NOTES FROM t21Research Society WEBINAR MARCH 20, 2023

Down Syndrome Regression Disorder :

Presentation by Jonathan Santoro MD

- Regression is defined as a loss of previously acquired developmental skills
- Commonly aged between 10-30 years (too late to be autism, too early for Alzheimer's)
- Rare : thought to be <5% of persons with DS
- Unknown cause but likely to be more than one, possibly combination of factors
- Difficult to diagnose- is a diagnosis of exclusion
- Timing is critical : acute onset(few days/ sudden) or sub acute (few weeks)- thought to be immune related. If changes occur slowly, more likely to be genetic in origin, possibly Alzheimer's if older or undiagnosed ASD
- It is well known that there is an increase in immune disorders in people with DS

- One theory is that there is a genetic predisposition to immune dysregulation, which if added to a stressor can lead to an increased inflammatory interferon mediated cascade, causing neuropsychiatric disease and multi-system dysregulation.

Symptoms:

Behaviour dysregulation - confusion, disorientation

-inappropriate laughter

- being "in their own world" for extended periods

- increased or decreased eating leading to weight loss/ gain

Cognitive decline -apathy or lack of interest in things going on around them

-avolition or lack of interest in initiating activity

- memory impairment

Insomnia or Circadian Rhythm Dysregulation – inability to sleep or sleeping > 16 hrs/day

-reversal of sleep patterns

Developmental Regression - social withdrawal

-inability to perform ADL (eg toileting, brushing teeth, dressing)

-decreased eye contact

- extreme inflexibility with change to routine

- OCD/ repetitive motor behaviours

New Focal Neurological Deficits - weakness

-numbness

Skin Changes -development of dark patches

Movement Disorders - catatonia/ muscle stiffness

- bradykinesia (slow movement) or freezing behaviour
- gait disturbance

Language Deficits -expressive and/or receptive aphasia

- whispered speech

-neologisms (using new or garbled words)

-mutism

Psychological Symptoms -anxiety

-delusions or hallucinations

-new OCD

-aggression/ agitation

-derealisation (living in a fantasy or dream world)

Diagnosis:

Blood work to rule out metabolic, infectious or inflammatory disorders

MRI -? Is there a structural cause that may explain the symptoms

EEG- ? Is there seizure activity

Lumbar puncture – Is there inflammation present in the CSF

Treatment:

There is no singular treatment, there is an overlap between psychiatric and neurological disease. Need to use elimination to determine the source of the regression and start with that form of treatment.

Most common first line therapy are Benzodiazepines (lorazepam) and immunotherapy (IVIg).

IVIg therapy is monthly infusions for 12 months. 50% maintain improvement when weaned off. Those with neurodiagnostic abnormalities are 8 times more likely to regress.

Stress can be a causative factor (possibly due to increased levels of interferon, which regulates the immune system) and those with a cluster of stressors in the 3 months prior to regression seem to respond less well to IVIg.

One study showed that IVIg was effective in 88% of cases (n=72). It was most effective in those who showed changes on MRI and/or lumbar puncture. A second study showed that those with MRI/ LP changes did not maintain improvement when therapy ceased.

Median time to deteriorate was 5 weeks, median time to regain improvement was 6 weeks after restarting therapy (IVIg).

The first clinical trial will be starting in the later part of 2023, in the US (2 sites), of 12 weeks' duration.

It is an open label, three arm study of

- Lorazepam
- IVIg (once/ month infusion)
- Tofacitinib (unknown use in DSRD but effective in other autoimmune diseases in persons with DS)

More information:

dsresearch@chla.usc.edu