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Tatton-Brown-Rahman syndrome: cognitive and behavioural phenotypes

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Abstract

The aim of this case series was to assess and characterise cognitive abilities, autistic traits and adaptive behaviour in Tatton-Brown-Rahman syndrome. The sample included 18 individuals with a clinical and genetic diagnosis of TBRS (11 males, seven females; mean age 17y 7mo, SD 9y 5mo, range 7y 2mo–33y 10mo). The British Ability Scales, Third Edition and the Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) were administered to all participants. The Social Responsiveness Scale, Second Edition and the Vineland Adaptive Behaviour Scales, Third Edition were completed by a parent/caregiver. The majority of participants (n=15) had intellectual disability and General Conceptual Ability scores ranged from 39 - 76 (mean 53.17, SD 12.13). Participants displayed a profile of better verbal ability compared with non-verbal reasoning ability and spatial ability. Autistic traits were prevalent and eight participants scored above the cut-off on the ADOS-2, though symptoms were less pronounced in older individuals. Adaptive functioning was impaired but commensurate with intellectual ability. Overall, TBRS is associated with an uneven cognitive profile and a high prevalence of autistic traits. This has implications for identifying appropriate services and support which may be beneficial for individuals with TBRS.

What this paper adds

- Tatton-Brown-Rahman syndrome is associated with intellectual disability and impaired adaptive functioning.
- Autistic traits were prevalent within the sample.
- Lower intellectual ability and adaptive behaviour were associated with greater severity of autistic traits.

Tatton-Brown-Rahman syndrome: cognitive and behavioural phenotypes

Tatton-Brown-Rahman syndrome (TBRS), also known as the DNMT3A overgrowth syndrome, is a congenital overgrowth disorder associated with intellectual disability (OGID). The syndrome was initially identified in 2014 and is caused by constitutive variants of the *DNMT3A* gene [(1)]. The major clinical features are overgrowth (defined as height and/or head circumference at least two standard deviations above the population mean) and intellectual disability [(2)]. The syndrome is diagnosed based on the presence of these two major clinical features, as well as a constitutive variant of the *DNMT3A* gene. Other frequent clinical features, reported in 20 – 80% of individuals with TBRS, include joint hypermobility, obesity, hypotonia, kyphoscoliosis and afebrile seizures [(2)]. TBRS is one of several OGID syndromes, with other examples including Sotos syndrome and Weaver syndrome [(3)]. All of these disorders have similar clinical phenotypes but are caused by distinct genetic abnormalities.

Investigating the cognitive and behavioural characteristics associated with congenital syndromes is important for identifying and implementing appropriate management strategies and support. As TBRS was only identified as a syndrome in 2014, current understanding of the cognitive and behavioural phenotype associated with the syndrome is limited. In a recent study investigating the clinical phenotype associated with TBRS, intellectual disability and behavioural/psychiatric issues were reported in a sample of 55 individuals with TBRS [(2)]. The majority of participants (65%) were reported as requiring a high level of support in a mainstream school or special educational needs school and living with support as an adult, which was defined as ‘moderate intellectual disability’, though no standardised cognitive assessments were administered. Thus, the exact nature and range of intellectual functioning in this population is unknown.

Autistic traits have been reported in the most prevalent OGID syndrome, Sotos syndrome [4, 5], indicating that overgrowth syndromes may be associated with increased prevalence of autism spectrum disorder (ASD). Research investigating the genetic basis of ASD has identified an association between the *DNMT3A* gene and ASD [6]. Furthermore, Tatton-Brown et al., [2] found that the most prevalent co-occurring diagnosis was ASD and this was reported in 36% of the participants (20/55). Other co-occurring diagnoses included anxiety, neurodevelopmental regression, psychosis/schizophrenia, aggressive outbursts and bipolar disorder [2]. However, to date, the prevalence and profile of behavioural characteristics associated with TBRS has not been assessed using standardised measures. Thus, the primary aim of this study was to advance understanding of the cognitive and behavioural phenotypes associated with TBRS and specifically, to assess and characterise cognitive abilities, autistic traits and adaptive behaviour within a sample of individuals with TRBS, using a combination of standardised in-person assessments and parental questionnaires.

