Down Syndrome

UPDATES AND HOT TOPICS FOR THE PCP

Ochsner Children's Hospital

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Disclosures

I HAVE NO RELEVANT FINANCIAL DISCLOSURES OR CONFLICTS OF INTEREST.

Overview

- AAP Guidelines and 2022 updates
- Hot topics in Down Syndrome
- Resources for families and their care teams

American Academy of Pediatrics
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Down Syndrome guidelines

Health Supervision for Children and Adolescents With Down Syndrome

Marilyn J. Bull, MD, FAAP,[a] Tracy Trotter, MD, FAAP,[b] Stephanie L. Santoro, MD, FAAP,[c] Celanie Christensen, MD, MS, FAAP,[a] Randall W. Grout, MD, MS, FAAP,[d] THE COUNCIL ON GENETICS

- New in 2022
  - More associated conditions added, more info on known associations
    - Feeding difficulty
    - Respiratory infection
    - Autoimmune
    - Dermatologic problems
    - Moya Moya
    - Increased prevalence of autism (7-19%) and vision disorders (60-80%)
  - Increased guidance on counseling families
    - cfDNA testing and newborn testing guidance
    - Tips for unbiased counseling
  - Health supervision
    - Updated growth charts (2015)
    - Testicular exam due to increased risk of cancer
    - Photoscreening for vision yearly if available
    - Iron studies

Pearls from guidelines

- Prenatal/Neonatal
  - cfDNA testing
    - Not considered diagnostic but very high sensitivity and specificity
    - Prenatal diagnostic testing is CVS or amniocentesis
  - Additional counseling guidelines and resources
    - Offer genetic counseling prenatally and postnatally
  - Health supervision
    - If no prenatal diagnostic testing was performed, postnatal karyotype should be done to rule out translocation
    - If only FISH or microarray is performed, karyotype is needed to rule out translocation
    - Echocardiogram with referral if abnormal
    - CBC with diff by 3 days of life
    - Referral to early intervention services

Percentage	Chromosomal Basis
96	Meiotic nondisjunction (95% occur in egg, with recurrence risk of 1% until mother's age risk exceeds 1% at age 40, and it then increases according to maternal age)
3–4	Translocation (usually occurs with 1 chromosome 21 attached to chromosome 14, 21, or 22)
	14/21 translocation (1/3 of patients have a parent carrier with balanced karyotype)
	90% have mother as the carrier parent, with a recurrence chance of 10%–15%
	10% have father as the carrier, with a recurrence chance of 2%–5%
	21/21 translocation (1/14 of patients have parent carrier with a balanced karyotype); carrier parent equally likely mother or father, with recurrence chance of 100%[13]
1–2	Mosaicism: number of affected cells vary between individuals; clinical findings vary widely
	Medical complications fewer and intellectual disability often less severe
Partial trisomy: duplication of delimited segment of chromosome 21 present; extremely rare	

Adapted from Bull MJ. Down syndrome.[14]
Information regarding meiotic nondisjunction and translocation is from Hook,[15] information regarding mosaicism is from Papavassiliou et al,[15] and information regarding partial trisomy is from Pelleri et al.[16]

Pearls from guidelines

- Infants
  - Frequent feeding difficulties
  - Plot on Down Syndrome growth chart (available in Epic)
  - At 6 months: audiology for repeat hearing screen, establish with ENT, ophthalmology referral, repeat thyroid studies
  - At 1 year: CBC with diff, iron studies
- Early Childhood (Age 1-5 years)
  - Annually: CBC with diff, iron studies, thyroid studies
  - Hearing testing every 6 months until about age 4 then yearly
  - Yearly vision testing
  - Sleep study by age 4
  - No routine imaging for atlanto-axial instability- screen for symptoms
  - Celiac testing for GI and growth concerns

