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Do clinical features of Lesch-Nyhan disease correlate more closely with hypoxanthine or guanine recycling?

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Abstract

Lesch-Nyhan disease (LND) is a rare, X-linked recessive neurodevelopmental disorder caused by deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGprt), an enzyme in the purine salvage pathway. HGprt has two functions; it recycles hypoxanthine and guanine. Which of these two functions is more relevant for pathogenesis is unclear because some evidence points to hypoxanthine recycling, but other evidence points to guanine recycling. In this study, we selectively assayed hypoxanthine (Hprt) and guanine (Gprt) recycling in skin fibroblasts from 17 persons with LND, 11 with an attenuated variant of the disease (LNV), and 19 age-, sex-, and race-matched healthy controls (HC). Activity levels of both enzymes differed across groups ($p < 0.0001$), but only Gprt distinguished patients with LND from those with LNV ($p<0.05$). Gprt also showed slightly stronger correlations than Hprt with 13 of 14 measures of the clinical phenotype, including the severity of dystonia, cognitive impairment, and behavioral abnormalities. These findings suggest that loss of guanine recycling might be more closely linked to the LND/LNV phenotype than loss of hypoxanthine recycling.

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Conflict of Interest

Wynne Callon, Rebecca Ward, and Barry Gordon declare that they have no conflict of interest.

The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies.

Introduction

Lesch-Nyhan disease (LND) is a rare X-linked recessive disorder caused by deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGprt), an enzyme in the purine salvage pathway. The classic LND phenotype emerged when residual HGprt levels are 1.5 % of normal or less. It is characterized by hyperuricemia, repetitive self-injury, severe dystonia, and cognitive impairment. Persons with residual HGprt enzyme activity between 1.5 % and ~20 % of normal develop an attenuated variant (LNV) of the phenotype that is characterized by hyperuricemia and varying degrees of neurological, cognitive, and behavioral abnormalities, but not self-injury (Kelley et al 1969; Mateos and Puig 1994; Schretlen et al 2005; Jinnah et al 2010; Torres et al 2012). Many investigators distinguish variants at the mildest end of the spectrum who have only HGprt-related hyperuricemia (HRH) from those who also demonstrate at least some neurological dysfunction (HND) (Jinnah et al 2004; Torres and Puig 2007).

While LND, HND, and HRH are often conceptualized as subgroups, they likely represent points along a continuum of disease severity (Fu and Jinnah 2012; Fu et al 2014). Nevertheless, most previous explorations of the LND spectrum have relied on subgroup comparisons, thereby sacrificing the potential to elucidate disease processes and mechanisms that might emerge from a more fine-grained analysis of individual differences in aspects of the phenotype and underlying metabolic defect.

As shown in Fig. 1, HGprt is responsible for recycling two substrates, hypoxanthine and guanine. This raises the question of whether features of the LND phenotype are more closely associated with defective metabolism of hypoxanthine or guanine, as shown by residual levels of hypoxanthine phosphoribosyltransferase (Hprt) or guanine phosphoribosyltransferase (Gprt). One previous study found that Hprt levels correlate more closely with clinical severity than Gprt levels, suggesting that hypoxanthine metabolism might play a more central role in the pathophysiology of LND symptoms. However, that study was based on just 12 patients, no replication of the finding has been reported in 30+ years, it divided the sample into just two subgroups, and it did not include healthy controls (Page et al 1981). A more recent study examined Hprt and Gprt activity in vitro by creating mutations through site-directed mutagenesis, and it also found evidence that clinical severity may be more closely associated with hypoxanthine recycling (Fu and Jinnah 2012). Given that LND is pleiotropic, with a single gene mutation resulting in cognitive, motor, and behavioral symptoms, it also could be that different characteristics of the phenotype depend differentially on Hprt or Gprt.

Despite evidence that mutations of the *HPRT1* gene cause varying degrees of HGprt enzyme deficiency that likely produce a spectrum of LND/LNV phenotypes, no studies have measured both the enzyme defect and behavioral features as continuous variables for a direct correlation over the full phenotype spectrum. Therefore, in this study we examined the association of Hprt and Gprt function of HGprt (henceforth referred to as Hprt and Gprt "enzyme activity") separately with known behavioral, cognitive, and motor characteristics of the LND phenotype across the full range of enzyme activity. Given previous evidence regarding uric acid's association with cognition and cerebral ischemia in healthy adults

(Schretlen et al 2007; Vannorsdall et al 2008), and the fact that enzyme levels vary widely in the general population, we included both patients and healthy controls in our analysis. Based on previous studies (Page et al 1981; Fu and Jinnah 2012; Fu et al 2014) we hypothesized that both hypoxanthine and guanine recycling would correlate with cognitive, behavioral, and motor characteristics of LND, but that when they differed, clinical features would correlate more highly with Hprt than Gprt enzyme activity.