Method

Participants

The sample comprised 18 participants (11 males, seven females) with a clinical and genetic diagnosis of TBRS. Mean age of the participants was 17 years 7 months (SD 9y 5mo, range 7y 2mo–33y 10mo). Participants were recruited via clinicians in the NHS (n=2), the Child Growth Foundation (CGF; a UK charity that supports families of individuals affected by growth conditions) (n=8) and the Tatton-Brown Rahman Syndrome Community (a US patient support organisation that supports families of individuals with TBRS) (n=8). Eligibility criteria were a confirmed clinical and genetic diagnosis of TBRS and a minimum age of 4 years.

Measures

British Ability Scales, third edition (BAS3) [7]. The BAS3 is a standardised battery of tests designed to assess a range of cognitive abilities. A general conceptual ability (GCA) score provides a measure of overall intellectual ability (mean 100, SD 15). GCA scores are calculated on the basis of T-scores (mean 50, SD 10) for the six core scales. These core scales form three distinct clusters: verbal ability (word definitions task and verbal similarities task), non-verbal reasoning ability (matrices task and quantitative reasoning task) and spatial ability (recognition of designs task and pattern construction task). Cluster scores are calculated as standard scores (mean 100, SD 15).

Autism Diagnostic Observation Schedule, second edition (ADOS-2) [8]. The ADOS-2 is a semi-structured, standardised, observational assessment. A range of age-appropriate activities and social presses are used to assess behaviours associated with ASD, such as social skills, restricted interests, repetitive behaviours and creativity/imaginative play. One of four developmentally appropriate modules is used, depending on the chronological age and language ability of an individual. Each module comprises individual items which are used to assess behaviours of interest, with item scores ranging from 0 (no evident abnormality) to 3 (marked abnormality). Algorithm items are combined to provide a total ADOS-2 score and this can be converted to a calibrated severity score (maximum 10), meaning that comparisons can be made between the modules. Higher scores indicate greater severity of autistic behaviours. An individual can be classified as scoring in the non-spectrum, autism spectrum or autism range, depending on the cut-offs provided for each module. Algorithm items can also be used to calculate domain-level scores for social affect and restricted and repetitive behaviours. All participants completed modules 2, 3 or 4. In order for calibrated severity scores and domain-level scores to be calculated for all participants, the revised algorithm was used for module 4 [9].

Social Responsiveness Scale, second edition (SRS-2) [10]. The SRS-2 is a 65-item standardised questionnaire designed to assess behaviours associated with ASD. The questionnaire is consistent with the DSM-5 criteria for ASD and has two subscales which provide an indication of difficulty with social communication impairment (SCI), as well as difficulty with restricted interests and repetitive behaviours (RRB). Items are coded on a 4-point Likert scale (0, not true to 3, almost always true) and this provides an indication of the frequency of behaviours of interest. Items are combined to provide a total score which indicates overall severity of autistic behaviours. Higher scores represent greater severity and total scores can be categorised as non-clinical, mild, moderate or severe. Age-appropriate versions were used and the questionnaire was completed by the parent/caregiver of each participant.

Vineland Adaptive Behaviour Scales, third edition (Vineland-3) [11]. The Vineland-3 domain-level parent/caregiver form is a standardised questionnaire designed to assess adaptive behaviour. An adaptive behaviour composite (ABC) score, provides an indication of an individual's overall level of adaptive functioning (mean 100, SD 15). Separate domain-level scores can be calculated for communication, daily living skills and socialisation (mean 100, SD 15). The questionnaire was completed by the parent/caregiver of each participant.

