A CLINICAL APPROACH TO THE NEURODIVERSE PATIENT

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OBJECTIVES

- By the end of the presentation the participant will be able to :
  - describe the boundaries of the description for neurodiversity in a clinical context
  - describe the two major groups of neurodiverse patients (Neurodevelopmental disorders and inflammatory related conditions)
  - describe the overlap in these two groups and an approach to optimize functioning

WHAT IS MEANT BY NEURODIVERSITY?

- Neurodiversity is a term that describes patients with atypical nervous system development
- It includes those conditions described as neurodevelopmental disorders
- This includes patients described as ‘autism’ and autism spectrum disorders

CONSIDER THE COMMON CLINICAL SITUATION

- Patient with history of below average performance in school or delayed developmental milestones such as language
  - Family is told ‘he is on the spectrum’.
- No major behavioral problems until adolescence when social demands are greater
  - Subtle impairment in prosodic function impedes social communication
  - Aggressive behavior is identified and is the cause for the referral

MENTAL STATUS EXAM

- Concrete process
- Stilted language
- Mild tic like behaviors, subtle poor coordination
- Poor eye contact. Tends to look past you or look at your mouth.
- Affect is somewhat flat

SUSPECT A NEURODEVELOPMENT CONDITION

- Is it important to identify a molecular diagnosis? Why or why not?
- Are there behavioral approaches that help?
- How do you proceed?

DSM 5 DIAGNOSIS OF AUTISM IS A BEHAVIORAL DX

- A. Impairment in social interaction and communication and restricted repetitive behaviors
  - (1) Qualitative impairment in social interaction
  - (2) Qualitative impairments in communication
  - (3) Restricted repetitive and stereotyped patterns of behavior, interests and activities,
- B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years:
  - (1) social interaction,
  - (2) language as used in social communication,
  - (3) symbolic or imaginative play.
- C. The disturbance is not better accounted for by Rett's disorder or childhood disintegrative disorder.

TYPICAL PSYCHIATRIC CONCERNS IN NEURODIVERSE POPULATIONS

- Aggression
- Loss of skills and regression
- Sleep disturbance
- ‘psychosis’

AGGRESSION

- Target of aggression
  - Self injurious behavior
  - Others
- Prodrome
  - Motor activity
  - Verbal warnings
  - Impulsive response to frustration
- Post episode behaviors
  - Remorse
  - Confusion

SELF INJURIOUS BEHAVIOR

- Evaluate for pain, Many patients do not verbalize pain and many poorly localize or describe pain
  - Dental
  - Abdominal (constipation)
  - UTI
- May be a depression equivalent
  - Inquire about other neurovegative symptoms including sleep, appetite/eating, sensitivity to others
- May be OCD equivalent as well
  - Is it ritualistic

EXTERNALIZED AGGRESSION

- Inanimate vs animate objects
- History of outburst in the past
- Premeditated (targeted) vs territorial or impulsive
- Role of reinforcements

PRODROME

- Can you tell it's about to happen? How?
  - Psychomotor agitation, with or without sterotypies
  - Increased volume and rate of speech
  - Face and eyes
- Role of sympathetic nervous system- feed forward response

POST EPISODE BEHAVIOR

- Remorse- good sign for behavioral management
- Some indications for a paroxysmal cause
  - Confusion and decreased verbal output or quality of speech
  - Increased clumsiness
- If possible a good neuro exam during the immediate post episode period may point to possible localizing signs.

LOSS OF SKILLS AND REGRESSION

- Classic is Rett's syndrome in girls
  - Development in toddlerhood is normal and then skills begin to be lost
- This also happens in other neurodevelopmental disorders
  - May be an indication of an inflammatory state
  - May also be a sign of severe depression, even catatonia
- The loss of skills is accompanied by a regression in behavior which may be the primary reason they come to clinic.
- May present as reduced self care and difficulty doing things around the house like chores and even operating electronics like TVs

LOSS OF SKILLS AS SIGN OF INFLAMMATION

- May be initial indicator of an infection
- May also be a sign of an autoimmune disorder such as Hashimoto's encephalopathy
  - W/U typically includes usual inflammatory markers as well as TPO, Celiac w/u, immunoglobins, hCRP, ESR, CBC with diff, CMP, B-12

