DOWN SYNDROME REGRESSION DISORDER

LATEST RESEARCH UPDATES

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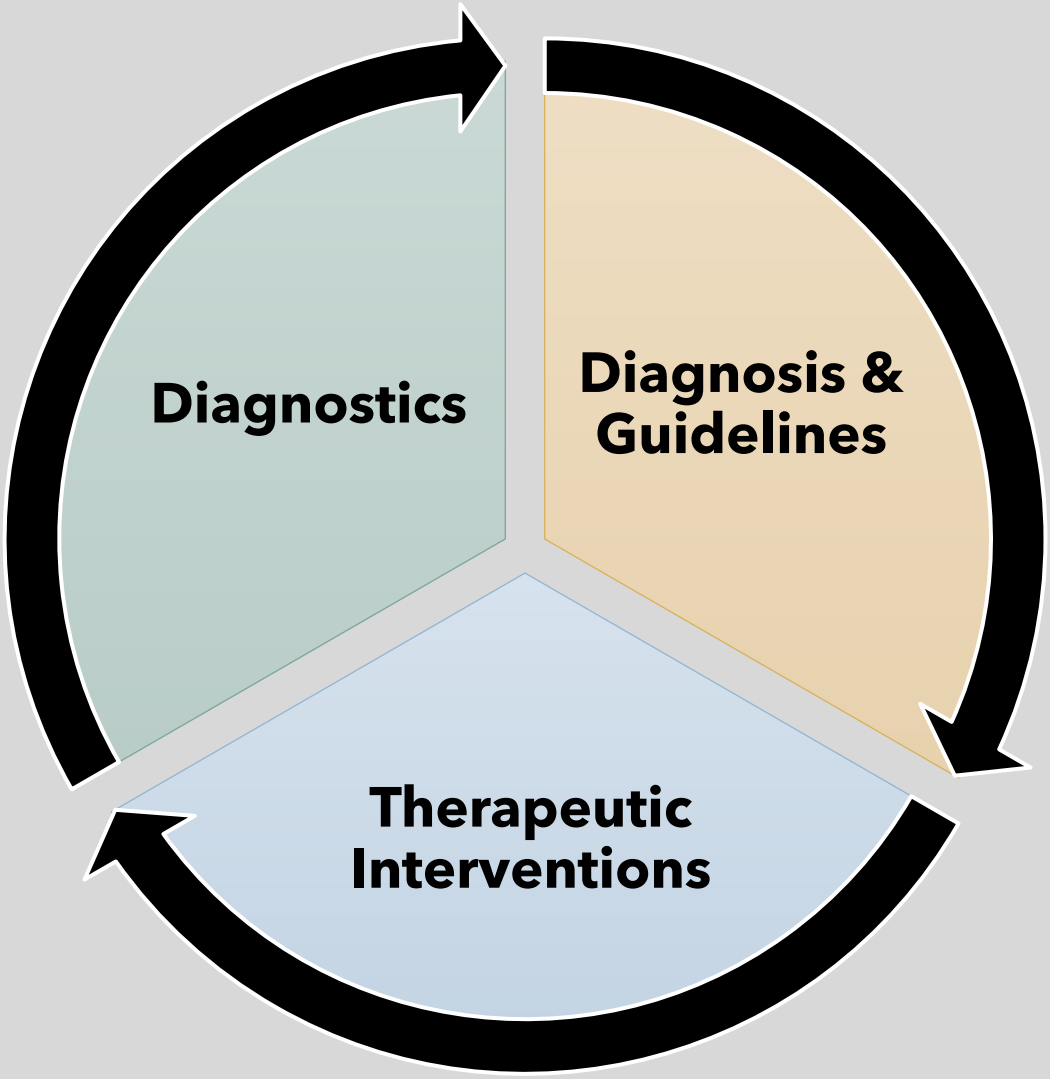

Diagnostics
Diagnosis & Guidelines
Therapeutic Interventions

The Problem of Diagnosis…

- While we can now identify that a patient fits a *phenotype* consistent with DSRD, the challenge remains that there are no specific guidelines to guide the diagnosis of the condition.

- Superimposed on this problem is that there are no definitive biomarkers of the disease itself or severity.

