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REVIEW

Myxedema Psychosis: Systematic Review and Pooled Analysis

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Background and Objective: The term myxedema psychosis (MP) was introduced to describe the occurrence of psychotic symptoms in patients with untreated hypothyroidism, but the optimal assessment and treatment of this condition are unclear. We aimed to synthesize data from the literature to characterize the clinical presentation and management of MP.

Methods: We performed a systematic review according to the PRISMA (preferred reporting items for systematic reviews and meta-analyses) guidelines in PubMed (Medline), Embase, Google Scholar, and Cochrane databases, including observational studies, case series, and case reports published from 1/1/1980 to 31/12/2019 in the English language. Descriptive statistics along with univariate and multivariate analysis were used for data synthesis.

Results: Out of 1583 articles screened, 71 case reports met our inclusion criteria providing data on 75 MP cases. The median age at diagnosis was 42 years [32–56]. About 53% had no prior hypothyroidism diagnosis. Delusions occurred in 91%, with a predominance of persecutory ideas (84%), while hallucinations occurred in 78%. Physical symptoms and signs of hypothyroidism were absent in 37% and 26%, respectively. If symptoms occurred, nonspecific fatigue was seen most frequently (63%). The median thyroid-stimulating hormone value was 93 mIU/L [60–139]. Thyroid peroxidase antibodies were found positive in 75% (23/33) of reported cases. Creatinine kinase was reported abnormal in seven cases. Cranial imaging (CT or MRI) and electroencephalogram were normal in 89%, 75%, and 73% of the cases reported. The majority of patients were treated orally with thyroxine in combination with short-term antipsychotics. More than 90% of them showed complete recovery. Univariate analysis revealed a trend towards a shorter duration of psychosis with IV thyroid hormone therapy (p= 0.0502), but the effect was not consistent in a multivariate analysis.

Conclusion: While we identified a substantial lack of published research on MP, our pooled analysis of case observations suggests that the condition presents a broad spectrum of psychiatric and physical symptoms lending support to the value of screening for thyroid dysfunction in patients with first-ever psychosis.

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Keywords: psychosis, hypothyroidism, madness, myxedema, depression, neuropsychiatric

Background

Hypothyroidism is a common disease with an estimated global prevalence of 0.1–3.6%.[1–4] The Committee on Myxedema of the Clinical Society of London issued the first report that described the development of delusions and hallucinations in almost half of hypothyroid patients (109 patients).[5] Sixty years later, in 1949, Asher et al reexamined this relationship in fourteen patients who had psychosis and clinical evidence of hypothyroidism. The patients received thyroid hormones supplements,

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with nine patients achieving full recovery.[6] He labeled this association "myxedema madness," which later was renamed "myxedema psychosis" (MP).[6] MP is a secondary psychotic disorder resulting from other medical conditions according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[7]

The underlying pathophysiology is poorly understood. Previous research linked hypothyroidism to changes in neurometabolic activity that might contribute to MP, including;[8] tyrosine hydroxylase imbalance in the anterior locus coeruleus;[9] abundance of T3 receptors in the amygdala and the hippocampus;[10] altered serotonin-mediated neurotransmission[11,12] and attenuation of cerebral regional blood flow and glucose metabolism.[13,14]

Diagnostic discrimination between MP and other secondary psychoses is clinically relevant as the management differs according to the exact etiology. An important differential diagnosis of psychosis in hypothyroidism patients is Hashimotos' encephalopathy (HE), also called steroids responsive encephalopathy with autoimmune thyroiditis.[15] While the pathophysiological mechanism underlying MP is related to brain neurochemical alterations accompanying thyroid hormones deficiency, neuropsychiatric changes in HE are caused by an autoimmune response not directly linked to hypothyroidism. This explains the excellent response to steroids in most HE cases.[15]

Seventy years have elapsed since Asher's description, yet, little is known about MP, likely due to the paucity of available literature.[8] Thus, we aimed to review the literature and synthesize data on its clinical symptomatology, diagnosis, management strategies, and clinical outcomes.

Methods

This systematic review complied with preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines.[16] The review protocol was registered at PROSPERO (registration number: CRD42020160310) and was published.[17]

Eligibility Criteria

Observational studies, case series, and case reports providing data on patients diagnosed with MP were eligible for inclusion. We only included reports on adult patients (18 years or older) with confirmed hypothyroidism (thyroid stimulating hormone> normal range plus low thyroid hormones, or clinical evidence of hypothyroidism) and psychotic features meeting the DSM-5 criteria of psychosis due to a general medical condition in whom myxedema psychosis was the likely diagnosis as per the treating physician. We excluded cases of Hashimoto's encephalopathy (HE), thyroxine-induced mania, subclinical hypothyroidism, secondary hypothyroidism (due to possible confounding by other hormonal imbalances or mass effect), or cases with alternative diagnoses more likely than MP.

