Research Proposal: Psychiatric Phenotypes in Autoimmune vs. Non-Autoimmune Hypothyroidism

Executive Summary

Objective: Identify clinical and psychiatric phenotype differences between autoimmune and non-autoimmune hypothyroidism to establish foundations for biomarker discovery

Design: Multicenter cross-sectional study with 12-month prospective follow-up

Population: Pediatric (6-17 years) and adult (18-65 years) patients

Sample Size: 600 participants (150 per group across 4 groups)

Duration: 36 months

Background & Rationale

The Problem

Hypothyroidism affects 4-5% of the population, with autoimmune thyroiditis (Hashimoto's) being the most common cause

Despite adequate thyroid hormone replacement, many patients report persistent symptoms:

- Depression and anxiety
- Cognitive dysfunction
- Fatigue
- Psychotic symptoms (rare but significant)

Knowledge Gaps

- Current literature treats hypothyroidism as homogeneous
- Relationship between autoimmune processes and neuropsychiatric symptoms poorly characterized
- Age-dependent effects (pediatric vs. adult) understudied
- No systematic clinical characterization to guide biomarker discovery

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Primary Hypothesis

Autoimmune hypothyroidism presents with distinct psychiatric and clinical phenotypes compared to non-autoimmune hypothyroidism, independent of thyroid hormone levels, due to immune-mediated mechanisms affecting the CNS

Study Design Overview

Design Type

Cross-sectional + Prospective Cohort

- Baseline comprehensive phenotyping
- Follow-up at months 3, 6, and 12

Four Study Groups

1. **Pediatric Autoimmune** (n=150)
2. **Pediatric Non-Autoimmune** (n=150)
3. **Adult Autoimmune** (n=150)
4. **Adult Non-Autoimmune** (n=150)

Total enrollment target: 600 (accounting for 15% attrition)

Inclusion Criteria

Autoimmune Group

- Positive anti-TPO antibodies (>100 IU/mL) and/or anti-thyroglobulin antibodies
- With or without ultrasound evidence of thyroiditis

Non-Autoimmune Group

- Confirmed hypothyroidism with negative antibodies
- Includes iatrogenic, congenital, or idiopathic causes

All Participants

- Minimum 6 months since diagnosis
- Stable thyroid hormone replacement ≥3 months (if applicable)
- Age 6-17 (pediatric) or 18-65 (adult)

Exclusion Criteria

- Other autoimmune diseases (to isolate thyroid-specific effects)
- Major psychiatric disorders predating hypothyroidism diagnosis
- Neurological conditions affecting cognition
- Current psychotropic medications (except stable antidepressants >6 months)
- Pregnancy or postpartum period (<12 months)
- Substance abuse disorders

Assessment Timeline

Baseline (Month 0)

Comprehensive clinical and psychiatric phenotyping

Follow-up Visits

Months 3, 6, and 12 - abbreviated assessments

Clinical Characterization

Thyroid Function Assessment

- TSH, free T4, free T3 (all visits)
- Anti-TPO and anti-thyroglobulin antibodies (baseline, month 12)
- Thyroid ultrasound (baseline)
- Medication history and dosing

General Clinical Measures

- Complete medical history and physical examination
- Symptom checklist (fatigue, cold intolerance, weight changes)
- Vital signs and anthropometrics
- Comorbidity assessment

Psychiatric Phenotyping (Primary Outcomes)

Structured Clinical Interviews

Adults: SCID-5 (Structured Clinical Interview for DSM-5)

Pediatrics: K-SADS-PL (Kiddie Schedule for Affective Disorders and Schizophrenia)

Standardized Rating Scales

Depression:

- Adults: BDI-II, HAM-D
- Pediatrics: CDI-2

Anxiety:

- Adults: GAD-7, HAM-A
- Pediatrics: SCARED

Psychiatric Assessment (Continued)

Cognitive Function

Adults:

- Montreal Cognitive Assessment (MoCA)
- Trail Making Test A/B
- Digit Span

Pediatrics:

- Age-appropriate Wechsler Intelligence Scale subtests
- NEPSY-II attention/executive function domains

Additional Measures

- Fatigue Severity Scale (FSS)
- Pittsburgh Sleep Quality Index (PSQI)
- Quality of Life: SF-36 (adults), PedsQL (pediatrics)

Psychosis Assessment Protocol

Three-Tier Approach

Tier 1: Universal Screening (all participants)

- Prodromal Questionnaire-Brief Version (PQ-B)
- Lifetime psychosis history questions
- Clinical red flags checklist

Tier 2: Detailed Assessment (positive screens)

- SCID-5 or K-SADS-PL psychotic disorders module
- Brief Psychiatric Rating Scale (BPRS)
- Cognitive screening (MMSE/MoCA)
- Functional assessment (SOFAS)

Tier 3: Specialized Evaluation (severe cases)

- Psychiatrist evaluation
- Hashimoto's encephalopathy assessment
- Neurological examination
- Advanced investigations (EEG, MRI, CSF if indicated)

Psychotic Manifestations: Special Focus

Why Focus on Psychosis?