Pearls from guidelines

- Late Childhood (5-12 years) – very similar to early childhood
  - Annual CBC with diff, iron studies, thyroid studies, hearing and vision screening
  - BMI chart- use CDC chart (better predictor of increased adiposity)
    - Obesity prevention
  - Screen for sleep disorders, sleep study as needed after baseline study by age 4
- Adolescence to Early Adulthood (12-21 years)
  - Annual CBC with diff, iron studies, thyroid studies
  - Monitor for acquired mitral and aortic valvular disease
  - Transition to adulthood – considering options for decision-making at age of majority

Heme/Onc screenings

- CBC
  - Screening for TAM, polycythemia in neonates
  - Screening for Leukemia, anemia in children
    - Leukemia risk around 1%
  - Common normals in DS: mild leucopenia, elevated MCV
- Iron studies
  - *New recommendation for annual testing
  - either iron level+TIBC or CRP+ferritin
  - Baseline MCV elevations make iron deficiency anemia difficult to diagnose without iron levels
  - More common due to feeding issues/restrictions
  - Ask about restless sleep
    - Treat with iron if ferritin <50
- Solid tumor risk decreased
  - EXCEPT testicular cancer- recommend regular exams

Thyroid

- Risks of up to 50% by adulthood, congenital risk is 2-7%
  - Mostly hypothyroidism
    - Slightly increased risk of hyperthyroidism (Graves')
  - Newborn screening- ensure testing both TSH and free T4 (LA NBS does)
  - TSH and free T4 at 6 months and then 12 months and annually
    - If infant or toddler with elevated TSH with normal free T4, repeat in 1 month and consider anti-TPO Ab; watch growth closely if continues to have elevated TSH; refer to endo if persistent elevation in child <3 years
    - If antibodies+, check every 6 months

Hearing and Vision

- Hearing
  - much higher risk of hearing loss 75% (usually conductive- stenotic canals and increased risk of otitis/effusions)
  - Referral for repeat hearing screen at 6 months
  - Testing every 6 months until age 4 then yearly

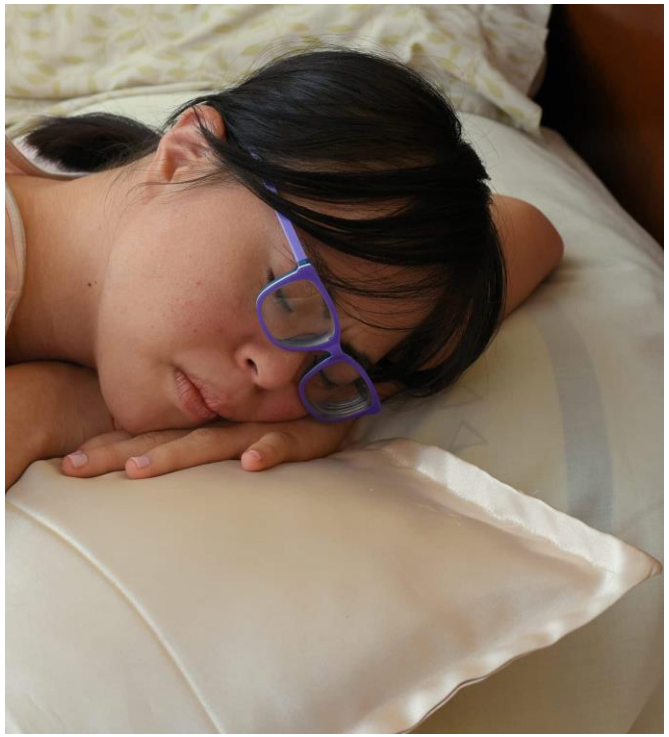
- Vision
  - Vision abnormalities in 60-80%
  - many different types- strabismus, cataracts, NLDO, nystagmus, refractive errors, glaucoma
  - Referral by 6 months is recommended