- Solution! In 2021, an international consensus study was performed to develop diagnostic and evaluation standards for the condition

Table 4: Consensus recommendations for the diagnosis of Down syndrome regression disorder

Category	Criteria	Possible DSRD	Probable DSRD
Symptom Onset	Onset of new neurologic, psychiatric, or mixed symptoms over a period of less than 12 weeks in previously health individual with Down syndrome	Yes	Yes
Clinical Evidence of Neurologic Dysfunction	1. Altered mental status or behavioral dysregulation - Anorexia/decreased oral intake or hyperphagia - Confusion/disorientation - Inappropriate laughter - Encephalopathy 2. Cognitive decline - Apathy - Abulia and/or avolition - Acute memory impairment (including new difficulty with recall) 3. Developmental regression with or without new autistic features - Social withdrawal - Loss of previously developmental acquired milestones - Inability to perform activities of daily living - Stereotypy - Rigidity around routine changes - Decreased eye contact 4. New focal neurologic deficits on examination and/or seizure 5. Insomnia or circadian rhythm disruption 6. Language deficits - Expressive and/or receptive aphasia - Global aphasia (mutism) - Whispered speech 7. Movement disorder (excluding tics) * - Catatonia - Bradykinesia - Freezing - Gait disturbance 8. Psychiatric symptoms - Anxiety - Delusions or hallucinations - Derealization/depersonalization - Obsessive compulsive tendencies - Aggression/agitation	≥ 3 symptom clusters present	≥ 6 symptom clusters present
Exclusion of other etiologies	Reasonable exclusion of alternative causes of regression including other systemic and central nervous system disorders. Other primary psychiatric disorders are also considered exclusionary.	Yes	Yes

Legend: * must be included as one of the symptom clusters for possible or probable diagnosis