Search Strategy and Information Source

We conducted a comprehensive search in the following databases; PubMed, Medline, EMBASE, Google Scholar (first 300 hits), and Cochrane databases for studies published from 1/1/1980 to 31/12/2019. We included articles labeled "letter to the editor" if they were, in fact, case reports. We limited our search to articles written in the English language only. We used combinations of free text, keywords, Emtree, and MesH-terms, including psychosis, psycho, madness, psychiatric, hypothyroid, myxedema, myxoedema. Search strings used in each database are detailed in the supplement. (Supplementary 1) We also performed a snowball search in bibliographies of identified full-text articles and relevant review articles.

Screening, Data Extraction, and Quality Assessment

Two independent reviewers (MFHM) and (SS) performed the literature search and screening. First, the titles and abstracts were screened. Subsequently, the full text of potentially eligible articles was reviewed and assessed for inclusion. At each step, the two reviewers discussed discrepancies noted, and if consensus could not be reached, a third reviewer (MD) settled the discrepancy per protocol. We used a web-based literature screening application (Rayvan; http://rayyan.qcri.org) to conduct article screening and duplicate removals.[18]

We extracted general data on included publications such as type, author, year, and journal as well as demographic data of the patients reported such as sex, age, gender, history of psychosis, history of hypothyroidism, and causes of hypothyroidism. Moreover, data on clinical presentation data was extracted, including psychiatric presentation, duration of psychosis, hypothyroidism symptoms or signs, associated rhabdomyolysis, cranial imaging finding; electroencephalography (EEG) findings; thyroid stimulating hormone level; thyroid hormone levels; anti-thyroid peroxidase status; creatinine kinase levels. We used the tool proposed by Murad et al to adjudicate the quality of included case reports and

series.[19] The tool comprises eight questions assessing four domains (selection, ascertainment, causality, and reporting). We generated an overall score, and we then graded the quality as either good (> 5), fair (4–5), or poor (< 3).

Statistical Analysis

We used the Jamovi 1.1.9 software for statistical analysis.[20] Descriptive statistics were applied to summarize data using the median (IQR) for continuous variables and frequencies for categorical variables. We used (n/N) and percentage values for presenting numbers of cases with a specific characteristic amongst cases that reported either the presence or the absence of this characteristic. Acknowledging the subjective nature of reporting in case studies, the two reviewers had to agree on whether a specific characteristic was present in any given case before inclusion in the final analysis. Exploratory multivariate logistic regression including potentially clinically relevant variables (gender, age, symptoms duration, TSH level, FreeT4, antipsychotic drugs duration, IV thyroid hormone therapy, and starting thyroxine dose) associated with recovery (resolution of psychosis) or rapid recovery (less than 2 weeks) was also performed.

Results

The initial search retrieved 2733 articles; 50 additional articles were identified through other means, of which 71 references describing 75 cases were included for the final analysis.[21–91] The PRISMA flow diagram is shown in Figure 1. All included studies were case reports due to the absence of other forms of evidence (Table 1). Quality assessment utilizing the methodological quality and synthesis of case series and case reports tool revealed fair to good quality of most of the included cases (Supplement 2).

Baseline Characteristics

The female-to-male ratio was 2:1. The median age was 42 [32–56] years, with the oldest case reported aged 90 years. The majority of cases were Caucasians, 44%, followed by Asians, 36%. 53% of patients had no prior history of hypothyroidism, and 82% had no prior psychosis history. Autoimmune thyroiditis was the most common reported cause of hypothyroidism 51%.

Clinical Features

The median duration of psychotic symptoms was 14.5 [7–82.5] days ranging from two days to three years. Delusions were present in 91%. The most common form of delusions was paranoid/persecutory 84%. Hallucinations were present in 77.5%, with auditory hallucinations being the most prevalent 77.6%. Manic symptoms accompanied psychosis more than depressive symptoms, 52% and 36%, respectively (Table 2). Hypothyroidism symptoms and signs were not always reported, and when presented, often lacking sufficient details. Hypothyroidism symptoms were present in 63% (26/41) of the cases. Only 22 cases described the nature of hypothyroidism symptoms. Fatigue occurred in 63% (14/22), weight gain 36%, cold intolerance 36% (7/22), and hoarse voice was seen in 18% of the cases (4/22). Hypothyroidism signs were present in 75% of the cases (39/52). The most common abnormal findings were dry skin 60% (23/43), facial or pretibial edema 52% (20/43), delayed relaxation, or diminished deep tendon reflexes (DTR) 47% (18/38), while hoarseness of voice occurred 26% (10/38).