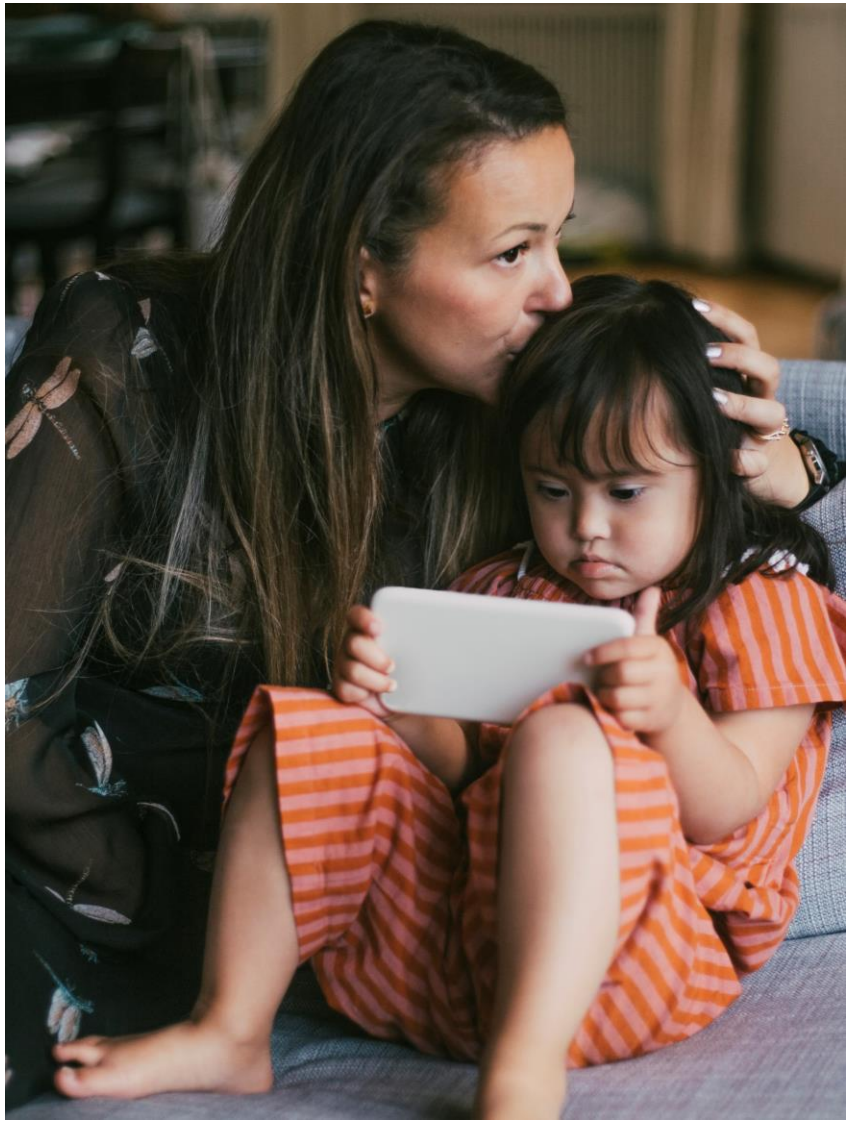
Feeding

- Reflux and dysphagia in 30-80%
- Etiology
  - Anatomy
    - smaller and narrower upper jaw, high palatal arch, relative macroglossia
  - Physiologic differences- hypotonia, weak orofacial muscles
  - Sensory difficulties
- Recurrent lower respiratory infections- consider aspiration
- Low threshold for evaluation by SLP evaluation and MBSS

Sleep Apnea

- Risk of 50-79% by adulthood
- Recommendation: polysomnogram between age 3-4
- Frequently asymptomatic
- Obesity increases risks later
- Treatment usually starts with ENT procedures
  - Remember post-procedure follow up sleep study
- CPAP is commonly poorly tolerated
- Hypoglossal nerve stimulator