CRITERIA

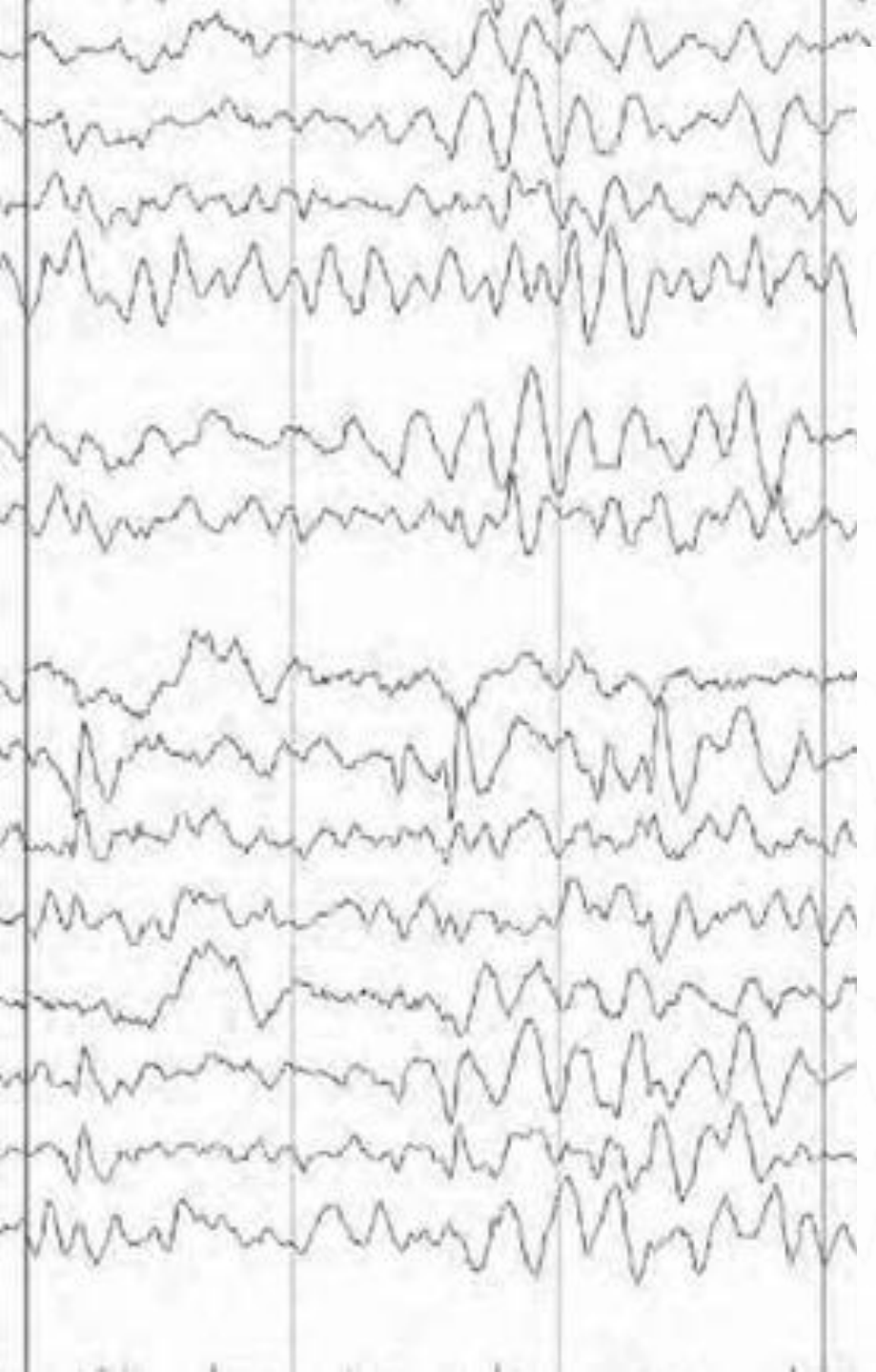
Diagnostics in DSRD

- The etiology of DSRD has remained elusive since its first description in 1946 by Rollin although research over the last two years has revealed neurodiagnostic abnormalities in a variety of domains.
- Labwork
- EEG
- MRI
- Lumbar Puncture/Spinal Tap

Table 2: Serum and Neurodiagnostic studies

Study	DSRD Results Abnormal (n, %)	DS Results Abnormal (n/N, %)	p Value	95% CI
Serum Analysis				
ANA	9 (13%)	21/422 (5%)	**0.01**	**1.20-5.26**
Anti-DNAseB	0 (0%)	1/125 (1%)	0.70	0.11-27.95
ASO (n= 58)	0 (0%)	6/204 (3%)	0.47	0.05-3.87
B12 level	7 (12%)	64/1125 (6%)	0.17	0.79-4.05
Celiac panel	2 (3%)	24/506 (5%)	0.46	0.13-2.48
Complete metabolic profile	5 (7%)	88/1256 (7%)	0.98	0.39-2.52
CRP (n= 62)	0 (0%)	15/433 (3%)	0.36	0.05-2.98
dsDNA (n= 61)	6 (10%)	3/108 (3%)	0.11	0.77-13.12
ESR (n= 66)	0 (0%)	16/612 (3%)	0.53	0.07-3.96
Infectious screen[a]	12 (18%)	n/a	n/a	n/a
Neopterin (n= 42)	0 (0%)	0/12 (0%)	n/a	n/a
Methylmalonic acid (n= 61)	9 (21%)	14/203 (7%)	0.15	0.79-4.67
Neurometabolic studies* (n= 32)	1 (2%)	3/188 (2%)	0.90	0.09-8.49
Thyroid dysfunction (untreated)	2 (4%)	160/842 (19%)	**0.01**	**0.04-0.58**
TPO antibodies (n= 43)	25 (37%)	110/478 (23%)	**0.02**	**1.06-2.16**
Thyroglobulin antibodies (n= 42)	20 (30%)	107/465 (23%)	0.37	0.80-1.82
Vitamin D (median, IQR)	26.5 (15-34)	39 (32-47)	**<0.001**	**10.57-16.9**
Cytokine analysis (n= 50)	20 (40%)	3/24 (13%)	**0.02**	**1.23-17.74**
TNF-alpha	1 (5%)	0 (0%)		
IL-2	0 (0%)	0 (0%)		
sIL-2 receptor	13 (62%)	0 (0%)		
IL12	0 (0%)	0 (0%)		
Interferon gamma	1 (5%)	1 (4%)		
IL-4	0 (0%)	0 (0%)		
IL-5	0 (0%)	0 (0%)		
IL-10	5 (24%)	2 (8%)		
IL-13	0 (0%)	0 (0%)		
IL-17	0 (0%)	0 (0%)		
IL-1beta	0 (0%)	0 (0%)		
IL-6	1 (5%)	0 (0%)		
IL-8	0 (0%)	0 (0%)		

SERUM ANALYSIS



Electroencephalography

- Traditionally EEG has been used to evaluate for seizure activity in individuals with epilepsy, but it remains a useful biomarker of cortical function in individuals with conditions such as encephalopathy or autoimmune encephalitis.