Rare but clinically significant (5-15% of severe hypothyroidism)

Distinct autoimmune syndrome: Hashimoto's encephalopathy (SREAT)

- Psychosis with elevated anti-thyroid antibodies
- Often normal thyroid function
- Responds to corticosteroids

Proposed mechanisms:

- Neuroinflammation
- Anti-thyroid antibodies cross-reacting with brain antigens
- Cytokine dysregulation
- Blood-brain barrier disruption

Clinical Decision Algorithm

Severity Triage

High Urgency → Emergency intervention

- Active suicidal/homicidal ideation
- Severe disorganization
- Acute confusional state

Moderate Urgency → Prompt assessment (48-72 hours)

- Psychotic symptoms causing distress
- Functional impairment
- Suspected Hashimoto's encephalopathy

Low Urgency → Routine follow-up (1-2 weeks)

- Mild attenuated symptoms
- Historical symptoms, currently stable

Biological Sample Collection

For future biomarker studies (stored, not analyzed in this phase):

- Serum (10 mL) - inflammatory markers, cytokines
- Plasma (5 mL) - metabolomics
- Whole blood (5 mL) - genetic studies
- Storage at -80°C with standardized protocols

Enhanced collection for psychotic cases:

- Antibody panels (anti-neuronal antibodies)
- Inflammatory markers (IL-6, TNF-α, CRP)
- Neuroimaging (if clinically indicated)

- CSF (only if clinically indicated)

Statistical Analysis Plan

Sample Size & Power

Based on detecting medium effect size (Cohen's d = 0.5):

- 80% power, α = 0.05
- n = 128 per group
- Total n = 512 (600 with 15% attrition)

For psychotic outcomes (assuming 5-10% prevalence):

- Power to detect OR ≥ 2.0: ~75-85%
- Expected 30-60 cases for analysis

Primary Statistical Analyses

Analysis 1: Prevalence Comparison

Outcome: Any psychotic symptoms (lifetime or current)

Method: Logistic regression

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Psychotic_Symptoms ~ Etiology + Age_Group +
                     Etiology × Age_Group + Covariates
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Covariates: TSH, free T4, disease duration, age, sex, family history

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Primary Analyses (Continued)

Analysis 2: Symptom Severity Among Cases

Outcome: BPRS total score (continuous)

Method: Linear regression or quantile regression

Analysis 3: Symptom Profile Analysis

Outcome: Specific psychotic symptom types

Method: Multiple logistic regressions with FDR correction

Symptom categories:

- Auditory/visual hallucinations
- Paranoid/persecutory delusions
- Thought disorder
- Negative symptoms

Secondary Analyses

Analysis 4: Temporal Relationship

Research question: Does psychosis onset relate to thyroid diagnosis timing?

Categories:

1. Predated thyroid diagnosis
2. Concurrent with diagnosis
3. Emerged after diagnosis
4. Emerged after treatment initiation

Analysis 5: Longitudinal Trajectory

Model: Mixed-effects regression

Key parameters:

- Time effect (overall change)
- Etiology effect (baseline differences)
- Time × Etiology interaction (differential trajectories)

Advanced Statistical Techniques

Handling Rare Outcomes

Propensity Score Matching

- Control for confounding by disease severity
- 1:1 matching on key covariates

Firth's Penalized Likelihood

- Reduces bias for rare events
- Better confidence intervals

Bayesian Analysis

- Incorporates prior knowledge
- Probability statements about effect sizes
- Better for small samples

Latent Class Analysis

- Identify distinct psychotic phenotype subgroups
- Test associations with etiology

Multiple Comparison Correction

Hierarchical Testing Approach

Primary hypothesis family ($\alpha = 0.05$):

1. Any psychotic symptoms (primary)
2. If significant → test secondary outcomes

Method: Holm-Bonferroni sequential procedure

Exploratory Analyses

False Discovery Rate (FDR) Control

- Benjamini-Hochberg procedure
- Control FDR at $q = 0.05$
- Appropriate for hypothesis-generating analyses

Expected Outcomes

Primary Hypotheses

Hypothesis 1: Autoimmune hypothyroidism will show higher rates and severity of:

- Depressive symptoms
- Anxiety disorders
- Cognitive complaints
- Fatigue independent of thyroid hormone levels
- **Psychotic symptoms**

Hypothesis 2: Pediatric populations will show distinct patterns:

- Greater neurodevelopmental impact
- Different symptom profiles

- Potentially stronger autoimmune-psychiatric associations

Expected Outcomes (Continued)