Laboratory Testing

The median thyroid-stimulating hormone median value was 93 mIU/L [60–93]. The median-free T4 was 0.2 ng/dl [0.13–0.39]. The median thyroid peroxidase value was 138 IU/L [82.5–323]. In 7 of the reported cases, creatinine kinase was observed abnormal with a median value of 4490 [1767–9485] IU/L. Lumbar puncture was reported in six patients. Analysis of cerebrospinal fluid revealed mild protein elation in two cases (33%) and was found normal in four cases (67%).

Diagnostic Imaging

Cranial magnetic resonance imaging was normal in 75% (12/16) of the cases and showed structural brain changes in four patients, including crescent-shaped foci of T2 hyperintensity visualized as slight effusion below the dura matter (n=1), nonspecific white matter changes (n=1), and age-related atrophic changes (n=1). Similarly, patients who underwent cranial computed tomography displayed normal brain scans in 89% of cases (24/27). The electroencephalogram was normal in 73% (11/15) and showed generalized slowing without a focal change in 27% of cases (4/15) (Supplementary 3).

Antipsychotic Medications

Antipsychotic medications were utilized in the treatment of 92% (n=55/60) of the cases. The median duration of

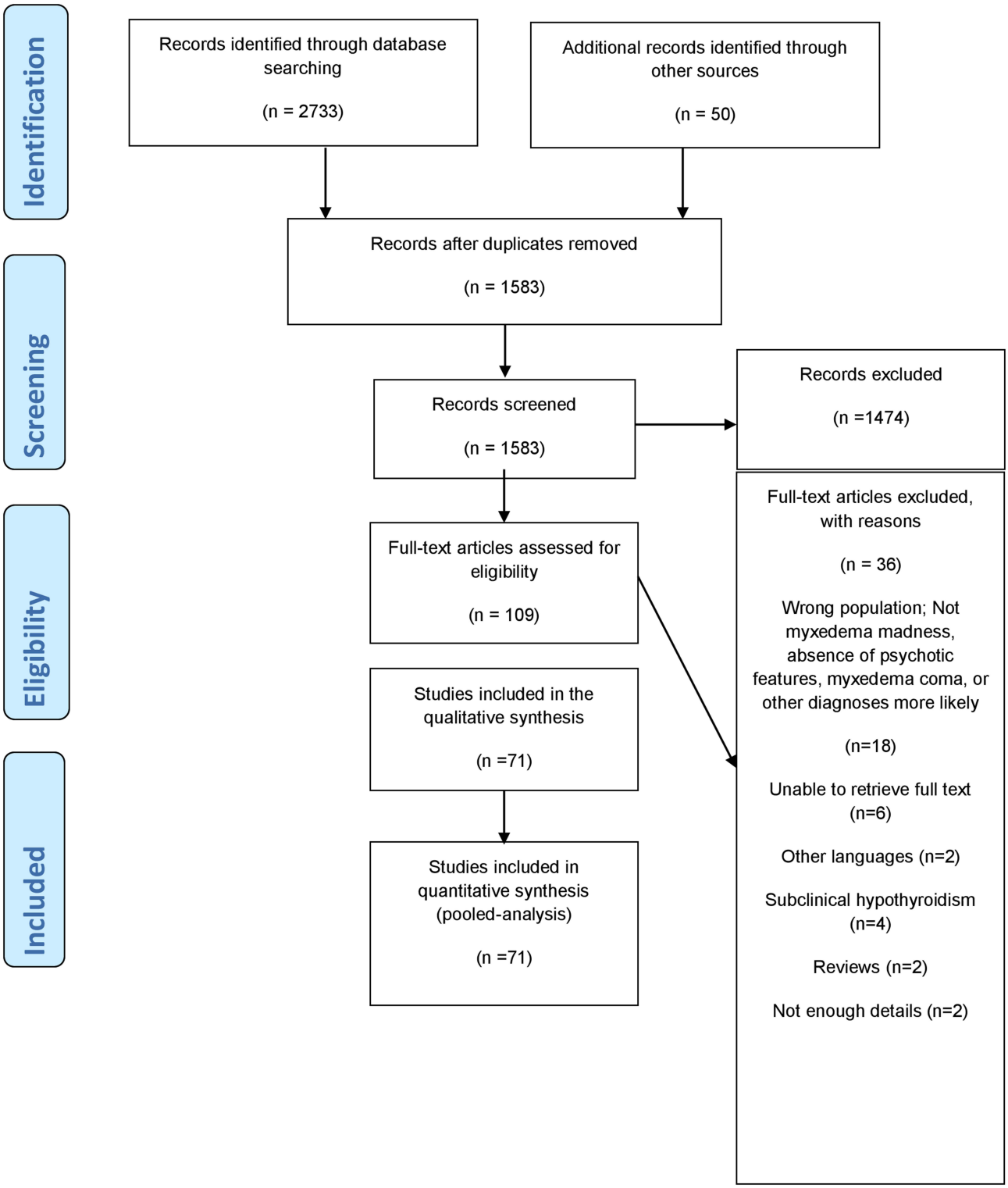

Figure 1 PRISMA flow diagram.
Note: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ.* 2021;372:n71. doi: 10.1136/bmj.n71. Creative Commons.[93]