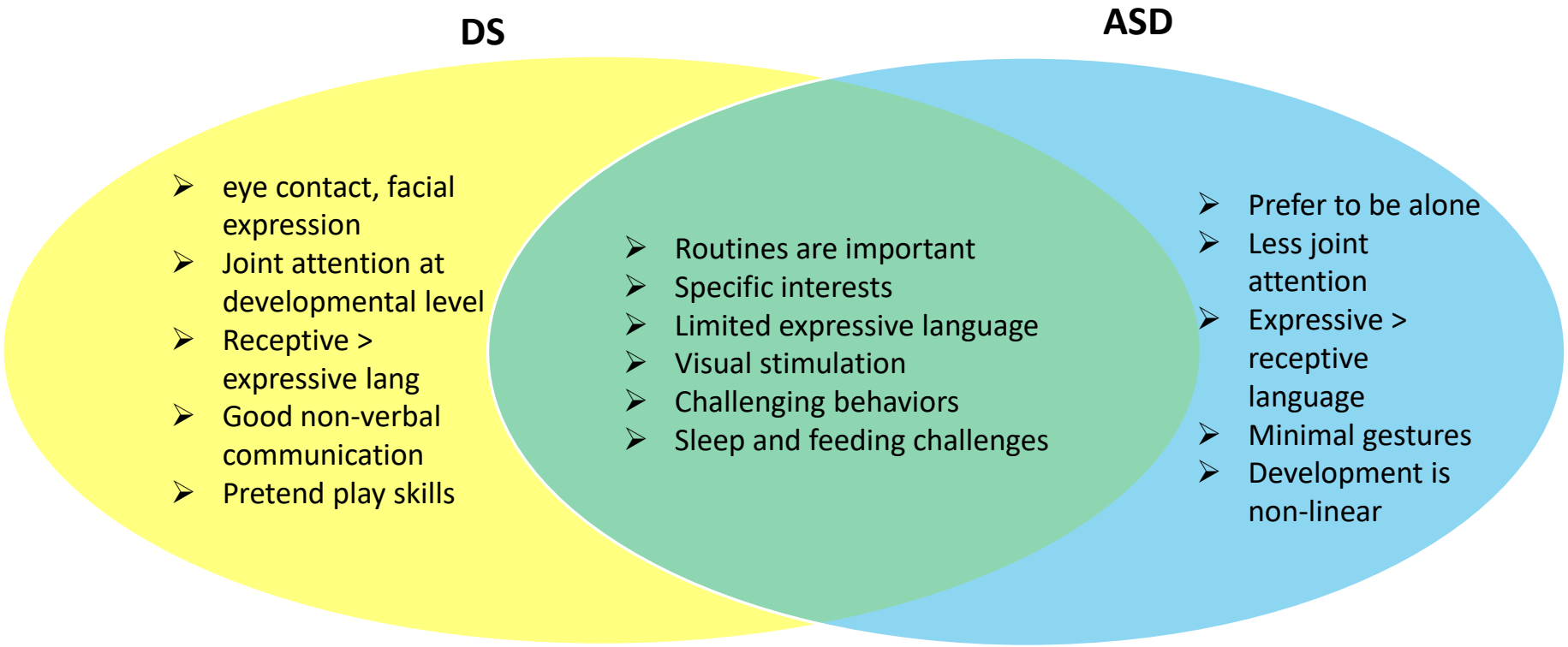


Case 1

- 5 yo F with Down Syndrome
  - “Different than other kids with DS”
  - Prefers to play alone
  - Watches the same 10 minutes of Monsters, Inc. over and over
  - Carries around a pom pom at all times
  - Says 3 words, no mama/dada
  - Only eats a handful of different foods
  - Not potty trained

Autism and Down Syndrome

- Incidence of up to 19%
- More challenging to diagnose, lots of overlap of symptoms