Method

Participants

The study participants include 17 persons with LND, 11 with LNV, and 19 healthy controls (HC). Thirty-six participants (76.6 %) are Caucasian, seven (14.9 %) are African-American, two (4.3 %) are Hispanic, and the other two did not state their race. The sample includes only males, as LND is a sex-linked disease. Most participants were native English speakers, but two were from Spain or Hungary, and they spoke only Spanish or Hungarian, respectively. All participants were accompanied by a family member or other informant who provided behavior ratings.

Patients with LND ranged in age from 14 to 38 years (M= 23.1; SD=8.3) at the time of study. The clinical diagnosis of LND was based on the presence of hyperuricemia, characteristic motor neurological abnormalities, a history of self-injurious behavior (resulting in tissue damage), and cognitive impairment. Diagnoses were confirmed by a fibroblast assay showing residual HGprt enzyme activity that was less than 1.6 % of normal, or a mutation of the *HPRT1* gene that predicted null enzyme activity. As in our previous studies, the diagnosis of LNV was based on documentation of hyperuricemia and the absence of self-injurious behavior. In most cases, the clinical diagnosis was supported by evidence of reduced HGprt enzyme activity, a mutation of the *HPRT1* gene, or both. The participants with LNV ranged from 15 to 50 years old (M=27.2; SD=11.1). Participants with LND or LNV were recruited through our clinics, other physicians, the Lesch-Nyhan Disease Patient Registry, and the Matheny School and Hospital in Peapack, New Jersey, USA (Schretlen et al 2013).

Healthy controls were recruited from the local community or from another unrelated study in which they also served as healthy controls. They ranged in age from 16 to 49 years (M= 30.4; SD=12.2). The participants reported no history of neurological disorders, substance abuse or dependence, or psychiatric illness.

Fifty-six informants (22 mothers, four fathers, one sister, eight friends, seven spouses/ partners, ten professional caregivers, and four “others”) provided behavior ratings of each study participant. Most participants (38) were rated by one informant, seven were rated by two informants, and one was rated by four informants. The length of time that informants had known study participants ranged from two years for the girlfriend of a healthy control to 50 years for the mother of a patient. The mean was 17.4 years (SD=11.7).

This study was approved by the Johns Hopkins Medicine and Emory University Institutional Review Boards. All participants, including each informant, gave written informed consent or

oral assent. A parent or legal guardian gave written informed consent for study participants who were unable to give written consent and gave oral assent instead.

Procedure

Skin biopsies from the 47 participants were collected under local anesthesia. The samples were used to establish fibroblast cultures and measure residual Hprt and Gprt enzyme activity as previously described. In brief, the cultures were established by mincing the tissue followed by enzymatic dispersion. Fibroblast cultures were used after 5–10 passages. Cultures at 50-80 % confluency were suspended in tissue culture medium with 25 μM [8-^{14}C]-hypoxanthine or 25 μM ^{14}C-guanine for 2 hr at 37 °C. The cells were then pelleted by centrifugation and intracellular purines were extracted with 0.2 M perchloric acid. The nucleotides were captured using diethylaminoethyl anion exchange filters (Millipore, Billerica MA) and radioactivity counted using a 2450 MicroBeta Microplate Scintillation Counter (Perkin Elmer, Finland). Hprt and Gprt activities were normalized to total protein content of the cell pellet (Shirley et al 2007; Göttle et al 2013). The methods used to assay Hprt and Gprt enzyme activity were identical to those described in detail in our recent report (Fu et al 2015).

The severity of dystonia shown by each study participant was rated based on the Burke-Fahn-Marsden Dystonia Rating Scale (Burke et al 1985). A neurologist who specializes in movement disorders and Lesch-Nyhan disease (H.A.J.) examined each participant and rated both the severity of dystonia (0–4) and how easily it was provoked (0–4) in each of nine body parts. Thus, higher scores denote more severe, widespread, and easily provoked dystonia. We recorded each person's total dystonia rating for correlation with residual Hprt and Gprt enzyme activity.