Table 1 Summary of Included Case Studies

Case Study	Gender	Symptom Duration [Days]	Psychiatric Symptoms Reported	TSH Level	Antipsychotic Treatment [Yes/No], Duration [Weeks]	T4 Starting Dose (mcg)	T4 Maintenance Dose (mcg)	Recovery Outcome	Duration to Outcome in Weeks	Follow Up Duration [Weeks]
Reddy 2019[52]	Male, 37	15	Delusions with no hallucinations	100	No	100	300	Complete recovery	2	2
Mohamed 2019[21]	Male, 44	14	Hallucinations and delusions	100	Yes, 20	300	100	Complete recovery	2	24
Singh 2019[76]	Female, 30	365	Hallucinations, but delusions not explicitly mentioned	60	Yes, NS	NS	NS	Complete recovery	3	3
Fernandes 2019[55]	Male, 33	90	Hallucinations with no delusions	350	Yes, 8	100	100	Complete recovery	2	13
Todorov 2019[60]	Female, 43	7	Hallucinations and delusions	152	Yes, 4	50	125	Complete recovery	1.5	8
Natarajan 2019[67]	Female, 30	90	Hallucinations and delusions	100	No	100	100	Complete recovery	2	2
Mavroson 2017[24]	Male, 31	4	Hallucinations and delusions	306	Yes, 0.5	150	125	Complete recovery	0.5	2
Philip 2017[77]	Female, 51	365	Hallucinations and delusions	109	NS	100	100	Complete recovery	2	2
Gupta 2017[37]	Female, 44	21	Delusions with no hallucinations	100	Yes, 4	300	100	Complete recovery	0.6	4
Rizvi 2017[78]	Female, 35	15	Hallucinations and delusions	70.7	Yes, 5	75	75	Complete recovery	1.7	13
Zorkin 2017[58]	Male, 40	7	Delusions with no hallucinations	100	Yes, NS	100	112	Complete recovery	2	2
Das 2017[69]	Male, 68	14	Delusions with no hallucinations	55	Yes, 39	88	88	Complete recovery	3	52
O'Hanlon 2017[72]	Female, 63	NS	Delusions with no hallucinations	NS	Yes, NS	NS	NS	Complete recovery	0.5	NS
Shlykov 2016[30]	Female, 65	60	Hallucinations and delusions	61	Yes, 1	50	100	Complete recovery	3	12

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Table 1 (Continued).

Case Study	Gender	Symptom Duration [Days]	Psychiatric Symptoms Reported	TSH Level	Antipsychotic Treatment [Yes/No], Duration [Weeks]	T4 Starting Dose (mcg)	T4 Maintenance Dose (mcg)	Recovery Outcome	Duration to Outcome in Weeks	Follow Up Duration [Weeks]
Er 2016[34]	Female, 60	7	Hallucinations and delusions	45	Yes, 1.3	25	100	Complete recovery	1	28
Nazou 2016[39]	Female, 48	14	Hallucinations and delusions	145	Yes, 0.6	75	75	Complete recovery	3	52
Agachanli 2016[79]	Male, 31	45	Hallucinations and delusions	105.9	Yes, 3	150	150	Complete recovery	1.6	14
Morgado 2016[49]	Male, 36	2	Hallucinations and delusions	98	Yes, 26	100	100	Complete recovery	2	104
Mehta 2016[59]	Female, 21	730	Delusions, but hallucinations not explicitly mentioned	200	Yes, NS	100	100	Recovery with other cognitive deficits	4	4
Larouche 2015[45]	Female, 29	7	Delusions with no hallucinations	100	Yes, 0.5	200	100	Complete recovery	1	26
Ueno 2015[23]	Male, 90	2	Hallucinations and delusions	105	Yes, NS	50	75	Partial recovery	2	7
Hines 2015[26]	Female, 48	14	Delusions with no hallucinations	93	Yes, 0.1	50	50	Complete recovery	0.3	0.4
Bel Feki 2015[27]	Female, 60	NS	Hallucinations and delusions	45	NS	NS	NS	Complete recovery	NS	
Amdouni 2015[29]	Female, 36	NS	Hallucinations and delusions	135	NS	NS	NS	NS	NS	
Berkowitz 2015[32]	Female, 28	NS	Not specified	20	NS	50	75	Complete recovery	0.4	104
Hynicka 2015[35]	NS	NS	Hallucinations and delusions	60	Yes, NS	50	88	Complete recovery	1.6	2
MorosÃ¡n 2014[63]	Female, 62	7	Hallucinations and delusions	62.9	Yes, 8	200	150	Complete recovery	0.6	24
Baziki 2014[80]	Female, 54	90	Delusions with no hallucinations	85	Yes, NS	200	NS	Complete recovery	1.4	3