Procedure

Data were collected between May and November 2018. All participants were individually administered the BAS3 and the ADOS-2 in one session. The parent/caregiver of each participant was asked to complete the SRS-2 and the Vineland-3 and these were returned for 12 participants (seven males, five females; mean age 19y 5mo, SD 9y 2mo, range 8y 2mo–33y 9mo). NHS ethical approval was obtained (17/WA/0426). Participants aged 18 years and over provided written informed consent and for children under the age of

18 years, the parent/caregiver of the participant was required to give written informed consent. All participants provided verbal assent.

Results

General conceptual ability

As assessed by the BAS3, the mean GCA of the 18 participants was 53.17 (SD 12.13) and GCA scores ranged from 39 to 76. The majority of participants (n=15) had intellectual disability (GCA < 70) and the remaining participants (n=3) had borderline intellectual functioning (GCA of 70 – 89). None of the participants had GCA scores in the average intellectual ability range (GCA of 90 – 109). There was no association between age and GCA, $r = .229$, $N = 18$, $p = .362$. A one-sample *t*-test revealed that the GCA of the TBRS participants was significantly lower than the mean GCA of 61 that has been reported in the Sotos syndrome population, $t(17) = -2.74$, $p = .014$. Figure 1 shows the distribution of GCA scores for the participants.

[Insert Figure 1 about here]

Cognitive profile

BAS3 cluster scores were compared in order to determine whether participants displayed an uneven cognitive profile in relation to verbal, non-verbal reasoning and spatial abilities. A Friedman test revealed a significant difference between the three cluster scores; $x^2(2) = 23.08$, $p < .001$. Post-hoc Wilcoxon signed-rank tests ($p < .017$ required for significance) identified that performance on the verbal ability (mean 68.33, SD 14.53) cluster was significantly better than performance on the non-verbal reasoning ability (mean 55.78, SD 7.84), ($Z = -4.16$, $p < .001$), and spatial ability (mean 59.11, SD 11.77) clusters, ($Z = -4.07$, $p < .001$). There was no significant difference between performance on the non-verbal

reasoning ability and spatial ability clusters, (Z = -0.81, p = .416). Overall, participants displayed an uneven profile of relative strength with verbal ability, compared to both non-verbal reasoning and spatial abilities (see Figure 2).

[Insert Figure 2 about here]

In order to establish whether participants displayed an uneven cognitive profile in relation to specific cognitive abilities, paired samples t-tests were used to compare T-scores for the two core scales within each cluster. The comparisons revealed no significant difference between performance on the word definitions task and the verbal similarities task, $t(17)$ = -1.58, p = .132, d = 0.37, and no significant difference between performance on the matrices task and the quantitative reasoning task, $t(17)$ = -0.23, p = .819, d = 0.05. There was a significant difference between performance on the recognition of designs task and the pattern construction task, $t(17)$ = 3.79, p = .001, d = 0.89. This indicates that participants displayed an uneven profile of performance in relation to spatial abilities, with better visuospatial memory ability, compared to visuoconstructive ability.

Autistic traits

ADOS-2 calibrated severity scores ranged from 1 – 9 (mean 3.83, SD 2.48). At the domain-level, social affect scores ranged from 1 – 13 (mean 5.28, SD 3.58) and restricted and repetitive behaviour scores ranged from 0 – 6 (mean 1.78, SD 1.86). On the basis of total scores, five participants had scores in the autism range, three had scores in the autism spectrum range and 10 had scores in the non-spectrum range. Spearman's rank identified a strong negative correlation between ADOS-2 calibrated severity scores and age, r_s = -.547, N = 18, p = .019, indicating that autistic traits were less pronounced in older individuals with TBRS (see Figure 3).

[Insert Figure 3 about here]

This relationship held after accounting for GCA via partial correlation, r_s = -.613, N = 18, p = .008. All of the adults in this sample (n = 6) scored in the non-spectrum range. Spearman's rank identified a strong negative correlation between GCA scores and ADOS-2 calibrated severity scores, r_s = -.600, N = 18, p = .008, indicating that lower intellectual ability is associated with greater severity of autistic traits (see Figure 4).