SLEEP DISTURBANCE

- May be sign of pain, constipation etc
  - Dental pain is common
- May also be sign of a cyclic mood disorder
- Changes in home environment are also important to consider

‘PSYCHOSIS’- FAMILIES USUALLY COMPLAIN OF THIS

- The presence or absence of reported ‘hearing voices’ or talking to unseen others is less important than change in overall demeanor and behavior
- Patients with neurodevelopmental disorders often answer yes if you ask whether they hear voices when no one is around
  - Failure to recognize their internal dialog
- Important to determine if it is mood congruent or incongruent
- May be a sign of severe depression (inquire about the content of these experiences)

PSYCHOTROPIC USE

- The algorhithm
  - Is it new?→look for new inflammatory conditions
  - No sign of inflammation→Evaluate neurovegative signs for depression
  - If depression equivalents are present → treat for MDD
  - If sleep is a problem→Trazodone to start.
  - If aggressive and not depressed and no signs of inflammation or pain→neuroleptics can be considered in a short term targeted manner, Risperidone and aripiprazole are both FDA approved for 'autism related irritability'
  - If catatonia is present-→Ativan and ECT can be considered but scan the head.

COMPARATIVE GENOMICS OF AUTISM AND SEVERE PSYCHIATRIC DISORDERS

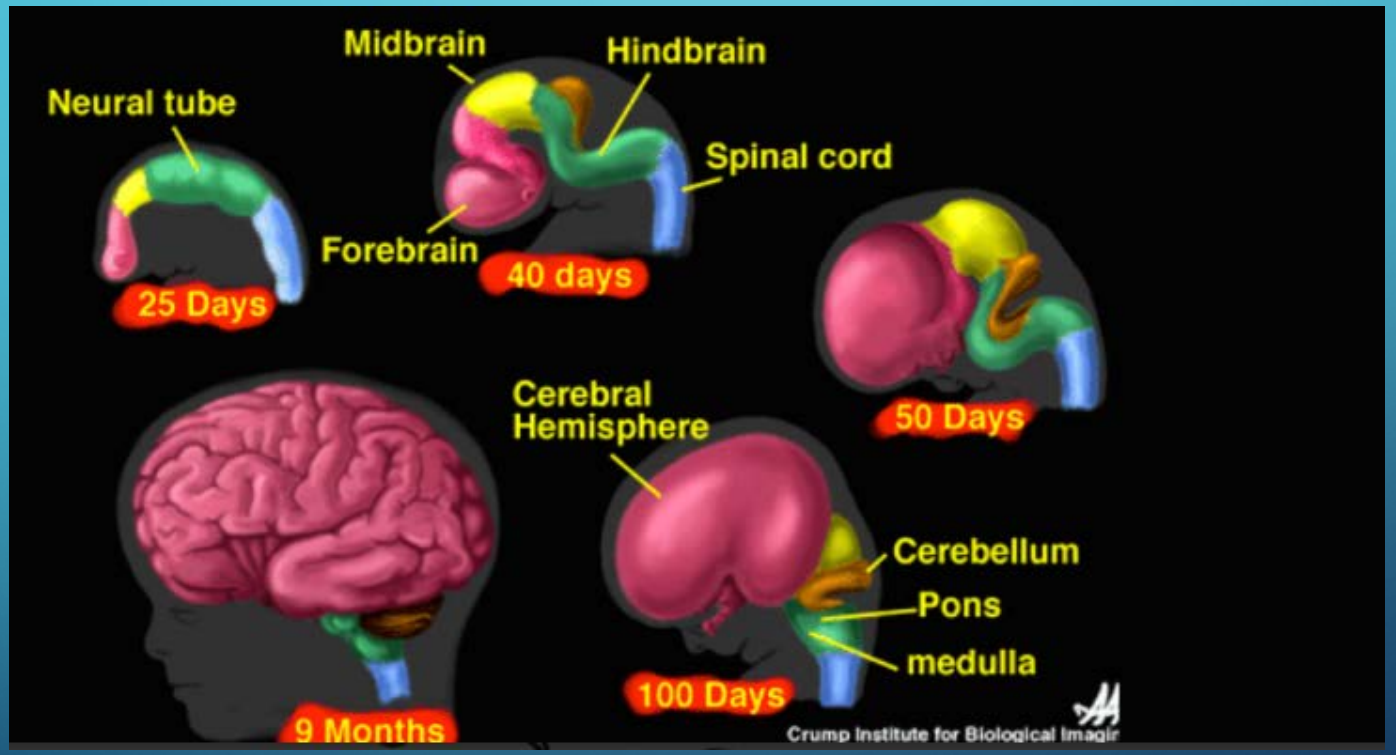
- There are four models relating schizophrenia to autism
  - First model assumes that autism is a specific subtype of schizophrenia
    - Early model of Kanner
  - Second model was that they are distinct conditions and did not share biology
    - Rutter proposed this one
  - Third is that Autism and schizophrenia are at polar ends of a spectrum with a zone of 'normality' between them
  - Fourth model is that autism has overlapping biology with both schizophrenia and mood disorders