Juneja 2014[47]	Female, 34	NS	Hallucinations and delusions	100	Yes, NS	NS	NS	Complete recovery	6	6
Parikh 2014[64]	Female, 30	547	Hallucinations and delusions	63.7	Yes, 1	100	100	Complete recovery	1	6
Islam 2013[81]	Female, 39	7	Hallucinations and delusions	87	Yes, 1.6	NS	NS	Complete recovery	0.6	39
Tuman 2013[82]	Female, 56	180	Hallucinations and delusions		Yes, NS	NS	NS	Complete recovery	1	1
Lazaro 2013[28]	Female, 45	60	Delusions with no hallucinations	70	Yes, 39	NS	75	Complete recovery	4	77
Lin CL 2013[42]	Female, 41	7	Hallucinations and delusions	18.7	Yes, 7	90	75	Complete recovery	3	104
Dastjerdi 2013[56]	Male, 53	NS	Hallucinations and delusions	32	Yes, NS	150	NS	Complete recovery	2	104
Hyams 2013[57]	Female, 26	14	Delusions with no hallucinations	38	Yes, 0.4	100	100	Complete recovery	2	26
Atilan 2013[83]	Male, 25	NS	Hallucinations and delusions	150	Yes, NS	150	150	Complete recovery	0.4	NS
Weston 2013[70]	Male, 60	NS	Hallucinations and delusions	150	NS	NS	150	Complete recovery	3	22
Sharma 2013[71]	Female, 24	1100	Hallucinations and delusions	60	Yes, NS	NS	NS	NS	NS	NS
Neal 2012[22]	Male, 32	6	Hallucinations, but delusions not explicitly mentioned	98	No	150	150	Complete recovery	0.4	NS
Martell 2012[68]	Female, 36	21	Hallucinations and delusions	209	Yes, NS	12.5	137	Complete recovery	5	8
Leung 2011[84]	Female, 38	NS	Hallucinations and delusions	220	Yes, NS	150	NS	Complete recovery	1.85	NS
Kumar 2011[85]	Male, 83	14	Hallucinations with no delusions	233	NS	NS	NS	Complete recovery	2	2

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Table 1 (Continued).

Case Study	Gender	Symptom Duration [Days]	Psychiatric Symptoms Reported	TSH Level	Antipsychotic Treatment [Yes/No], Duration [Weeks]	T4 Starting Dose (mcg)	T4 Maintenance Dose (mcg)	Recovery Outcome	Duration to Outcome in Weeks	Follow Up Duration [Weeks]
Manea 2011[36]	Female, 42	4	Not specified	75	Yes, NS	NS	NS	Complete recovery	4	52
Khemka 2011[46]	Female, 56	60	Hallucinations and delusions	14	Yes, NS	25	25	Complete recovery	NS	NS
Khemka 2011[46]	Female, 77	NS	Hallucinations and delusions	18	Yes, NS	25	100	Complete recovery	2.4	NS
Azzopardi 2010[75]	Male, 59	NS	Delusions with no hallucinations	100	NS	NS	NS	Partial recovery	NS	NS
Nielsen 2010[65]	Male, 47	90	Hallucinations with no delusions	47	No	112	NS	Complete recovery	6	6
Kandukuri 2010[66]	Male, 23	NS	Hallucinations and delusions	200	Yes, NS	NS	NS	Recovery with other cognitive deficits	NS	104
Greene 2009[86]	Female, 39	NS	Hallucinations and delusions	53	Yes, NS	NS	NS	Complete recovery	NS	NS
Sathya 2009[74]	Female, 47	3	Hallucinations and delusions	63	Yes, 4	25	100	Complete recovery	1	4
Moeller 2009[38]	Female, 51	NS	Hallucinations and delusions	176	Yes, 0.1	100	100	Complete recovery	0.7	1
Selvaraj 2008[54]	Male, 65	21	Delusions, but hallucinations not explicitly mentioned	60	No	NS	NS	Complete recovery		NS
Tor 2007[33]	Female, 72	60	Hallucinations and delusions	79	Yes, NS	50	50	Complete recovery	2	13
Khaldi 2006[50]	Female, 53	10	Delusions with no hallucinations	387	Yes, 0.9	NS	100	Complete recovery	0.8	6
Stowell 2005[43]	Female, 35	14	Delusions with no hallucinations	150	Yes, 0.9	200	150	Complete recovery	0.5	NS
Heinrich 2003[87]	Female, 73	14	Hallucinations with no delusions	53	Yes, 2	NS	NS	Complete recovery	2	NS