- **EEGs are abnormal in 26% of cases** with the most frequent abnormalities being:
  - Epileptiform discharges in the frontal/temporal lobes (58%)
  - Diffuse slowing (38%)
  - Focal slowing (11%)

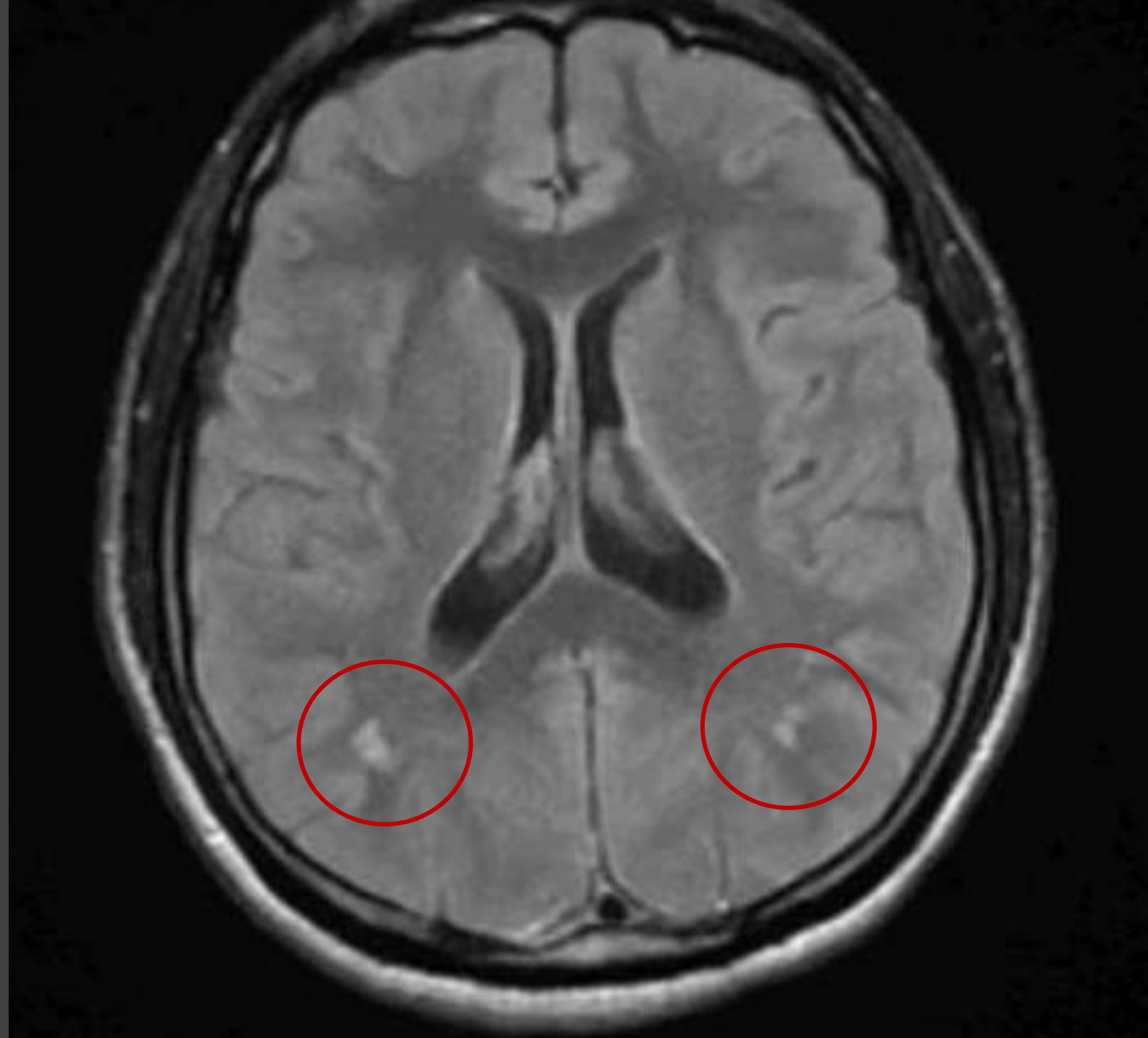
- Notably, these abnormalities can be quickly and non-invasively monitored in a low-cost manner
  - **Of patients with abnormalities, 78% have improved their EEG findings *after* the initiation of immunotherapy**