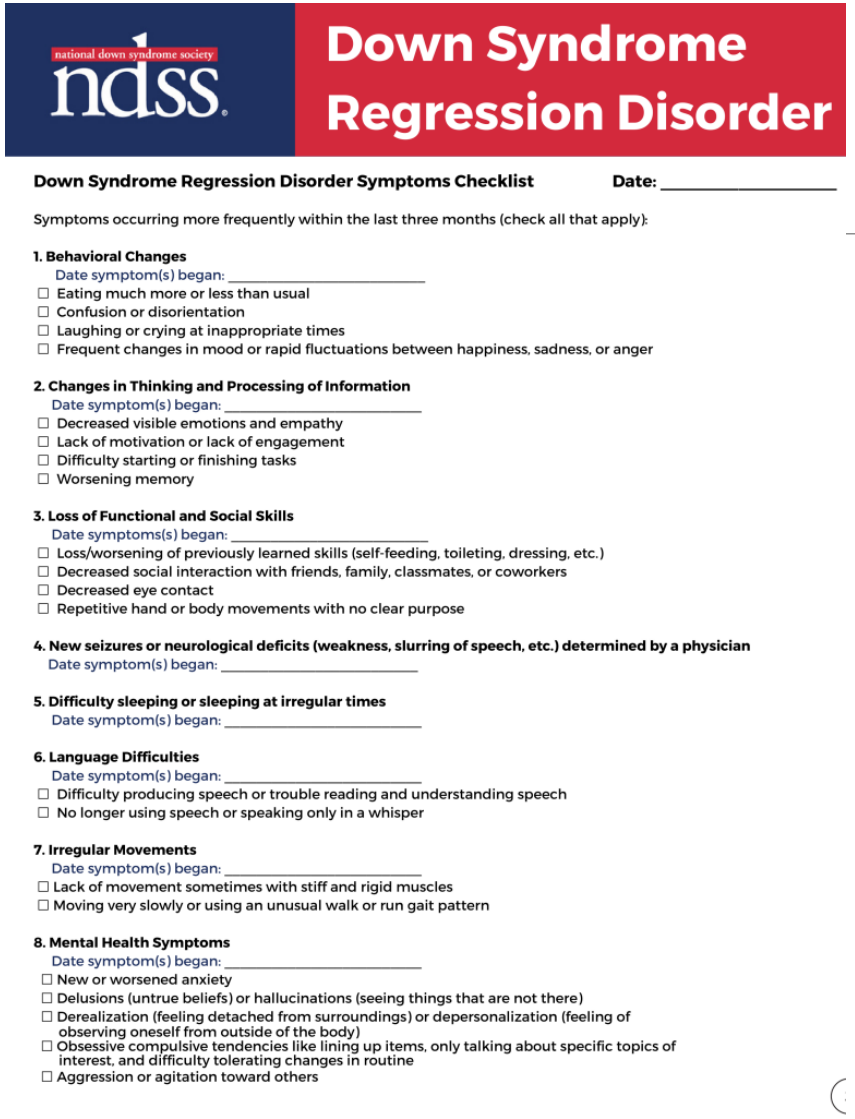


Autism and Down Syndrome

- When to consider
  - Repetitive and perseverative behaviors
    - 60% of children with DS alone have repetitive behaviors
    - Children with DS-ASD have more and harder to redirect
  - Abnormal play skills
    - Lining up toys
    - Only playing with parts of a toy
    - Mouthing at older age
  - Impaired social and language skills
    - Expressive and receptive language delays
    - Acquire language in a different order
  - Sensory challenges
    - Significant feeding issues
    - Difficulty with loud noises, laughing
  - Mood and behavior issues
    - Increased tantrums
    - Self-injury
    - anxiety

Case 2

- 17 yo F with Down Syndrome, VSD s/p repair, hidradenitis suppurativa, seizure disorder, ?autism, depression
  - Establishing care
  - Mom mentions a regression that occurred in behaviors about 3 years ago
    - Previously a cheerleader at school, loved to dance, talkative and engaged well with others
    - **Moving slower**, talking much more quietly, very hard to motivate, decreased interest in activities
    - PCP at time started SSRI- helped a little?