Benvenga 2003[88]	Female, 55	90	Hallucinations with no delusions	30	Yes, 21	100	100	Complete recovery	0.6	625
Chari 2002[89]	Male, 28	180	Delusions with no hallucinations	70	Yes, 8	25	150	Complete recovery	NS	26
Nathan 1997[25]	Male, 43	30	Hallucinations and delusions	46.6	NS	NS	NS	Complete recovery	1	20
Westphal 1997[61]	Male, 46	5	Hallucinations and delusions	139	Yes, 0.5	50	50	Complete recovery	0.5	26
Westphal 1997[61]	Female, 29	NS	Hallucinations with no delusions	1500	Yes, 1.4	100	NS	Complete recovery	1.3	52
Ward 1994[90]	Female, 73	21	Hallucinations and delusions	61	Yes, NS	NS	NS	Complete recovery	NS	14
Pearce 1991[53]	Female, 86	5	Hallucinations and delusions	60	Yes, NS	NS	NS	Complete recovery	2	NS
Rao 1990[62]	Female, 28	3	Hallucinations, but delusions not explicitly mentioned	40	NS	NS	NS	Complete recovery	4	4
Darko 1989[31]	Male, 24	NS	Hallucinations and delusions	353	Yes, NS	50	150	Recovery with other cognitive deficits	3	25
Davis 1989[91]	Male, 40	21	Hallucinations and delusions	370	Yes, 0.1	NS	NS	Complete recovery	1	52
Santiago 1987[41]	Female, 36	7	Hallucinations and delusions	110	NS	NS	NS	Complete recovery	1.6	8
Cook 1986[44]	Male, 25	NS	Delusions with no hallucinations	97	NS	NS	NS	Complete recovery	0.3	
Cook 1986[44]	Male, 42	NS	Hallucinations and delusions	29	NS	NS	NS	Complete recovery	0.4	
Shaw 1985[73]	Female, 53	730	Hallucinations and delusions	NS	Yes, NS	100	NS	Complete recovery	2	26
Samuel 1984[48]	Female, 32	365	Hallucinations and delusions	24	Yes, NS	100	300	NS	2	NS

(*Continued*)

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Table 1 (Continued).

Case Study	Gender	Symptom Duration [Days]	Psychiatric Symptoms Reported	TSH Level	Antipsychotic Treatment [Yes/No], Duration [Weeks]	T4 Starting Dose (mcg)	T4 Maintenance Dose (mcg)	Recovery Outcome	Duration to Outcome in Weeks	Follow Up Duration [Weeks]
Hall 1982[51]	Female, 34	NS	Hallucinations and delusions	NS	NS	NS	NS	Complete recovery	NS	208
Hall 1982[51]	Female, 35	NS	Hallucinations and delusions	NS	NS	NS	NS	Complete recovery	NS	13
Madakasira 1981[40]	Female, 68	14	Delusions with no hallucinations	NS	NS	NS	NS	Complete recovery	NS	NS

Note: Partial recovery means improvement of psychosis symptoms with no complete resolution.
Abbreviations: MP, myxedema psychosis; T3 triiodothyronine; T4 thyroxine, NS; not specified.

antipsychotic use was 1.8 [0.6–8] weeks. The longest antipsychotic treatment duration was 39 weeks.

Thyroid Hormone Supplementation

The median initiating and maintenance dose of thyroxine was 100 mcg [50–141]. Intravenous thyroid hormone therapy was administered in 10% of the patients (5/50). In 85% (44/52) of the cases, no thyroxine loading was given. Triiodothyronine was administered to 8% (n=5/58) of the cases.

Steroids

Steroids were administered in 3% of the cases (2/67). The median dose used was equivalent to 50 mg of prednisolone that was used for periods of three days and two weeks, respectively.

Outcome and Follow-Up

Clinical outcome data were reported for 96% of the cases (72/75). The majority of patients, 97% (66/68), required hospitalization, and 93% demonstrated remission. However, two patients (3%) showed no improvement or residual psychosis,[23,75] while another three cases (4%) displayed recovery of psychosis with persisting residual deficits in cognition, memory, orientation, attention.[31,66] The duration-to outcome occurrence was reported in 83% (62/75) of the cases. The median duration to the outcome (recovery) was 1.93 [0.8–2] weeks. The use of intravenous thyroid hormone supplementation (4/46) was associated with faster recovery compared to oral administration (0.55 [0.5–0.85] weeks vs 2.0 [1–2.85] weeks (p= 0.022). The univariate analysis also revealed a trend towards a shorter duration of psychosis (p= 0.0502) with IV thyroid hormone therapy. However, this effect could not be confirmed in the multivariate analysis (Table 3). Recovery duration did not differ between patients who received triiodothyronine and those who did not 0.5 [0.37–1.95] weeks vs 2 [1–2] weeks, p= 0.2). In the multivariate analysis (Table 3), gender (p= 0.33), age (p=0.46), symptoms duration (p=0.98) TSH level (p=0.29), FreeT4 (p=0.32), antipsychotic drugs duration (p=0.22), IV thyroid hormone therapy, and starting thyroxine dose (0.52) were not associated with shorter duration of psychosis (<2 weeks).