Each study participant also was administered a battery of neuropsychological tests that included the Kaufman Brief Intelligence Test (K-BIT; Kaufman and Kaufman 1997), Peabody Picture Vocabulary Test (PPVT; Dunn and Dunn 1959), or both to assess intelligence. Because data were collected between 1996 and 2013, different versions of the KBIT and PPVT were used over time. The Hopkins Verbal Learning Test, Revised (HVLT-R; Brandt 1991) was used to assess learning and memory. The Brief Test of Attention (BTA; Schretlen 1997) was used to assess attention/working memory, and the Benton Facial Recognition Test (BFRT; Benton et al 1994) was used to assess visual perceptual accuracy.

It is difficult to test patients with LND because they are physically restrained more-or-less continuously, tire quickly, have short attention spans, and occasionally give wrong answers to test questions on purpose in order to tease or "trick" the examiner. As a result, one must often depart from standard administration procedures when testing persons with LND, and several patients with LND did not complete all the tests in our assessment.

We recorded six scores from cognitive testing for correlation with enzyme levels. First, we drew Composite IQ scores from the K-BIT (Kaufman and Kaufman 1997) unless a patient was unable to complete the K-BIT, in which case we substituted the PPVT (Dunn and Dunn 1959) total score. Both of these assess intellectual functioning and express performance as age-adjusted standard scores. The HVLT-R is a test of verbal learning and memory in which

the examiner reads a list of 12 words aloud three times. The examinee is asked to recall as many words as possible after each oral presentation. This is followed by delayed free recall and recognition memory trials 20 minutes later. From this test, we recorded the number of words recalled over all three learning trials, the number of words recalled after a delay, the percentage retained, and delayed recognition memory (hits minus false positive errors) (Brandt 1991). The BTA is a computer-administered test in which a voice reads 20 strings of letters and numbers (e.g., 2-5-L-R-3-M-Q), and the examinee must keep a mental tally of the number of letters (or numbers) in each string (Schretlen 1997). The total number of correct responses was recorded. Finally, the BFRT tests the ability to match unfamiliar faces pictured under varied lighting and exposure conditions (Benton et al 1994). We recorded the total number of correct responses (out of 27) for this test.

An informant rated each participant's behavior on several questionnaires. These included the Adaptive Behavior Scale-Residential and Community, 2nd edition (ABS-RC:2; Nihira 1998) and either the Adult (ABCL) or Child (CBCL) Behavior Checklist (Achenbach and Rescorla 2001; Achenbach and Rescorla 2003). The ABS-RC:2 assesses both everyday functional independence (part 1) and aberrant behaviors (part 2). For the present analysis, we recorded scores for scales that assess aggression (social behavior), self-injury (self-abusive behavior), disruptiveness (disturbing interpersonal behavior) and inappropriate/disinhibited sexual expression (sexual behavior). Behavior ratings based on the ABCL or CBLC were combined, depending on which test was administered. The CBCL contains 118 items on a 3-point scale (0=not true to 2=very or often true) and was designed to assess various behavior problems in children between the ages of 4 and 18 years. The ABCL is a 132-item version of the CBCL that is used for adults. Both versions yield scores for several subscales and two summary scales that assess internalizing (e.g., anxiety, withdrawal) and externalizing (e.g., aggression, rule-breaking) problems. Based on the similarity of the CBCL and ABCL test items and scales, we recorded T-scores of the Internalizing and Externalizing Problems scales for correlation with residual Hprt and Gprt enzyme activity levels.

Data analysis

One-way analysis of variance (ANOVA) with Bonferroni-corrected post-hoc comparisons to maintain an experiment-wise alpha of ($p<0.05$) was used to compare subgroup differences in age and enzyme activity levels. The Chi-squared test was used to assess group differences in race. Because most measures were normally distributed in the overall sample, Pearson r correlations were used to examine the strength of associations between residual Hprt and Gprt activity levels and the motor, cognitive, and behavior measures described above. Steiger's Z statistic (Steiger 1980) was used to compare each pair of Pearson r correlation coefficients linking Hprt and Gprt enzyme activity level with each clinical feature. Assuming that differences between Hprt and Gprt correlation coefficients would be small, we also compared the direction of the absolute values of Pearson r coefficients against the binomial distribution to test the null hypothesis that hypoxanthine and guanine recycling are equally associated with clinical features of LND/LNV. If the null hypothesis is true, then approximately 50 % of the clinical features should correlate more highly with Hprt enzyme activity and 50 % should correlate more highly with Gprt enzyme activity.