national down syndrome society ndss

Down Syndrome Regression Disorder

Down Syndrome Regression Disorder Symptoms Checklist **Date:** _____

Symptoms occurring more frequently within the last three months (check all that apply):

1. Behavioral Changes
Date symptom(s) began: _____
☐ Eating much more or less than usual
☐ Confusion or disorientation
☐ Laughing or crying at inappropriate times
☐ Frequent changes in mood or rapid fluctuations between happiness, sadness, or anger

2. Changes in Thinking and Processing of Information
Date symptom(s) began: _____
☐ Decreased visible emotions and empathy
☐ Lack of motivation or lack of engagement
☐ Difficulty starting or finishing tasks
☐ Worsening memory

3. Loss of Functional and Social Skills
Date symptoms(s) began: _____
☐ Loss/worsening of previously learned skills (self-feeding, toileting, dressing, etc.)
☐ Decreased social interaction with friends, family, classmates, or coworkers
☐ Decreased eye contact
☐ Repetitive hand or body movements with no clear purpose

4. New seizures or neurological deficits (weakness, slurring of speech, etc.) determined by a physician
Date symptom(s) began: _____

5. Difficulty sleeping or sleeping at irregular times
Date symptom(s) began: _____

6. Language Difficulties
Date symptom(s) began: _____
☐ Difficulty producing speech or trouble reading and understanding speech
☐ No longer using speech or speaking only in a whisper

7. Irregular Movements
Date symptom(s) began: _____
☐ Lack of movement sometimes with stiff and rigid muscles
☐ Moving very slowly or using an unusual walk or run gait pattern

8. Mental Health Symptoms
Date symptom(s) began: _____
☐ New or worsened anxiety
☐ Delusions (untrue beliefs) or hallucinations (seeing things that are not there)
☐ Derealization (feeling detached from surroundings) or depersonalization (feeling of observing oneself from outside of the body)
☐ Obsessive compulsive tendencies like lining up items, only talking about specific topics of interest, and difficulty tolerating changes in routine
☐ Aggression or agitation toward others

Down Syndrome Regression Disorder

- In the past AKA catatonia and psychosis, Down Syndrome Disintegrative Disorder
- Affects adolescents to young adults
- Symptoms
  - Catatonia
  - Social withdrawal
  - Mutism
  - Decreased ADL's
  - Mood lability
  - Sleep changes

Down Syndrome Regression Disorder (ndss.org)

Down Syndrome Regression Disorder

	All patients	As clinically indicated
Diagnostic imaging	Brain MRI with and without gadolinium contrast on a 3T scanner	MRI spine with and without contrast PET/SPECT imaging MR angiography of the head and neck MR spectroscopy
Blood tests	Ammonia CBC w/differential CMP ESR CRP Lipid panel HbA1c B12 level Vitamin D 25-OH level TSH w/reflex T4 TPO antibodies Anti-thyroglobulin antibodies Anti-thyroid stimulating hormone receptor ANA Celiac serology or panel Cell-based autoimmune encephalitis panel	Infectious testing[a,b] dsDNA Complement 3 and 4 Immunoglobulin levels Cytokine panel Celiac panel ASO Anti-DNAse B Vitamin B1 level Methylmalonic acid Vitamin B6 level Homocysteine level Iron level, TIBC, and Iron Saturation Selenium level Heavy metal screen (lead, manganese, mercury, zinc, nickel, thallium) Myelin oligodendrocyte glycoprotein (MOG) antibodies (if not covered in cell-based panel) Lactate Pyruvate Advanced biochemical profiling (neurometabolic disorder evaluation) Fragile X testing Chromosomal Microarray Whole exome sequencing
Urine tests	n/a	Urinalysis with reflex culture Urine toxicology Total porphyrin and porphobilinogen Organic acids Acylglycines Glycosaminoglycans Oligosaccharides Sialic acid
Lumbar puncture	Cell count with differential Total protein Glucose Gram stain and culture IgG index Oligoclonal bands Cell-based autoimmune encephalitis panel	Infectious testing[a,b] Opening Pressure Neopterin Angiotensin converting enzyme (ACE) Lactate Pyruvate CSF amino acids Alpha aminoadipic semialdehyde Folate receptor antibody assay 5-Methyltetrahydrofolate Tetrahydrobiopterin Neurotransmitter metabolites (homovanillic acid, 3-O-methyl-dopa, and 5-hydroxyindole acetic acid) Pyridoxal 5′-phosphate Sialic acid Succinyladenosine Sepiapterin and dihydrobiopterin Amyloid-beta 42/40 Phosphorylated tau
Electroencephalogram	Routine (60 min) EEG	Prolonged EEG (4–6 h) Overnight EEG (24+ h)
Other testing	n/a	Polysomnogram (OSA evaluation) Audiogram (hearing evaluation) Neurocognitive assessment