Discussion

The major finding of this systematic review is that evidence on the pathophysiology as well as the clinical course

Table 2 Summary of Baseline Characteristics, Clinical Features, and Diagnostic Workup of Included Cases

Basel line Characteristic	Frequency (n/N) %	Clinical Feature	Frequency (n/N) %	Laboratory and Diagnostic Workup	Frequency (n/N) %
Female	(49/74) 66%	Delusion	(46/70) 91%	Normal EEG	(11/15) 73%
Male	(25/74) 33%	Hallucination	(55/71) 77.5%	Normal CT head	(24/27) 89%
African	(5/25) 20%	Hypothyroid symptoms	(26/41) 63%		
Asian	(9/25) 36%	Hypothyroidism signs	(39/53) 74%	Normal MRI head	(12/16) 75%
Caucasian	(11/25) 44%				
Hypothyroidism history	(34/72) 47%	Manic symptoms	(23/44) 52%	Normal CSF	(4/6) 67%
Previous psychotic episode	(13/71) 18%				
Previous psychotic episode likely related to hypothyroidism	(9/13) 69%	Depression symptoms	(16/43) 37%	Normal Creatinine Kinase	(0/7) 0%
Family history of Psychotic disorder	(3/29) 10%				

Notes: (n/N) refers to the crude number of a certain characteristic divided by the number of cases where this specific feature was assessed as reported (either present or absent) by the two reviewers.

Table 3 Table Summarizing the Result of the Multivariate Analysis

Outcome Duration	Odds Ratio	Standard Error	Z	P value	95% Confidence Interval
Gender	0630998	0.1818115	−0.96	0.338	0.0002226–17.89051
Age	1.059715	0.0844381	0.73	0.467	0.906495–1.238833
Symptoms duration	0.9985847	0.0087879	−0.16	0.872	0.9815084–1.015958
TSH Level	1.011948	0.0115271	1.04	0.297	0.9896059–1.034795
Free T4 level	23.3286	74.00553	0.99	0.321	0.0465172–11,699.39
Antipsychotic duration	1.352324	0.3359208	1.22	0.224	0.8310751–2.200501
Intravenous thyroid hormones	1	(omitted)			
Thyroxine starting dose	1.011141	0176096	0.64	0.525	0.9772096–1.046251
_cons	0.0018515	0095248	−1.22	0.221	7.74e-08-44.30106

Notes: Log likelihood = −6.5106511 Pseudo R2 = 0.3718. The outcome of interest is a shorter duration of psychosis recovery (< 2 weeks).
Abbreviations: TSH, thyroid stimulating hormone; T4, thyroxine.

and management of MP is limited to case reports. Descriptive pooling of extracted data from these reports and exploratory analysis indicates that MP can manifest with a wide range of psychiatric and physical symptoms and is commonly treated with antipsychotics and thyroid hormone supplementation. Although the vast majority of patients needed to be hospitalized, very few displayed persisting residual deficits after treatment. Prospective research is urgently needed to improve our understanding of MP and identify factors that may modulate clinical outcomes in order to design standardized diagnostic and therapeutic regimens.

The prevalence of MP was not primarily studied. Therefore, it can only be indirectly estimated from studies evaluating psychotic symptoms in patients with hypothyroidism. Based on the Committee on Myxedema of the Clinical Society of London report, the prevalence of psychotic symptoms was around 50% in hypothyroid patients in the late

nineteenth century,[5] and was less than 2% in 1965 based on a study of four-hundred hypothyroid patients in which 2% of patients were described to have hypothyroidism associated mental changes (this study did not provide details about the nature of psychic changes, which could be non-psychotic or hypothyroidism unrelated).[92]