Neuroimaging

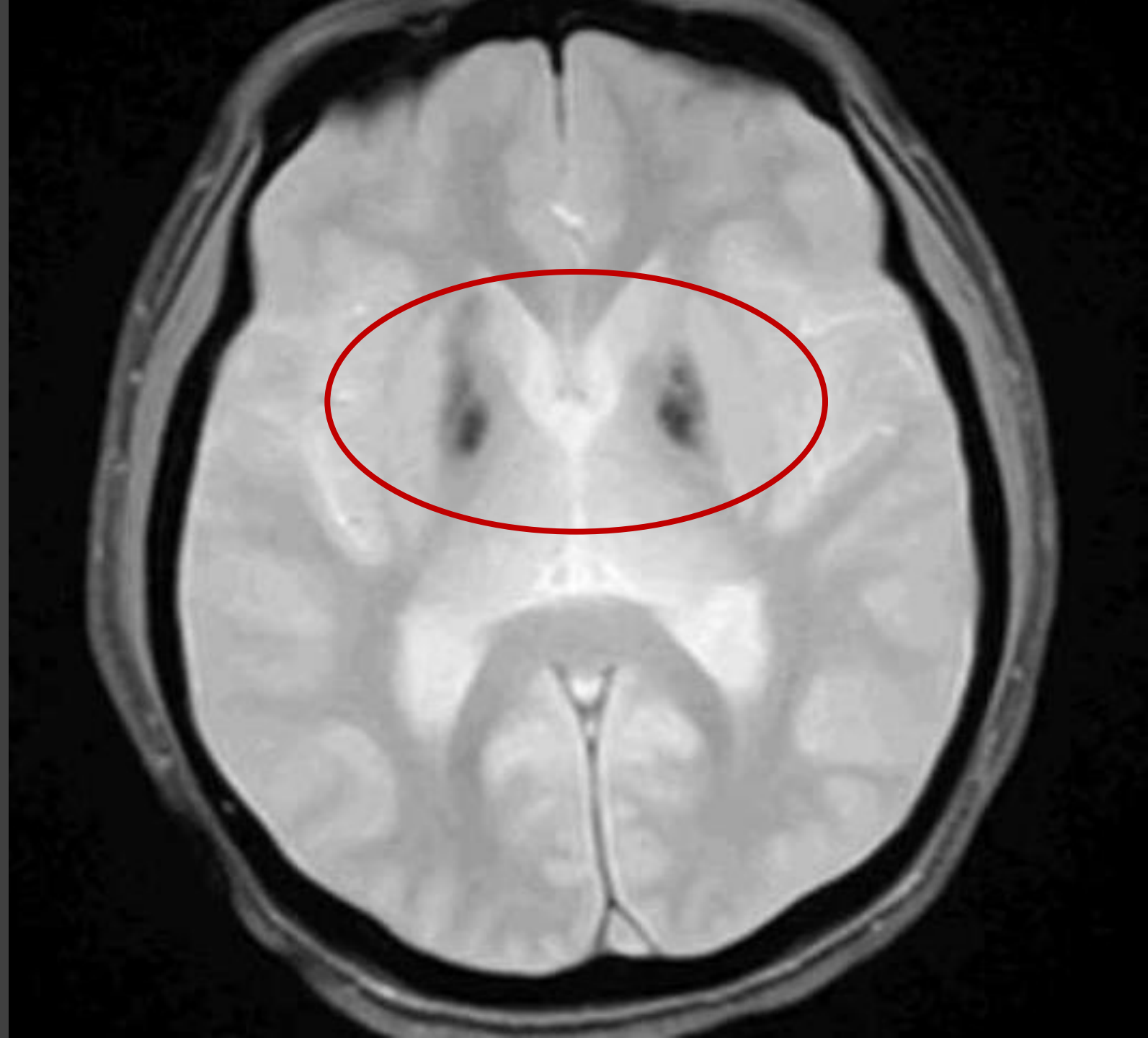
- **Neuroimaging was abnormal in 22%** (N= 16/72) of cases (next slides)
  - Punctate T2 signal abnormalities (81%, N= 13/16
  - Basal ganglia mineralization (18%, N= 2/16)

- Compared to a cohort of individuals with DS who had neuroimaging and met no DSRD exclusion criteria (n= 112), only 10 patients (8.9%) had abnormalities on neuroimaging that were not structural (e.g., arachnoid cyst, hypoplastic cerebellum) which was statistically significant compared to individuals with DSRD ($p<0.01$, 95% CI: 1.23-6.85).
  - In this comparator group, abnormalities were punctate T2 signal abnormalities (80%, N= 8/10) and calcifications in the basal ganglia (10%, N=1/10) and vermian/midline cerebellum (10%, N= 1/10).