Hypothesis 3: Clinical Phenotype Clusters

Expectation: Distinct disease subtypes will emerge that cross traditional diagnostic boundaries

Psychosis-Specific Predictions

1. Higher prevalence of attenuated psychotic symptoms in autoimmune group
2. Correlation between anti-thyroid antibody titers and psychotic symptom severity
3. Distinct psychotic symptom profiles (more perceptual disturbances in autoimmune cases)
4. Greater persistence despite thyroid normalization

Foundation for Biomarker Studies

This Study Will Establish:

Target phenotypes for biomarker correlation

- Which psychiatric symptoms to focus on

Patient stratification criteria

- Enriching future studies with high-risk groups

Biological sample repository

- Well-characterized clinical phenotypes

Effect size estimates

- Powering biomarker validation studies

Candidate mechanisms

- Inflammatory, autoimmune, neurometabolic pathways

Clinical Impact

Immediate Applications

- Improved recognition of psychiatric manifestations in autoimmune thyroid disease
- Screening recommendations for psychiatric comorbidity
- Patient stratification for clinical trials

Long-term Impact

- Etiology-specific treatment approaches
- Biomarker-guided therapy
- Personalized medicine for hypothyroidism
- Understanding of autoimmune neuropsychiatry

Training & Quality Assurance

Staff Training Requirements

All Research Staff (8-hour initial training):

- Recognition of psychotic symptoms
- Safety assessment basics
- Non-stigmatizing communication

Clinical Assessors (16-hour specialized training):

- Structured interview certification (SCID-5, K-SADS-PL)
- BPRS/PANSS reliability training (≥0.80 inter-rater reliability)
- Crisis intervention

Study Psychiatrists:

- Protocol-specific training
- Autoimmune neuropsychiatry expertise
- Supervision and consultation

Quality Assurance Procedures

Data Quality Monitoring

- Automated range checks and missing data alerts
- Monthly audits (10% random sample)
- Quarterly review of 100% psychotic symptom cases
- Quarterly inter-rater reliability testing

Protocol Adherence

- Checklist-based monitoring
- Supervisor review within 48 hours
- Protocol deviation tracking and remediation

Safety Monitoring

Data Safety Monitoring Board (DSMB):

- Independent experts review quarterly
- Authority to recommend modifications
- Focus on psychotic events, hospitalizations, suicide attempts

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Participant Support

Psychoeducation Materials

- "Understanding Thyroid Disease and Mental Health" booklet
- Educational videos
- Participant testimonials

Crisis Resources

24/7 Access:

- National Suicide Prevention Lifeline: 988
- Crisis Text Line: HOME to 741741
- Study team tiered contact system

Safety Planning

- Collaborative safety plans for high-risk participants
- Warning signs identification
- Coping strategies
- Emergency contacts

Ethical Considerations

Enhanced Consent for Psychosis Assessment

Specific consent elements:

- Risks of psychiatric assessment (distress, stigma)
- Benefits (early identification, treatment access)
- Confidentiality and mandatory reporting limits
- Right to refuse specific assessments

Capacity to Consent

- Assess decision-making capacity for participants with active psychosis
- Parental consent + child assent for pediatrics
- Reassess capacity when symptoms improve

Data Privacy

- Encrypted databases with role-based access
- De-identification for all publications
- Enhanced protections for sensitive psychiatric data

Timeline & Milestones

Months 1-3

Protocol finalization, ethics approval, site initiation

Months 4-18

Patient recruitment and baseline assessments

Months 7-30

Follow-up assessments (rolling enrollment)

Months 31-33

Data cleaning and statistical analysis

Months 34-36

Manuscript preparation and dissemination

Total study duration: 36 months

Budget Considerations

Major Cost Categories

- **Personnel**: Coordinators, assessors, data management, psychiatrists
- **Assessments**: Psychiatric tools licensing, cognitive testing materials

- **Laboratory**: Thyroid function tests, antibody assays, sample storage
- **Biobanking**: Sample processing, -80°C storage, tracking system
- **Participant compensation**: Time and travel reimbursement
- **Data management**: Secure database, statistical software
- **Publication**: Open access fees, conference presentations

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Limitations & Mitigation

Limitation 1: Cross-sectional Design

Issue: Limits causal inference

Mitigation: 12-month prospective component to assess temporal patterns

Limitation 2: Heterogeneous Non-Autoimmune Group

Issue: Multiple etiologies combined

Mitigation: Subgroup analyses by specific etiology; sensitivity analyses

Limitation 3: Medication Effects

Issue: Psychiatric symptoms may be medication-related

Mitigation: Strict inclusion criteria; control for treatment adequacy in analyses

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Limitations & Mitigation (Continued)

