3 neuroendocrine prescriptions in any given quarter. Complex polytherapy is common.

- Patients and caregivers unprepared for high burden of care
- TTR-HO is a distinct clinical entity requiring specific treatment and patient management
- Treatments for general obesity are largely ineffective
- Careful, personalized monitoring to identify early changes, such as hyperphagia

Patients have multiple inpatient and outpatient consultations; polytherapy common

•TTR-HO is a distinct clinical entity requiring specific treatment

Highly complex treatment and high burden of care. Treatment is a balancing act.

Cohort Definitions

- * Included tumor diagnoses based on ICD-10-GM 2011 to 2019-version: C96.6, D33.0, D33.2, D33.3, D33.7, D33.9, D35.2, D35.3, D43.2, D44.3, D44.4, D48.9, D76.3, Q04.8, Q85.0.
- ** Inclusion of obesity based on ICD-10-GM-codes: E66, E67, E68, R63.2, R63.5; diabetes insipidus: E23.0, E23.2, E23.3, E23.6, E23.7, P80, P81; Desmopressin prescription: ATCcode H01BA02.

Table 4. Share of TTR-HO patients with the most frequent prescription medication within the first two years following TTR-HOassociated index hospitalization (n = 37)

			Post observational period									
												DDD/
Prescriptions drug		Index	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Iotal	Patient
Average number of prescriptions per patient		4.0	5.8	5.5	5.7	5.5	5.5	5.3	5.4	5.8	22.1	-
Share of patie	nts with specific m	nedicatio	n	I	I		l		l	l		ł
	Desmopressin	38%	65%	76%	73%	62%	68%	70%	68%	65%	100%	339
	Hydrocortisone	59%	70%	62%	73%	68%	68%	73%	65%	65%	97%	344
Neuro-	Levothyroxine- sodium	41%	46%	51%	76%	68%	68%	73%	68%	68%	86%	473
	Prednisone	8%	8%	0%	0%	0%	0%	0%	0%	0%	24%	26
	Somatropin	0%	0%	0%	0%	8%	8%	11%	0%	14%	16%	145
rendocrine	Testosterone	0%	8%	16%	14%	22%	16%	16%	16%	16%	27%	356
replacement	Dydrogesteron -Estrogen	0%	0%	0%	5%	0%	5%	0%	0%	0%	5%	504
	Progesterone	0%	0%	0%	0%	8%	0%	0%	5%	0%	8%	200
	Estradiol	0%	0%	0%	0%	0%	0%	5%	0%	5%	11%	512
	Estriol	0%	0%	0%	0%	0%	0%	0%	0%	5%	8%	186
Others	Ibuprofen	27%	5%	8%	19%	14%	16%	24%	16%	16%	68%	63
	Metamizol- Natrium	24%	19%	16%	14%	0%	11%	19%	11%	11%	65%	29
	Pantoprazol	32%	22%	32%	27%	22%	19%	22%	19%	22%	54%	742
	Cholecalciferol	5%	8%	11%	0%	5%	19%	16%	8%	11%	38%	164
	Diclofenac	8%	8%	0%	0%	14%	0%	0%	0%	0%	30%	106



DDD: Daily defined dose; Q: Quarter; Y: Year

Note: Quarterly reporting based on Top 20 medications per quarter. Y2 reporting based on Top 20 medications overall in the two-year period. Total is reported cumulatively for all patients.

Treatment of TTR-HO is challenging, requiring frequent contact with multiple specialists, a complex regimen of medications, and sometimes hospitalization

Major tasks are balancing complex neuroendocrine replacement therapies and the interaction of symptoms, therapies, and co-morbidities

Disclosures

This study was funded by Rhythm Pharmaceuticals. Rhythm reviewed and provided feedback to the authors, but the authors had full editorial control and provided their final approval of all content. NT is an employee of Rhythm Pharmaceuticals. JW, BS and MW are employees of Vandage, which was paid by Rhythm Pharmaceuticals to conduct this research. JW owns shares of Vandage. MF received grants from Vandage. BJ, BS, HLM received no project specific grants.

Data availability:

Project-specific access to an anonymized, selected study data set for the analyses was provided by the GWQ ServicePlus AG. The data analyzed in this study are not publicly available due to data protection regulations and national legislation. All data-related processes of Vandage are under the data protection supervision of an external data protection officer.

ISPOR Europe 2024, 17 November – 20 November, Barcelona, Spain.