T2 SIGNAL PROLONGATION

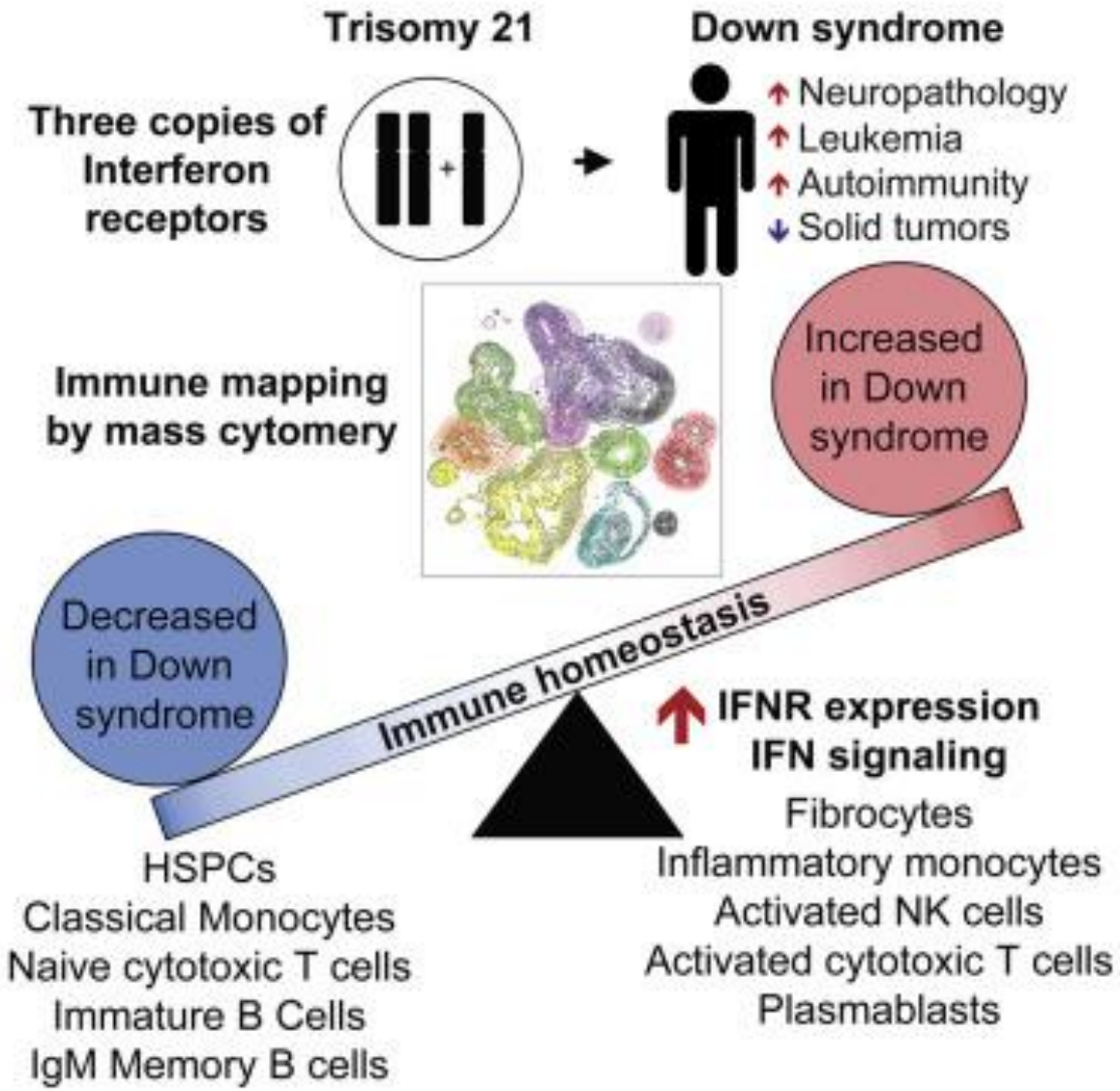


BASAL GANGLIA MINERALIZATION

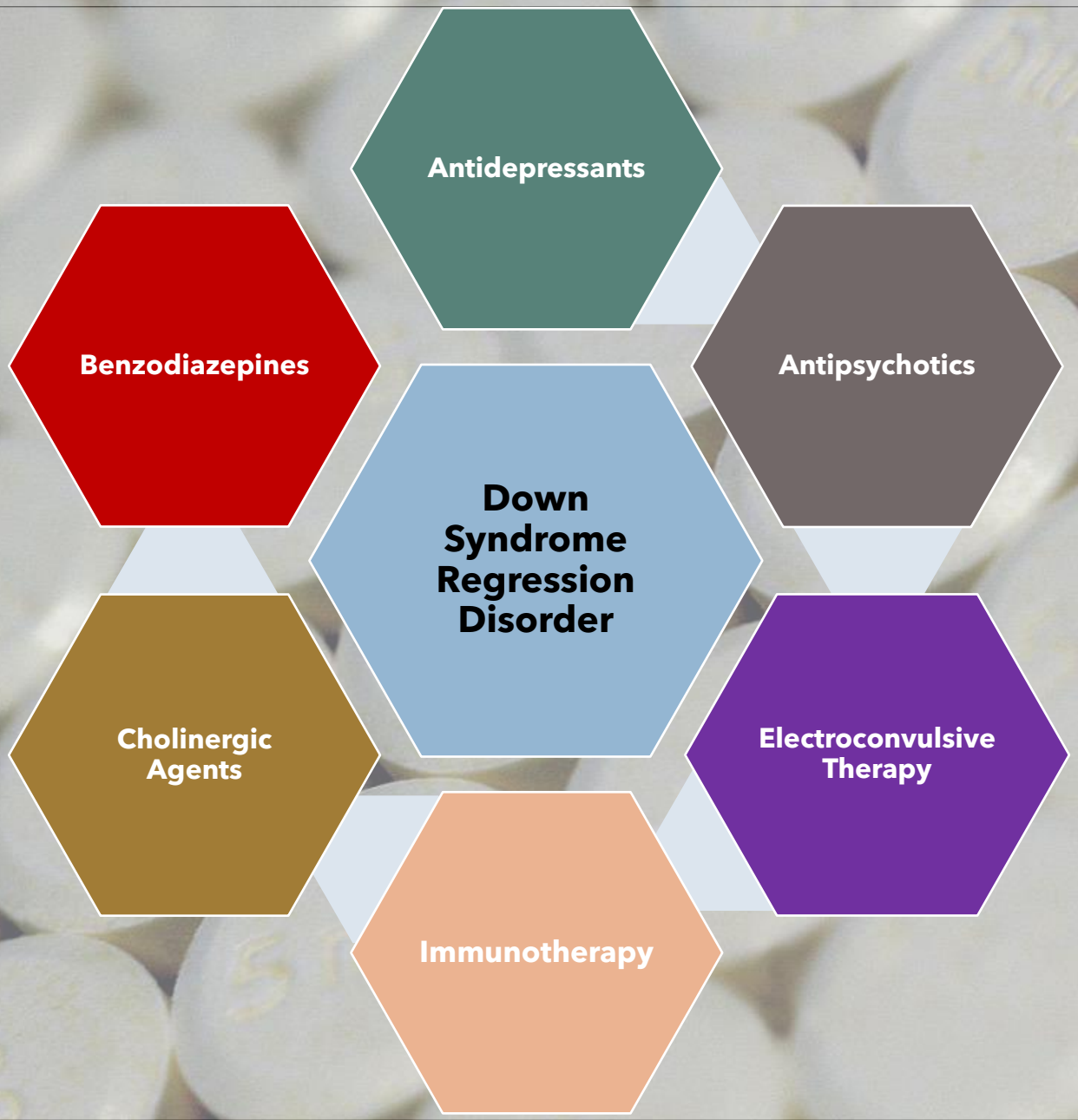


CSF Abnormalities	9 (17%) *(n, %, median if abnormal)*
WBC	5 (7%, 6)
RBC	0
Glucose	0
Protein	9 (13%, 68)
Oligoclonal bands (n= 60)	2 (3%, 2)
IgG index (n = 60)	7 (10%, 0.70)
Mayo autoimmune encephalitis panel (n= 59)	0
Neopterin (n= 43)	6 (8%, 45)

CEREBROSPINAL FLUID



IMMUNITY IN DOWN SYNDROME


Antidepressants
Benzodiazepines
Antipsychotics
Down Syndrome Regression Disorder
Cholinergic Agents
Electroconvulsive Therapy
Immunotherapy

