Beyond the Normative Data: Understanding the Bayley Scales of Infant Development Version 3 (BSID-III)

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Introduction

Mucopolysaccharidosis type II (MPS II, Hunter Syndrome) is an X-linked lysosomal storage disorder caused by the deficiency of iduronate-2-sulfatase. The neuronopathic form of MPS II is progressive and causes central nervous system dysfunction and cognitive developmental delay.

BSID-III is a standardized neurodevelopment assessment used by clinicians and researchers to assess the developmental functioning of children ages 1 to 42 months; five domains evaluate cognition, expressive and receptive language, and gross and fine motor skills.

- A consensus panel recommended BSID-III in evaluating neurodevelopment of children and is used to characterize disease severity, track change over time, and detect possible intervention benefits.
- Several scores representing each domain are available, with the Raw Score being the sum of the credited scores for each domain. The Standard Score (SS) is derived from the raw score to follow the normal distribution of a known mean and the standard deviation (SD). However, SS has limited utility for low functioning individuals (LFI) because when developmental function is delayed but age exceeds 42 months, BSID-III use is appropriate but SS are unavailable.
- Age equivalence score (AEq) and Developmental Quotient (DQ) are available in BSID-III for LFI and can be used to understand the neurodevelopmental natural history trajectory and measure intervention efficacy. AEq and DQ interpretive application is limited because there is no known distribution of the variables, and therefore no SD, although AEq and DQ are derived from samples representing the normal population.

Thousands of data points from the BSID-III manual normative data were simulated to characterize SD. An algorithm was created to map raw to discrete SS for all ages. AEq then referenced the corresponding ±1SD, ±2SD SS with a known mean and the SD to create the lower and upper bounds for age-specific AEq SDs. The slopes of linear equations were calculated by fitting respective linear regression lines between generated age-specific AEq SDs and age and were referenced in calculating DQ SDs.

An example of this application is demonstrated within a pediatric population of severe mucopolysaccharidosis type II (MPS II). RGX-121 is an investigational one-time gene therapy designed to deliver the gene that encodes the iduronate-2-sulfate (I2S) enzyme using the AAV9 vector. RGX-121 is administered directly to the central nervous system (CNS). In a Phase I/II Trial currently ongoing, Patients in Cohorts 1 and 2 received doses of RGX-121 at 1.3 × 10^10 genome copies per gram (GC/g) of brain mass and 6.5 × 10^10 GC/g of brain mass, respectively.

The BSID-III Scores

Raw Score

- Reflects the sum of credited scores and is used to derive the AEq and composite scores.
- The expected increase of raw score depends on the age of the child and the distribution is not well characterized.

Standard Score

- Composite score references a normative sample of children ages 16 days to 42 months with a mean of 100 and standard deviation (SD) of 15 in cognitive, language (expressive and receptive combined) and motor (fine motor and gross motor combined domains)
- Scaled Score references a normative sample with mean of 10 and SD of 3 in cognitive, expressive language, receptive language, fine more and gross motor domains
- LFI are at the floor of the standard score which is below -3SD from the mean when disease progression is severe (Shapiro 2018).

AEq : represents the mean age in the normative samples at which children achieve the raw score of interest. The expected increase of AEq depends on the age of the child (i.e., the rate of skill acquisition is different for different age group) and distribution is not well characterized.

DQ (AEq/chronological age × 100) : is useful in children beyond 42 months. A DQ close to 100 represents normal development. DQ is used in a similar context as composite score, but the distribution is not identical (Cho 2021).
Methods

Mock data were generated from raw, standard and AEq scores in the BSID-III manual for individuals between 4 and 42 months of age with “Normal”, “below and above 1SD from Normal”, and “below and above 2SD from normal” developmental status. Raw Score, AEq and DQ were derived to correspond to a mean scale score, and 1 and 2 SDs from the mean. The scores were fitted with a quadratic or linear regression line to approximate the range of the normal distribution.

The fitted ±1SD and ±2SD lines using the data from the BSID-III manual for cognitive domain were then applied to RGX-121 longitudinal BSID-III data to track change over time and to evaluate treatment efficacy.

Results

Figure 1 shows the Raw score over chronological age when cognition, expressive and receptive language are at the mean, at +/- 1SD and at +/- 2SD. The line is estimated with the quadratic regression over age to approximate the developmental pattern. Fine motor and gross motor raw scores are not shown in this poster.

Caution should be taken when extrapolating the boundary of -1SD and -2SD beyond the age of 42 months. BSID normative data is only collected from children up to age 42 months and the quadratic boundaries estimated from the normative data from younger children may not accurately describe the neurodevelopment function of older children.
Results (cont’d)

Figure 2 shows the AEq scores over chronological age when they are at the mean, at +/- 1SD and at +/- 2SD. The line is estimated with the linear regression over age to approximate the developmental pattern.

Since DQ is the slope of a linear line in the plot of AEq and age (Figure 2) times 100, the -1SD and -2SD lines of DQ are calculated and they are at 57 and at 76, respectively for the cognitive domain. DQ for other domains are similarly shown in the Figure 2.

Figure 2 1SD and 2SD with mean AEq from BSID-III

Figures 3 and 4 show the estimated boundaries of DQ and AEq, respectively, overlaid with the data collected from the First in Human clinical trial of the gene therapy of RGX-121 for severe MPS II (NCT03566043).
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1SD and 2SD boundaries applied to AEq and DQ support that the 4 patients who entered the study with cognitive skill above the -2SD of the normal range have continued to demonstrate neurocognitive development as of 6-month follow-up. One patient entered the study with significant delay in neurocognitive development at baseline but has demonstrated relative stabilization following RGX-121 administration at an older age (59 months) and has continued to acquire expressive and receptive language skills (expressive and receptive language presented at ASGCT 2021, Giugliani 2021).
Conclusions

- The expected gain in BSID-III raw score for normally developing children is different at each developmental milestone, so a linear line cannot be used to approximate the pattern but a quadratic line can best describe the pattern in cognition and expressive and receptive language.

- AEq boundaries are fitted with a linear regression line. The boundaries for AEq and slopes (i.e., DQ/100) are slightly different for each domain.

- DQ boundary is estimated from the AEq and age linear regression in Figure 2 with the slope times 100. The intervals of 1SD and 2SD for DQ are different, indicating that DQ may not be normally distributed, unlike composite score.

- Caution should be taken when applying findings of data from younger children to older children.

- Data interpretation from the FIH trial of RGX-121 using DQ and AEq were shown to be consistent, indicating that 4 patients with greater than 6 months of follow-up continued cognitive development and all patients with greater than 6 month of follow-up acquired motor and/or language skill (Giugliani 2021).

References

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