[Insert Figure 4 about here]

In relation to parent-reported autistic traits, SRS-2 total T-scores ranged from 51 – 108 (mean 73.42, SD 15.31). Clinical cut-off was considered as a total T-score ≥ 60 and 11 of the participants scored above the clinical cut-off. Within the total sample, four participants scored in the severe clinical range (total T-score ≥ 76), five scored in the moderate clinical range (total T-score of 66 – 75) and two scored in the mild clinical range (total T-score of 60 – 65). Spearman's rank identified a strong positive correlation between ADOS-2 calibrated severity scores and SRS-2 total T-scores, r_s = .712, N = 12, p = .009. A paired samples t-test was used to compare SRS-2 subscale T-scores for SCI (mean 72.00, SD 14.99) and RRB (mean 76.42, SD 16.17). This revealed that the difference between the SCI and RRB subscales was associated with a moderate effect size but was statistically non-significant, $t(11)$ = -1.79, p = .101, d = 0.52.

Adaptive behaviour

In terms of overall level of adaptive behaviour, ABC scores ranged from 47 – 76 (mean 62.83, SD 8.75), with the majority of participants scoring below the cut-off for

impaired adaptive functioning (ABC < 70). At the domain-level, communication scores ranged from 43 – 76 (mean 62.25, SD 11.46), socialisation scores ranged from 52 – 85 (mean 68.58, SD 11.46) and daily living skills scores ranged from 33 – 73 (mean 57.08, SD 14.58). Pearson's bivariate correlation identified a moderate, non-significant, positive correlation between ABC scores and age, $r = .439$, $N = 12$, $p = .153$, indicating that older individuals with TBRS were reported as having less impaired adaptive behaviour. Spearman's rank identified a strong negative correlation between ABC scores and ADOS-2 calibrated severity scores, $r_s = -.930$, $N = 12$, $p < .001$, indicating that more impaired adaptive functioning is associated with greater severity of autistic traits. Pearson's bivariate correlation identified a moderate, non-significant association between ABC scores and GCA scores, $r = .354$, $N = 12$, $p = .259$, indicating disparity between parent-reported adaptive behaviour and intellectual ability.

Discussion

The purpose of this study was to advance understanding of the cognitive and behavioural phenotypes associated with TBRS. Specifically, cognitive abilities, autistic traits and adaptive behaviour were assessed using standardised measures. This is the first in-depth characterisation of cognition and behaviour in TBRS. The findings identified that the mean GCA of the sample was 53 and the majority of participants had intellectual disability (n=15). Participants displayed a profile of better performance on the verbal tasks compared with the non-verbal reasoning ability tasks and spatial tasks, as well as relative strength with visuospatial memory, compared to visuoconstructive ability. Autistic traits were common, with eight participants scoring above the cut-off on the ADOS-2 and four participants scoring above the SRS-2 severe clinical cut-off. There was a negative relationship between severity of autistic traits and age, indicating that these traits were less pronounced in older individuals with TBRS. The majority of participants had impaired adaptive functioning and lower

intellectual ability and adaptive functioning were associated with greater severity of autistic traits.

Within the sample, intellectual ability ranged from severe intellectual ability to borderline intellectual functioning, indicating a range of ability within the TBRS population. The highest GCA score was 76, demonstrating that all of the participants had intellectual functioning below the population average. This has important implications for considering appropriate educational settings for individuals with TBRS as they are likely to require support with learning. The findings from the present study support the clinical description of intellectual functioning reported by Tatton-Brown et al., [2]. Furthermore, the findings indicate that intellectual ability is more impaired in TBRS than in Sotos syndrome, in which a mean GCA of 61 has been reported [12].

Participants displayed an uneven cognitive profile of better verbal ability compared with non-verbal reasoning ability and spatial ability. Furthermore, participants performed better on the verbal tasks and visuospatial memory task, compared with the non-verbal reasoning tasks and visuoconstructive ability task. This profile of performance is very similar to that observed in Sotos syndrome [12], indicating phenotypic overlap in relation to cognitive abilities in TBRS and Sotos syndrome, despite lower overall intellectual ability in TBRS.