In this review, we identified reports of MP in all adult age groups with a slightly higher proportion of reports on younger patients. Symptoms of hypothyroidism were observed in half of the cases, indicating that the absence of a prior history of hypothyroidism does not rule out MP. The majority of the cases did not have a personal nor family history of psychosis, supporting the direct link between thyroid pathology and psychosis. Although the pooled data from reported cases do not constitute a representative population, we observed a possible pattern in the clinical manifestation of the predominance of paranoid/persecutory delusions and auditory hallucinations. Manic symptoms tended to accompany MP more often than symptoms of depression. Fatigue was the most frequent somatic symptom; that is, however, nonspecific and can be seen in both primary and secondary psychiatric disorders. Although interesting, the predominance of manic symptoms and fatigue can be due to underreporting as many clinical features were reported in few cases only. Interestingly, almost 40% of the cases did not have any physical hypothyroidism symptoms, while TSH was elevated in all cases with low thyroid hormones supporting the value of screening for thyroid dysfunction in patients with first-ever psychosis. Cranial imaging data did not suggest any relevant changes in brain structure related to MP. Almost all patients needed hospital admission. Antipsychotic medications were given to most of the patients (92%) with remission following short-term administration. Whether this indicates that termination of antipsychotic therapy after remission of psychotic symptoms is safe in patients with MP remains to be answered by prospective research.

Our pooled data of MP cases showed that administration of thyroxin was performed either intravenously or orally. Explorative comparison of synthesized data did not show the superiority of one administration route over the other, although unadjusted comparison showed a possible trend toward faster recovery after IV administration. However, this observation is solely based on cumulative case reports and needs to be viewed in conjunction with the potential increased risk of arrhythmias associated with IV thyroxin.[94,95] Administration of triiodothyronine in MP was reported small fraction of the cases and should be investigated in prospective research. In most cases, steroids were not needed, questioning the value of immunosuppressive medication in MP, contrary to myxedema coma and HE. Most cases recovered completely, and only a few cases were left with residual psychosis or cognitive deficits. The etiology of partial improvement or residual cognitive deficits could be either a chronic and irreversible metabolic effect induced by hypothyroidism, as hypothesized by Asher et al or a primary psychiatric illness precipitated by hypothyroidism. All cases that recovered improved within two weeks on average, not exceeding six weeks at most. However, not all cases had long-term follow-up details to study recurrence of psychosis in the presence or absence of dysthyroid status.

Our review excluded two reports of patients with mania that did not exert psychotic features.[96,97] Although the reported cases would be classified under the initial term "Myxedema Madness," we have excluded them as they would not fit within the term "Myxedema psychosis."

Prior systematic reviews examining HE,[98–100] showed that only 20–25% of patients had clinical hypothyroidism, and most of them were euthyroid. It has been stated that psychosis occurs in around a third or less of the patients (26–36%) and is usually accompanied by other features such as; seizures in up to two-thirds (59–66%) and myoclonus (36–42%). These features were not seen in our patient population and their presence may help distinguish HE from MP, especially if the patients are euthyroid. Thyroperoxidase antibodies were found positive in almost all HE cases (86–100%), while our review revealed that 50% of MP cases had autoimmune thyroiditis. This may support the diagnostic value of a negative, not a positive, thyroperoxidase antibody test to differentiate MP from HE. Elevated protein in the cerebrospinal fluid is another characteristic feature of HE occurring in 71–78%, while electroencephalogram is usually abnormal (80–98%).[15] These may also help differentiate it from MP as shown in our review, abnormal CSF and or EEG are not common in MP cases. Moreover, the small number of MP cases with abnormal CSF or EEG as depicted by our review could have been simply misdiagnosed HE cases.

Our systematic review has strengths, including a comprehensive literature search following PRISMA guidelines after a priori registration and publication of the predefined review protocol. We were able to pool data from a wide variety of sources identified in the published literature. We provided data on the demographics, diagnosis, and management of myxedema psychosis. Our pooled analysis is solely

based on case reports constituting a non-representative population. However, our work clearly shows a substantial research gap, substantiating an urgent need for prospective well-designed research to characterize the clinical course and characteristics of myxedema and to test tailored diagnostic and therapeutic strategies. Publication and reporting bias cannot be ruled since cases considered not interesting or those with adverse outcomes could have been under-reported. Moreover, incomplete reporting of many clinical symptoms or details' reporting within individual cases may have biased the final conclusion with regards to background data, outcomes, and follow-up duration. Furthermore, the diagnosis of MP was a clinical diagnosis as deemed likely by the treating physicians. We limited our search to case reports starting from 1980. By doing this, we may have missed including a small number of cases; however, considering that the differential diagnosis of HE was first described in 1966,[101] we intended to collect comparable cases in order to differentiate between both conditions. Another reason for limiting our search to the time period since 1980 was changes in presentation and symptomatology of hypothyroidism due to improved diagnosis and disease management over time.

Conclusion

Our systematic review and pooled analysis identified a substantial lack of published research on MP. Available case observations indicate that patients with MP present with a broad spectrum of psychiatric and physical symptoms lending support to the value of screening for thyroid dysfunction in patients with first-ever psychosis.

Ethical Approval

Ethical approval is not required for this article as it is a secondary synthesis of publicly available data.

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