CONSIDER A MODEL TO THINK ABOUT MAJOR PSYCHIATRIC ILLNESS AS A NEURODEVELOPMENT DISORDER

NEUROEMBRYOLOGY- OVERVIEW

- Major stages of brain development
  - Embryonic- first 8 weeks
    - Neural folds are recognizable as early as 28 days after conception
    - The 5th thru the 8 th week post conception represent the major period of organogenesis
  - Fetal stage of development begins in week 9 post conception
    - Characterized by the neuronal and glial proliferation
    - Cell migration in the cortex begins
  - Perinatal period 24 weeks and post natal
    - Organization of the cortex
    - Myelination (continues to age 2 y/o)

GROSS ANATOMY OF THE DEVELOPMENT



THREE COMPONENTS NECESSARY FOR SUCCESSFUL DEVELOPMENT OF THE BRAIN

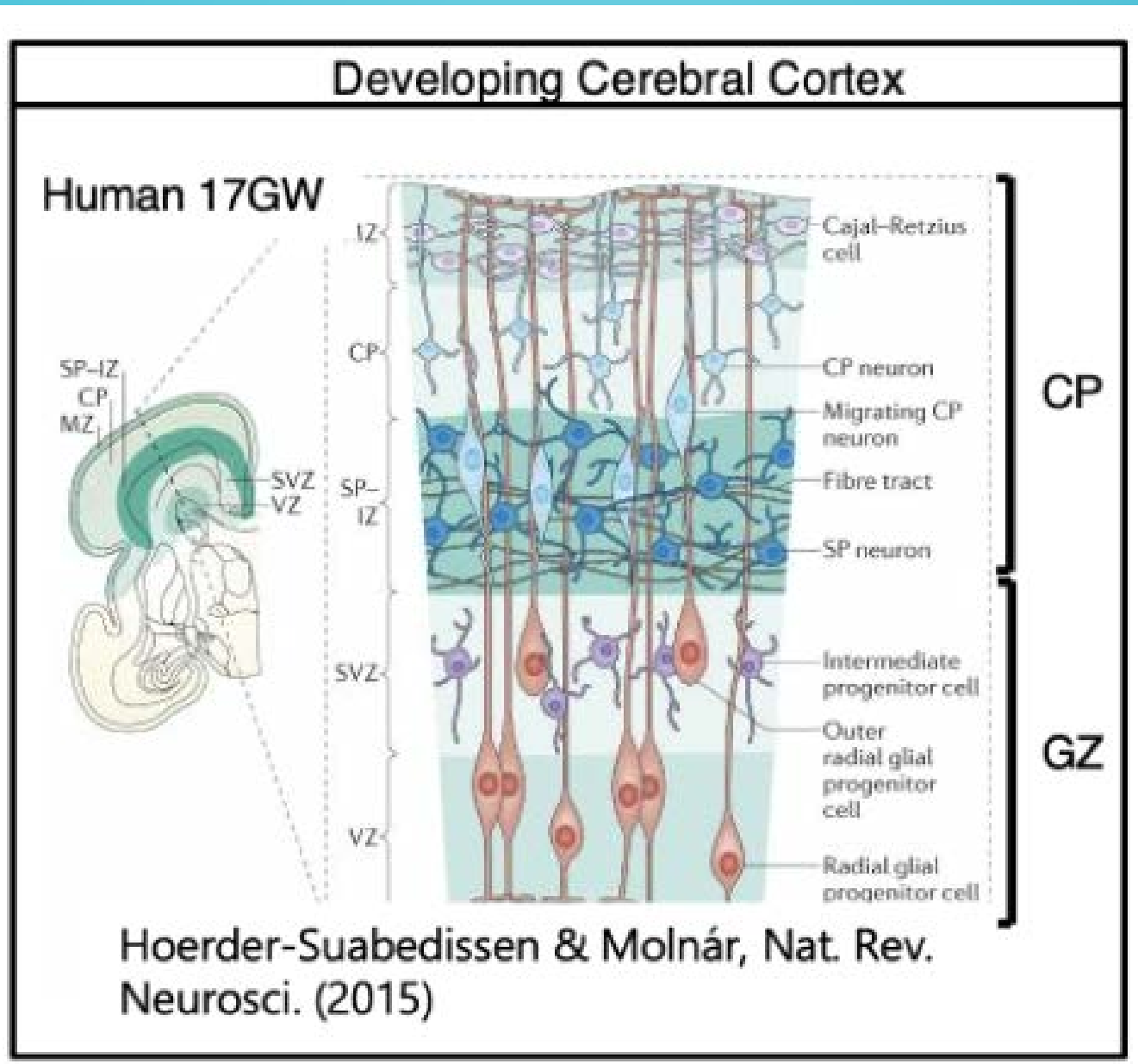
- Migration of primordial neurons
- Differentiation
- Synaptic development
- The last one is also important in neural plasticity
  - Therefore, understanding these conditions will inform typical development and psychiatric functioning