Results

A one-way ANOVA revealed no significant group differences in age ($F_{(2, 44)}$=2.15; p=0.13). Nor did the groups differ in racial composition ($\chi^2_{(4)}$=4.2; p=0.38). In contrast, large group differences were observed for Hprt ($F_{(2, 44)}$= 185.1; p<0.0001) and Gprt ($F_{(2, 44)}$=223.3; p<0.0001) enzyme activity levels. Bonferroni-corrected post-hoc comparisons revealed that all three groups differed significantly from each other in mean (±standard deviation) Gprt enzyme activity (LND=45±51, LNV=416±452, HC=2556±485 pmol/mg/h). However, while both patient groups had lower Hprt activity levels than healthy controls (LND=24±18, LNV=224±247, HC=2103±516 pmol/mg/h), they did not differ significantly from each other (p=0.441). The effect size was marginally larger for Gprt (η^2=0.91) than for Hprt (η^2=0.894). The within-subjects correlation between Hprt and Gprt enzyme activity levels was very high (Pearson r=0.98; p<0.0001). A boxplot of the Hprt and Gprt enzyme activity levels observed in each group is shown in Fig. 2.

Consistent with our primary hypothesis and as shown in Table 1, Hprt and Gprt activity levels both correlated significantly with all phenotypic measures except percent retained on the HVLT-R word list learning test (p=0.11 for Hprt; p=0.09 for Gprt). Contrary to our secondary hypothesis and based on Steiger's Z statistic (Steiger 1980) to test for the difference between two dependent correlations, Gprt enzyme activity levels correlated significantly more strongly than Hprt activity levels with BFM dystonia severity ratings (Z= −2.24; p=0.025) and BFRT performance (Z=−2.69; p=0.007). None of the remaining 12 pairs of Pearson r coefficients differed significantly from one another. In addition, only the difference between Hprt and Gprt correlations with BFRT performance remained significant after a partial Bonferroni correction (p<0.014) for multiple comparisons was applied (Shriner et al 2008). However, the Pearson r coefficient for Gprt enzyme activity was *nominally* higher (in absolute value) than its Hprt counterpart for 13 of the 14 phenotype measures shown in Table 1. If Gprt and Hprt enzyme activity levels contribute equally to pathogenesis, one would expect their true correlations with phenotype measures to be the same. Due to measurement error, Gprt might correlate more highly than Hprt for some measures, and Hprt might correlate more highly than Gprt with others. However, the binomial probability of finding that Gprt correlated more highly than Hprt with 13 of 14 phenotype measures is 0.00086 if the null hypothesis were true.

Discussion

In this study we measured the core metabolic defect of LND as two continuous variables (Hprt and Gprt activity) across the full spectrum of the clinical phenotype. We then correlated these with quantitative measures of the core features of the phenotype to test whether the latter depend more on deficient recycling of one enzyme or the other. Based on previous research (Page et al 1981; Fu and Jinnah 2012), we hypothesized that Hprt enzyme activity would correlate more highly than Gprt with phenotype severity. However, the absolute values of Pearson r coefficients for Gprt activity were larger than those for Hprt activity in 13 of 14 comparisons. The binomial probability of this finding, if the null hypothesis is true, is less than 1 in 1000. Thus, while the differences between most pairs of correlation coefficients were not statistically significant, the consistency with which Gprt

enzyme activity correlates more strongly than Hprt activity across features of the phenotype suggests that guanine recycling might play a more central role than hypoxanthine recycling in the pathogenesis of LND. Consistent with this idea, the effect size of group differences in Gprt enzyme activity also was slightly larger than the effect size of group differences in Hprt activity, and only Gprt distinguished all three groups from one another.

Another finding of this study is that both Hprt and Gprt enzyme activity levels correlated highly with nearly every component of the behavioral phenotypes that characterize LND spectrum disorders. The strongest correlations were found for dystonia severity, IQ, attention/working memory, facial discrimination, and word list learning/memory. Slightly weaker but still quite strong associations with measures of aberrant behavior also emerged. The strongest of these involve measures of aggressive, self-injurious, and disturbing interpersonal behaviors. Taken together, these findings clearly support the inference that dystonia, cognitive dysfunction, and certain (i.e., aggressive and self-injurious) behaviors relate directly to the metabolic defect that results from mutations of the *HPRT1* gene.