[a]*Potential bacterial/protozoal infectious testing: Borrelia burgdorferi, HIV, Listeria monocytogenes, Mycoplasma pneumoniae, Mycobacterium tuberculosis, Treponema pallidum.*
[b]*Potential viral infectious testing: adenovirus, enterovirus, Epstein-Barr virus, herpes simplex virus 1 and 2, human herpes virus 6 and 7, influenza virus A and B, John Cunningham virus, measles, rabies, varicella zoster, west Nile virus and other region-dependent viral testing.*

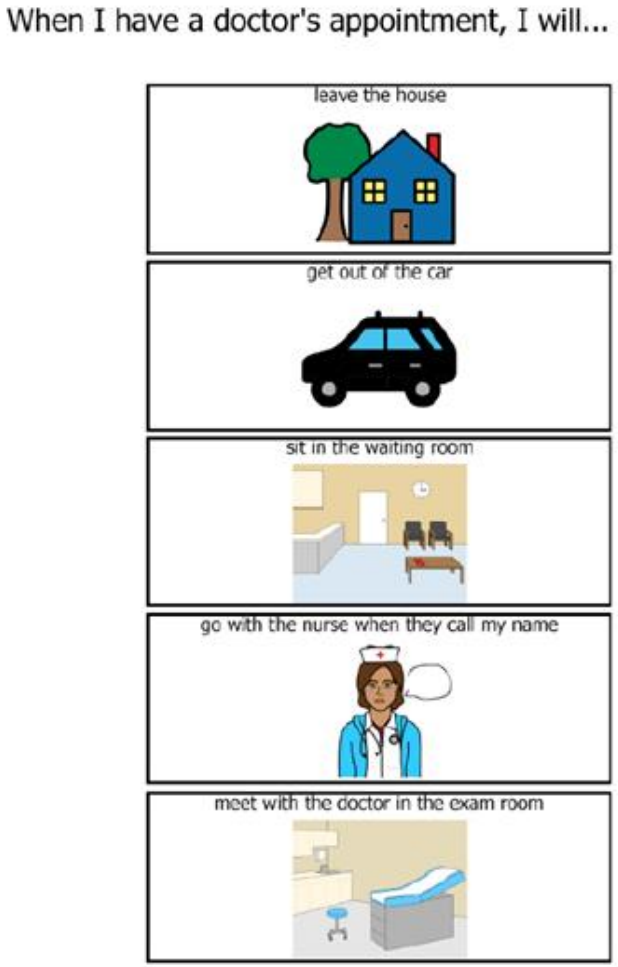
- Etiology largely unknown
  - Hypotheses: autoimmune, psychologic
- Labs/imaging needed to rule out other etiologies
- Treatments
  - high dose benzodiazepines
  - IVIG
  - ECT

Frontiers | Assessment and Diagnosis of Down Syndrome Regression Disorder: International Expert Consensus (frontiersin.org)