THREE ALPHABETS OF BIOLOGY- CRUCIAL FOR THE THREE COMPONENTS OF DEVELOPMENT

- Nucleic acids – DNA and RNA- code for amino acid sequences
- Amino acids- are arranged in specific sequences to create proteins with specific three dimensional shapes to provided structure and function in the cellular processes
- Neuramic acids- are arranged in specific sequences to create a glycocalyx around cells that influence cell adhesion and recognition.
  - Produce glycoproteins on cell surface that are critical in cell recognition and signalling for the immune system as well as synaptogenesis in response to cellular activity
  - These cell adhesion molecules are critical in neuronal migration during development

NORMAL MIGRATION OF NEURONAL PRECURSORS

- Begins in the ventricular zone where precursor cells divide into daughter cells.
- Some of the daughter cells retain precursor characteristics for a period and can also undergo mitosis
- Others begin to differentiate and migrate through the cortical plate and begin making synaptic connections
- The cortex develops a layered appearance based on these sequential migrations of differentiating neurons


Developing Cerebral Cortex
Human 17GW
SP–IZ
CP
MZ
SVZ
VZ
IZ
CP
SP–IZ
SVZ
VZ
Cajal–Retzius cell
CP neuron
Migrating CP neuron
Fibre tract
SP neuron
Intermediate progenitor cell
Outer radial glial progenitor cell
Radial glial progenitor cell
CP
GZ
Hoerder-Suabedissen & Molnár, Nat. Rev. Neurosci. (2015)

EPILEPSY AND AUTISM CONNECTION?

- Upto 40% of patients with ASD also have dx of epilepsy/seizures
- EEG abnormalities are frequent
- Does epilepsy cause autism? Or is it a co-occurring condition related to a common mechanism.