One phenotype measure of “internalizing” behaviors showed a reversed pattern of association with the underlying enzyme defect in that it correlated slightly more strongly with Hprt than Gprt enzyme activity. The significance of this finding is unclear, but it raises the question of whether such “internalizing” problems as depression, anxiety, and social withdrawal might represent a secondary effect of the disease process. In other words, we wonder if some persons with LND or LNV develop depression or anxiety in response to other symptoms and limitations caused by the disease, rather than as a more direct biological consequence of the metabolic defect.

While this study is one of the largest clinical studies of LND and its variants, the results may still be limited by small sample size. In addition, we acknowledge that patients with LND/LNV are at times difficult to work with, creating the potential for inconsistencies in test results. We included informants to partially ameliorate this concern. Further studies are needed to confirm whether Gprt is, in fact, more closely associated with clinical characteristics of the phenotype. Future studies are also needed to determine whether there is a biochemical basis for the differential role that guanine and hypoxanthine accumulation seem to play in the symptomology of LND.

In summary, this study found that both the level of metabolism of hypoxanthine and guanine by HGprt are highly associated with behavioral, cognitive, and motor characteristics across health individuals, LNV patients, and LND patients. While a small difference, this study also suggests that guanine metabolism by the HGprt enzyme may play a more direct role in the pathogenesis of LND than hypoxanthine metabolism.

Prior investigators have focused mostly on the significance of hypoxanthine recycling after one early study found a better correlation between clinical severity and Hprt than Gprt (Page et al 1981). This view has found support by evidence that hypoxanthine-related metabolites accumulate to a greater degree than guanine-related metabolites, implying HGprt has a more biologically important role in recycling hypoxanthine than guanine (Sweetman and Nyhan 1970; Harkness et al 1988). Conversely, some studies suggest Gprt to be more relevant. A

mathematical modeling study of purine metabolism implied that Gprt is more relevant to disease severity (Curto et al 1998), and others have pointed to the critical role of guanine nucleotides in neuronal development and function (Deutsch et al 2005; Shirley et al 2007). Resolving this controversy is important for guiding further studies of the neurobiology of LND and its potential treatments. If Hprt is more relevant, then further attention should be devoted to potential deficiency of hypoxanthine-based metabolic products. However, if Gprt is more relevant, then attention should focus instead on guanine-based metabolic products, such as GTP.

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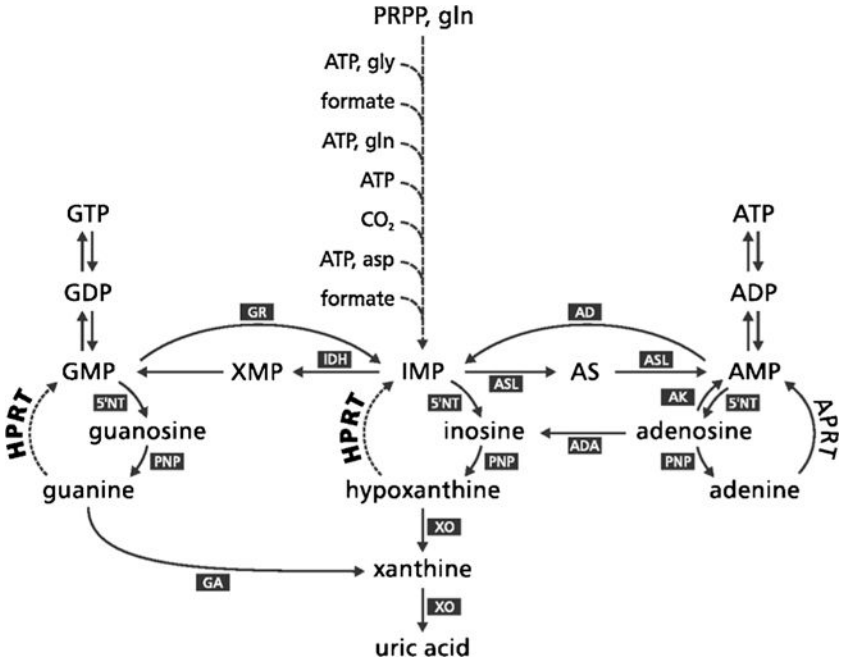

Fig. 1.