Down Syndrome Regression Disorder

Other Behavior Considerations

- ADHD
  - Stimulants- start low and go SLOW
  - Methylphenidates are most studied in autism
  - More susceptible to side effects
- Anxiety/depression
  - Consider medical causes for symptoms first- thyroid, sleep apnea, celiac, constipation



Behavior Intervention Resources

- ABA therapy
- Parent training with psychology
- Social stories
- Visual supports for difficulties with transitions

Case 3

- 2 yo F with Down Syndrome, congenital heart disease s/p repair
  - Recurrent respiratory hospitalizations (4 in past 4 months)
  - Recurrent pneumonia, needs long courses of antibiotics nearly every month, recurrent cough and purulent rhinitis within a week of antibiotic completion
  - PE tubes placed at age 9 months for recurrent otitis media
  - Has seen pulmonary- uses respiratory vest and nebulizers regularly
  - Labs- S.pneumo titers very low, normal lymphocyte subpopulations, normal Ig levels, normal CBC
  - Pneumovax given and S.pneumo titers remain low 6 weeks after vaccine

Immune Dysregulation

- Spans all areas of both innate and adaptive immune system placing them at risk for poor vaccine response, more severe infections and auto-immunity
- Severe respiratory infections are especially common
- Low threshold to do immunologic workup/referral

- Our patient was started on monthly IVIG and has had no hospitalizations since starting treatment 1 year ago

Immune Dysregulation

- Other autoimmune conditions associated (4-6x increased risk in Down Syndrome)
  - Thyroid- Graves', Hashimoto thyroiditis
  - Celiac
  - Autoimmune skin conditions (vitiligo, alopecia)
  - Type 1 DM
- Research ongoing into implications of immune dysregulation and different treatments for autoimmune conditions in DS
  - Human Trisome Project
  - Thought to be related to hyperactive interferon response
  - Trialing different meds that downregulate interferon

Adult Transition Considerations

- Supported Decision Making
  - Newer option
  - Adult with disabilities is considered decision maker and has supporters in place to assist
  - Sign supported decision making agreement with notary
- Continuing Tutorship/Interdiction
  - “Civil death”
  - Lose all rights, assigned guardian
  - Patients with severe limitations
  - Start process early- neuropsychologic testing at age 15-16 then legal process completed by age 18

Resources for families

- National resources
  - NDSC (advocacy, annual family conference)
  - Jack's Basket
  - DS-Connect (research), NDSS (advocacy)
  - Many listed in guidelines
- Local resources
  - DSAGNO, Gigi's Playhouse, Up21 (Northshore), Upside Downs (Bayou)
- Things to consider for families
  - Medicaid Act 421
  - Diaper prescription at age 4+
  - Medical daycares for technology dependent
  - Handicap tag
  - Medical stroller
  - ABA therapy
  - OCDD (waiver)

Resources for care team

- DS-MIG
- Jack’s basket- giving unexpected news training
- Down Syndrome podcast
- ARC of LA for transition information

Down Syndrome Resources at Ochsner

High Risk Newborn Clinic

Multi-disciplinary clinic (pediatrician MD/developmental peds NP, PT, OT, ST, SW)

- Birth-2 years

Down Syndrome Clinic

Multi-disciplinary clinic (pediatrician, psychologist, dietician, genetics counselor, PT, OT, ST, SW)

- 2-18 years

Place referrals through Boh center referral Ref 137 and message nurse coordinator Erica Caldera

Questions?

Sources

Health Supervision for Children and Adolescents With Down Syndrome | Pediatrics | American Academy of Pediatrics (aap.org)

Nicole Baumer Down Syndrome: Clinical Presentation (globaldownsyndrome.org)

THE DUAL DIAGNOSIS OF DOWN SYNDROME AND AUTISM (thematthewfoundation.org)

Immune Dysregulation in Children With Down Syndrome - PMC (nih.gov)

Supported Decision Making - The Arc of Louisiana (thearcla.org)

Down syndrome: Management - UpToDate