‘AUTISM’ RISK GENES

- Converge on early fetal development
- Involve transcription of gene sequences
  - necessary for neuronal differentiation
  - Synaptic development
- Impacts Glutaminergic/Gabaergic neurons in the upper layers of cortex differentially but not exclusively

MANY DISORDERS AFFECT MIGRATION OF NEURONAL CELLS OR DIFFERENTIATION

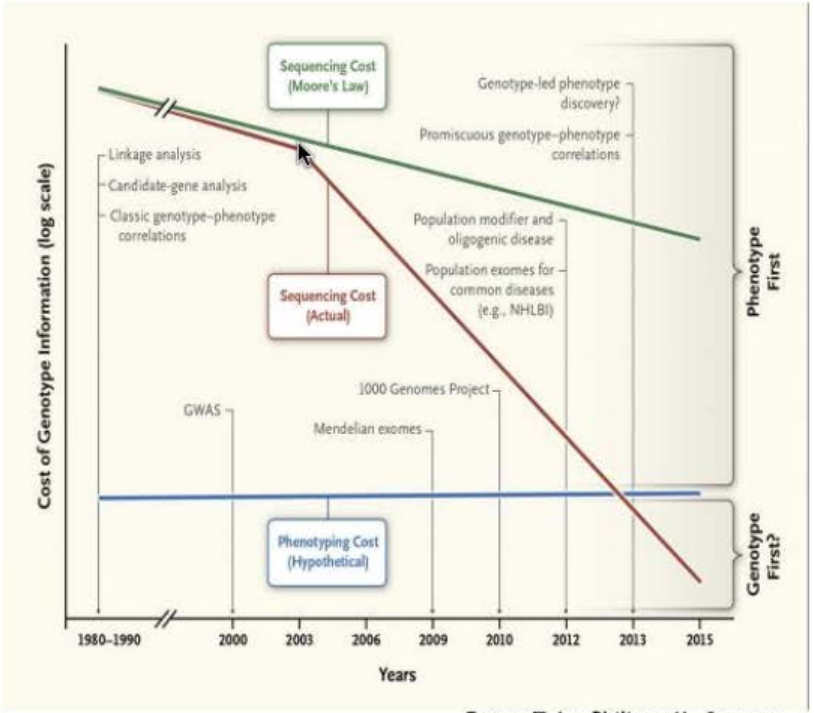
- Results in an imbalance in GABA/Glutamate functioning
- Consider the thalmo-cocortical-striatal pathways.
  - Essential a feedback loop
  - Impairment can lead to repetitive behaviors include OCD and repetitive behaviors

CONSIDER SCHIZOPHRENIA

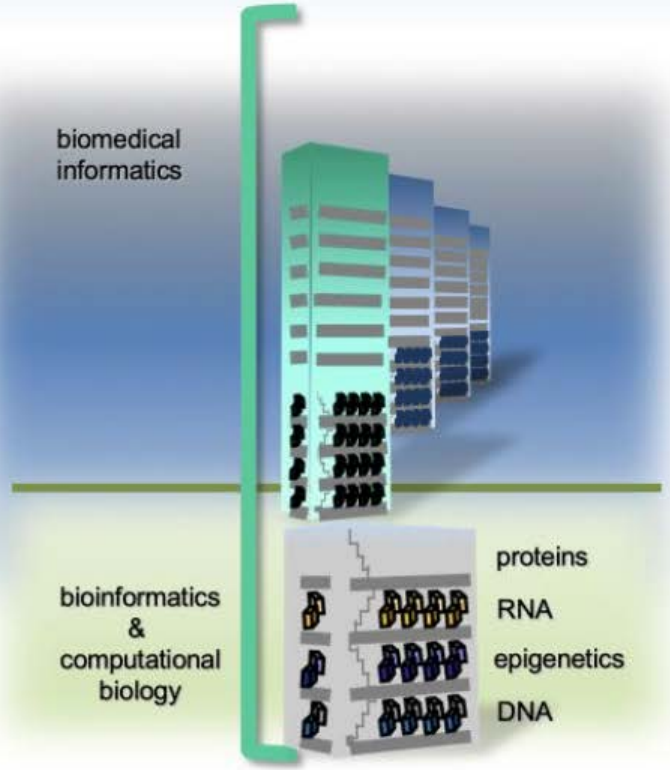
- OMIM (Online Manual of Inheritance in Man) is the largest curated site for defining genetic risk for various conditions
  - With in it there are 19 separate and distinct genetic susceptibility zones for schizophrenia in the human genome
  - Most of these genetic zones overlap with zones that have been identified with risk for autism
- Specific genes associated with schizophrenia are also identified in cases of autism, example is SHANK3
- The diagnosis of both major psychiatric illness and autism occurs greater than chance alone
- Is it appropriate then to consider serious psychiatric illness as neurodevelopmental disorders in some cases?