Limitation 4: Referral Bias

Issue: Clinical populations may not represent all cases

Mitigation: Multicenter recruitment including community practices

Limitation 5: Rare Psychotic Outcomes

Issue: Limited power for subgroup analyses

Mitigation:

- Broader phenotype definition (attenuated symptoms)
- Oversampling strategy for psychosis history
- Advanced statistical methods for rare events

Study Strengths

Methodological Rigor

✓ **Large, well-powered sample** (n=600)

✓ **Comprehensive phenotyping** across multiple domains

✓ **Standardized, validated assessment tools**

✓ **Prospective follow-up component**

✓ **Both pediatric and adult populations**

✓ **Biobank for future mechanistic studies**

Study Strengths (Continued)

Clinical Relevance

✓ **Addresses significant knowledge gap** in thyroid-psychiatric associations

✓ **Focus on understudied psychotic manifestations**

✓ **Practical clinical decision algorithms**

✓ **Foundation for biomarker discovery**

✓ **Potential to change clinical practice**

Innovation

✓ **First systematic comparison** of psychiatric phenotypes by hypothyroidism etiology

✓ **Novel three-tier psychosis assessment protocol**

✓ **Integration of autoimmune neuropsychiatry concepts**

Deliverables

Scientific Outputs

Primary manuscript: Psychiatric phenotype differences in autoimmune vs. non-autoimmune hypothyroidism

Secondary manuscripts:

- Psychotic manifestations and Hashimoto's encephalopathy
- Pediatric vs. adult phenotypic differences
- Longitudinal trajectory and treatment response
- Clinical predictors for biomarker studies

Conference presentations: Annual updates at major endocrinology and psychiatry meetings

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Deliverables (Continued)

Clinical Tools

- Validated screening protocol for psychiatric symptoms in hypothyroidism
- Clinical decision algorithm for psychosis management
- Patient education materials
- Training curriculum for healthcare providers

Research Infrastructure

- Well-characterized biobank (600 participants)
- Longitudinal clinical database
- Collaborative research network
- Platform for future intervention studies

Next Steps

Phase 1: Protocol Finalization (Months 1-3)

1. Finalize assessment tools and procedures
2. Develop training materials and participant resources
3. Submit IRB applications (all sites)
4. Establish DSMB and data management systems
5. Recruit and train research staff

Phase 2: Pilot Testing (Month 3)

1. Conduct staff training workshops
2. Pilot test protocols with mock participants
3. Refine procedures based on feedback
4. Establish quality assurance procedures

Next Steps (Continued)

Phase 3: Soft Launch (Months 4-6)

1. Begin enrollment with enhanced monitoring
2. Weekly team meetings to troubleshoot
3. First DSMB safety review
4. Adjust protocols as needed

Phase 4: Full Implementation (Months 7-36)

1. Continue recruitment to target n=600
2. Complete all follow-up assessments
3. Ongoing quality monitoring and safety reviews
4. Interim analyses and manuscript preparation
5. Plan next-phase biomarker studies

Conclusion

Summary

This comprehensive study will:

Systematically characterize psychiatric phenotypes in autoimmune vs. non-autoimmune hypothyroidism

Establish clinical foundations for future biomarker discovery

Address critical knowledge gap in thyroid-psychiatric associations

Generate high-impact findings with potential to change clinical practice

Create research infrastructure for ongoing investigations

Conclusion (Continued)

Unique Contributions

First large-scale comparison of psychiatric manifestations by hypothyroidism etiology

Comprehensive psychosis assessment including rare Hashimoto's encephalopathy

Both pediatric and adult populations to identify developmental differences

Rigorous methodology with prospective follow-up and biobanking

Translational potential from clinical phenotyping to biomarker studies to personalized treatment

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Questions & Discussion

Key Questions for Consideration

1. **Recruitment strategy**: Which clinical sites and patient populations to target?
2. **Funding sources**: NIH, private foundations, pharmaceutical partnerships?
3. **Collaborative opportunities**: Academic centers, clinical networks, patient advocacy groups?
4. **Timeline feasibility**: 36 months realistic given recruitment challenges?
5. **Priority outcomes**: Which findings would have greatest clinical impact?

Contact & Collaboration

Research Team

Principal Investigator: [Name, Institution]

Co-Investigators:

- Endocrinology expert
- Psychiatry expert
- Biostatistician
- Pediatric specialist

Collaboration Opportunities

- Clinical site partnerships
- Biomarker validation studies
- Patient advocacy engagement
- International consortium development

Thank You

For More Information

Study Protocol: [Available upon request]

Detailed Statistical Analysis Plan: [Available upon request]

Training Materials: [In development]

Questions: [Contact information]

This research has the potential to transform our understanding of the relationship between autoimmune thyroid disease and psychiatric manifestations, ultimately improving care for millions of patients worldwide.