Therapy Type[a]	Utilization (n, %)	Effectiveness (n, %)			Any Neurodiagnostic Abnormality v Normal Work up		
		All Patients (n= 72)	Any Neurodiagnostic Abnormality (n= 29)	EEG/MRI/CSF Normal (n= 43)	X^2 value	p Value	Odds Ratio (95% CI)
Antidepressant	45 (63%)	22 (49%)	4/16 (25%)	18/29 (62%)	5.67	0.02	0.20 (0.05-0.79)
Antipsychotic	52 (72%)	32 (61%)	9/19 (47%)	23/33 (70%)	2.54	0.12	0.39 (0.12-1.26)
Benzodiazepines	63 (87%)	49 (77%)	18/24 (75%)	31/39 (79%)	0.17	0.42	0.77 (0.23-2.59)
ECT	49 (68%)	36 (74%)	6/15 (40%)	30/34 (88%)	12.42	0.01	0.09 (0.02-0.39)
Nutritional Therapy	29 (40%)	0 (0%)	0/13 (0%)	0/10 (0%)	0	1.0	n/a
Immunotherapy	43 (59%)	74/120 (62%)	55/74 (74%)	19/46 (41%)	10.04	<0.001	4.11 (1.88-9.02)
Steroids	39 (54%)	14/39 (36%)	10/24 (42%)	4/15 (27%)	0.90	0.34	1.96 (0.48-7.99)
IVIg	43 (59%)	38/43 (88%)	24/26 (92%)	14/17 (82%)	0.05	0.33	2.57 (0.38-17.31)
Anti-CD20	19 (26%)	9/19 (47%)	9/11 (81%)	0/8 (0%)	9.89	0.01	49.5 (3.84-638.43)
MMF/AZ	19 (26%)	13/19 (68%)	12/13 (92%)	1/6 (17%)	12.17	0.01	60.0 (3.10-1159.84)

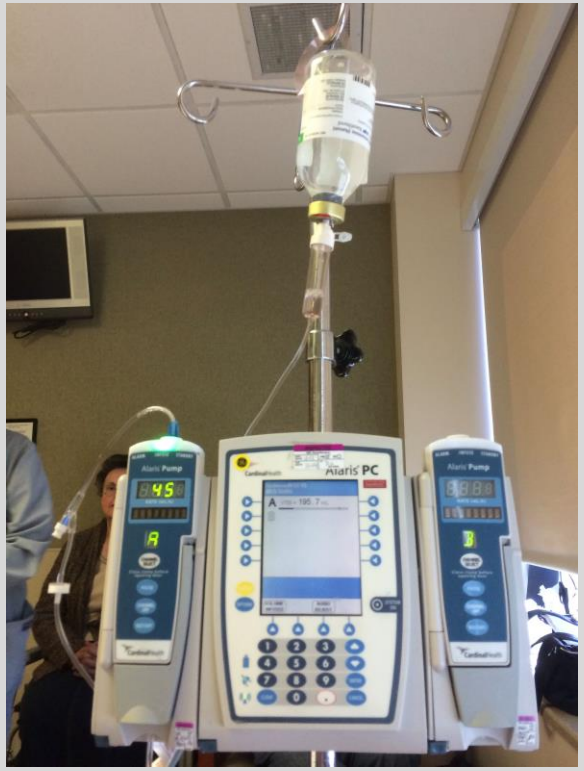
Immunotherapy:

- Santoro JD et al., *JNND*, 2022

Duration of Treatment?

- Unknown currently… but working on it…

- **In 82 patients treated with IVIg** for between 6-12 months
  - 38 (47%) were able to be weaned off of therapy without recurrence of symptoms
  - 44 (53%) were not able to be weaned off therapy
    - Recurrence of symptoms occurred at a median of five to six weeks between infusions (during taper)



Withdrawal Phenomenon

Interestingly, patients who did have recurrence of symptoms after they had discontinued IVIg clinically deteriorated in rapid succession with a **median time to symptom recurrence of just 5 weeks.**

Those with neurodiagnostic study abnormalities were **8 times more likely** to suffer a relapse when IVIg was discontinued on any protocol

In those patients who were restarted on therapy, all were able to achieve disease control but the **median time to symptom resolution was 6 weeks.**

Next Steps… the race is on!

- **Advancing Biomarkers in Regression**
  - *Advanced Neuroimaging Studies*
    - SPECT and CBF/ASL studies specifically interrogating the deep grey structures
  - *Neurogenetic Analysis*
    - Whole exome sequencing of individuals with DSRD to evaluate if there are associated variants that could be contributing or predisposing to the condition *beyond* trisomy of chromosome twenty-one
  - *CSF Biomarkers*
    - Proteomic analysis of the cerebrospinal fluid and the search for a targeted antigenic trigger and mast immune dysregulation sequence
- **Therapeutic Clinical Trial**
  - *First of its kind trial evaluating immunotherapy in DSRD… coming soon!*