MODERN APPROACH TO AUTISM

Dramatically *decreasing DNA sequencing costs* alter approach to human disease as *computing power increases*.



James T. Lu, Philippe M. Campeau, and Brendan H. Lee, N Engl J Med 2014; 371:593-59 August 14, 2014



WE ARE IN THE 21ST CENTRURY, WE CAN DO BETTER THAT A BEHAVIORAL DIAGNOSIS

- Previous approach was influenced heavily by therapeutic nihilism.
  - It is not 'curable' therefore what's the point in trying to get a molecular diagnosis?
  - Was probably reasonable 50-60 years ago.
    - Phenotypic definitions used were based primarily on dysmorphology and a few lab test looking for inborn error of metabolism
  - At the turn of the century we had some laboratory approaches that included SNP microarrays to screen large number genetic variants
    - 100K panel

TYPICAL ALGORITHM IN THE PAST

- Plasma for amino acids, urine for organic acids, carnitine
- Fragile X, FISH evaluation, specific genes based on dysmorphia
  - MECP for instance
- If negative then microarray
- If negative then full Exome with next generation sequencing

FINDINGS ON EXOME

- Sequences the parts of the genome that code for proteins
- Specific findings may include
  - Variants established as associated with phenotype of the patient
  - Variants predicted to be pathogenic by in silico analysis of the potential protein product of the variant
  - Variants that are ‘variants of unknown significance
    - Variants of genes that have not been reported by others, can be new variants
    - In silico analysis is important here
  - No findings

WHAT IS MISSED ON THE EXOME

- Introns which may have important regulatory functions
- CNV
- Previously unreported variants of important neurodevelopmental genes

HOW DO I APPROACH A NEURODIVERSE PATIENT?

- If no genetic evaluation in last 5 years we consider genetic testing
- If we have a molecular diagnosis
  - Make sure allied or comorbid conditions are screened
    - Examples are cardiac, cancer, orthopedic disorders, seizures
  - Review literature for animal models the disorder
- If it is a VUS of a structural gene predicted to by pathogenic we consider it likely responsible
- If it is a VUS of an gene coding for an enzyme we look for animal models of haplodeficiency
  - If lab testing can evaluate the functional activity of the gene we evaluate that.
    - Example may be mitochondrial functioning

SOME EXAMPLE CASES

- Known disorders we have seen in last 3 years
- 22q11.2 deletions
- 22q13.3 deletion
- Prader willi
- Tuberous Sclerosis
- SCN2A variant
- Down's syndrome
- Mitochondrial disorder associated with LHON
- POGZ
- Cornelia de Lange

- VUS with pathogenic potential
- SLC13A5 (Plasma Citrate Transporter)
- SLITRK2 duplication

WHAT ARE THE BENEFITS OF IDENTIFYING A MOLECULAR DIAGNOSIS

- Puts a name to the disorder
- May allay parent's feelings of guilt or inadequacy
- Identifies potential treatments for behavioral conditions by looking at down stream effects of dysfunction
- The hope for specific genetic treatments are advancing

GENE THERAPY (SPINAL MUSCLULAR ATROPHY)

- SMA is a neuromuscular disorder caused by a mutation in the *SMN1* gene, which leads to a decrease in SMN protein, a protein necessary for survival of motor neurons.
- Onasemnogene abeparvovec is a biologic drug consisting of AAV9 virus capsids that contains a *SMN1* transgene along with synthetic promoters.[1]
- Upon administration, the AAV9 viral vector delivers the *SMN1* transgene to the affected motor neurons, where it leads to an increase in SMN protein.

SUMMARY

- Neurodiversity result from abnormal development during the period of neuroembryology
- Many have comorbid conditions that need to be managed
- Collaborative care with genetic experts and primary providers is critical
- The biology of these conditions may provide insight into the biology of major psychiatric illnesses