Purine salvage pathway and HGprt function (Visser et al 2005). Abbreviations: 5′ NT=5′-nucleotidase; AD=adenylate deaminase; ADA=adenosine deaminase; AK=adenosine kinase; AMP=adenosine monophosphate; ADP=adenosine diphosphate; ATP=adenosine triphosphate; APRT=adenine phosphoribosyltransferase; AS=adenylosuccinate; ASL=adenine succinate-synthetase/lyase; GMP=guanosine monophosphate; GA=guanase; GDP=guanosine diphosphate; GTP=guanosine triphosphate; HPRT=hypoxanthine phosphorybosyltransferase (same as HGprt); IDH=IMP dehydrogenase; IMP=inosine monophosphate; PNP=purine nucleoside phosphorylase; PRPP=phosphoribosyl pyrophosphate XMP=xanthosine monophosphate; XO=xanthine oxidase

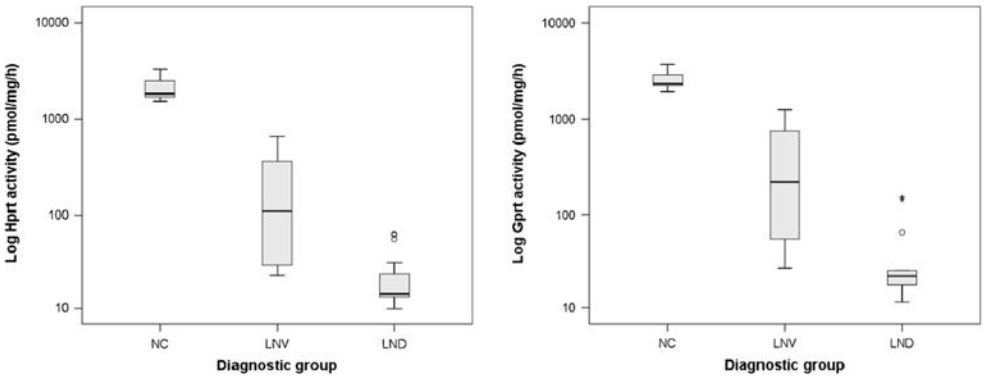

Fig. 2.

Box-and-whisker plots depicting Hprt (left panel) and Gprt (right panel) enzyme activity level by group. Each box shows the median (horizontal line) and interquartile range (IQR) of the logarithm of the values in pmol/mg/h. Circles show outliers that fall 1.5 × IQR from the nearest quartile, and stars show outliers that fall 3 × IQR from the nearest quartile. NC=normal control; LNV=Lesch-Nyhan variant; LND=Lesch-Nyhan disease

Table 1

Pearson correlations between residual enzyme activity and phenotype characteristics

Phenotype measure	Hprt (pmol/mg/h)	Direction of difference	Gprt (pmol/mg/h)
BFM dystonia severity	−.77***	<	−.81***
K-BIT/PPVT composite IQ	.86***	<	.87***
BFRT total correct	.74***	<	.79***
HVLT learning (trials 1–3)	.79***	<	.82***
HVLT delayed recall	.74***	<	.77***
HVLT percent retained	.26	<	.28
HVLT delayed recognition	.57***	<	.60***
BTA total correct	.87***	<	.89***
ABS:RC-2 social behavior	.60***	<	.61***
ABS:RC-2 self-abusive behavior	−.505**	<	−.51***
ABS:RC-2 disturbing interpersonal behavior	−.56***	<	−.58***
ABS:RC-2 sexual behavior	−.35*	<	−.37*
CBCL/ABCL internalizing problems	−.52**	>	−.50**
CBCL/ABCL externalizing problems	−.44**	<	−.45**

*** $p<0.001$;

** $p<0.01$;

* $p<0.05$

Note: BFM=Burke-Fahn-Marsden Dystonia Rating Scale (Burke et al 1985). K-BIT=Kaufman Brief Intelligence Test (K-BIT) (Kaufman and Kaufman 1997). PPVT=Peabody Picture Vocabulary Test (PPVT) (Dunn and Dunn 1959). BFRT=Benton Facial Recognition Test (Benton et al 1994). HVLT=Hopkins Verbal Learning Test (Brandt 1991). BTA=Brief Test of Attention (Schretlen 1997). ABS:RC-2=Adaptive Behavior Scale, Residential and Community, 2nd Ed (Nihira 1998). CBCL/ABCL=Achenbach Child or Adult Behavior Checklist (Achenbach and Rescorla 2001; Achenbach and Rescorla 2003)