Autistic traits were prevalent within the sample, with eight participants (44%) scoring in either the autism spectrum or autism classifications on the ADOS-2. In a systematic review and meta-analysis, prevalence estimates of ASD phenomenology were reported for a number of genetic syndromes, including 54% in Cohen's syndrome, 43% in Cornelia de Lange syndrome, 36% in Tuberous Sclerosis Complex (TSC) and 30% in males with Fragile X syndrome (FXS) [13]. Thus, the findings from the present study indicate that the prevalence of ASD in TBRS is high and perhaps more common than in TSC and FXS, which are often referred to as having a high prevalence of ASD [14, 15]. This has important implications for

screening for ASD within the TBRS population. Furthermore, it is possible that some individuals who have been diagnosed with ASD may meet the clinical criteria for TBRS, so genetic testing may be appropriate for determining whether these individuals have variants of the *DNMT3A* gene.

The relationship between age and severity of autistic traits was assessed and this identified a negative correlation between ADOS-2 calibrated severity scores and age, indicating that autistic traits were less pronounced in the older individuals with TBRS included in this sample. In particular, of the six adult participants, none scored above cut-off on the ADOS-2. This is consistent with the idiopathic ASD literature in which symptoms are reported to improve over time [16]. However, limitations of the present study include the use of a cross-sectional design and a relatively small sample, meaning that it is not currently possible to establish whether symptoms improve or worsen over time for individuals with TBRS. Thus, it will be important for future research to investigate relationships between age, behaviour and intellectual ability, particularly longitudinally, in a larger sample of individuals with TBRS in order to identify age-related changes and potential mechanisms underlying these changes.

As assessed using the Vineland-3, the majority of participants had impaired adaptive functioning. Relationships between intellectual ability, autistic traits and adaptive behaviour were explored and this revealed that greater severity of autistic traits was associated with lower intellectual ability and adaptive functioning but there was no significant association between intellectual ability and adaptive functioning. In genetic syndrome populations, it has been suggested that intellectual disability increases the presence of autistic behaviours as a result of difficulty with cognitive compensation [17]. As TBRS is associated with intellectual disability, typically in the moderate to severe range, this may account for the relationship observed between intellectual ability and severity of observed autistic behaviours. Overall,

the findings indicate that it will be important to screen for ASD within the TBRS population, particularly in individuals with moderate/severe intellectual disability.

In order to maximise recruitment, participants were recruited via the NHS and patient support groups in the UK and US. It is important to note that the majority of participants were recruited via patient support groups and it is therefore possible that recruitment bias may have affected the representativeness of the sample included in the present study. A further consideration is that the US participants completed the same cognitive assessment as the UK participants, which was standardised in the UK. Therefore, it will be important for future research to consider alternative recruitment strategies in order to ensure that studies are representative of the TBRS population.

In summary, the findings from the present study provide novel insights into the cognitive and behavioural phenotype associated with TBRS. Specifically, TBRS is characterised by intellectual disability, relatively better verbal ability, compared to non-verbal reasoning ability and spatial ability, impaired adaptive functioning and heightened prevalence of autistic traits. Overall, the findings have important implications for the management of TBRS and for identifying appropriate services and support which may be beneficial for this population.

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Figure Captions

Figure 1. Distribution of GCA scores.

Figure 2. Pirate plot of standard scores for the verbal ability, non-verbal reasoning ability and spatial ability clusters from the BAS3. Points represent the raw data, the bold horizontal lines depict the mean and the rectangles represent standard error of the mean.

Figure 3. Relationship between age and ADOS-2 calibrated severity scores (CSS).

Figure 4. Relationship between General Conceptual Ability (GCA) standard scores and ADOS-2 calibrated severity scores (CSS).