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ELECTRONIC LETTER

Behavioural phenotype of Bardet-Biedl syndrome

S Barnett, S Reilly, L Carr, I Ojo, P L Beales, T Charman

J Med Genet 2002;**39**:e76(<http://www.jmedgenet.com/cgi/content/full/39/12/e76>)

Bardet-Biedl syndrome (BBS), also known as Laurence-Moon-Bardet-Biedl syndrome (LMBBS), has long been regarded as an autosomal recessive condition but recent evidence now points to a more complex pattern of inheritance.¹⁻³ Prevalence rates range from 1 in 100 000 to 1 in 160 000,⁴⁻⁶ although there are communities in which BBS appears to be more common as a result of consanguinity.^{3,7} BBS is a heterogeneous genetic condition with six gene loci mapped to date: 11q13 (*BBS1*),⁸ 16q21 (*BBS2*),⁹ 3p12-13 (*BBS3*),¹⁰ 15q23 (*BBS4*),¹¹ 2q31 (*BBS5*),¹² and 20p12 (*BBS6/MKKS*).^{13,14} Three of these genes have now been identified, *BBS2*, *BBS4*, and *BBS6*.¹⁵ The phenotype of BBS varies from one family to another and within families, with only subtle phenotypic difference related to the different genes identified to date.^{16,17}

The accepted major criteria for diagnosis include retinal dystrophy, obesity, polydactyly, male hypogonadism, mental retardation, and renal dysfunction.³ In addition to the primary features, a number of associated secondary features, including neurological, speech, and language deficits, behavioural traits, facial dysmorphism, and dental anomalies have been identified.¹⁸ The motor problems identified include delay in acquisition of motor skills, unsteady gait, and ataxia.¹⁸ Language development is delayed in many cases, although this may be commensurate with overall intellectual function, and there are also reports of speech problems that include articulation difficulties, consonant omission or distortions, dysarthria and hypernasality.^{3,4,17-19} Developmental delay has been widely described as a major feature of BBS, with two-thirds to three-quarters of patients performing in the mental retardation range on formal testing^{4,18,20} (but see Green *et al*⁵ for an exception).

Disturbances in behaviour have been reported in some BBS patients. Traits reported include emotional immaturity, frequent volatile outbursts, inappropriate and disinhibited behaviour, inability to recognise social cues, and shallow affect.^{3,4,18} Some subjects are reported to show obsessive/compulsive tendencies and a preference for fixed routines. Both inattentiveness and docile, unwavering attention have been reported.¹⁸ However, to date no studies have systematically studied the behavioural phenotype of patients with BBS.

There is increasing recognition that genetic disorders may have specific effects on behaviour.²¹⁻²⁴ Behaviours that are common and specific to a genetic disorder are assumed to share an underlying genetic origin and have been termed behavioural phenotypes. It is generally accepted that such behaviour is neither unique (nor necessarily universal) to each genetic syndrome but rather that there is a heightened probability or likelihood that subjects with a syndrome will show a particular behaviour.^{21,25} Recent advances have been made in the elucidation of the behavioural phenotype of several genetic syndromes, including Rett syndrome,^{26,27} Smith-Lemli-Optiz syndrome,²⁸ and FG syndrome.²⁹ The recognition of behavioural phenotypes in genetic syndromes is important in aiding earlier recognition and diagnosis. This may be especially important in a syndrome such as BBS where the complex, multi-faceted presentation means that diagnosis is often considerably delayed.¹⁸ Recognition of behavioural phe-

Key points

- Although behavioural characteristics, including disinhibited behaviour, an inability to recognise social cues, and obsessive and compulsive tendencies, have been noted in patients with Bardet-Biedl syndrome (BBS), to date no studies have systematically studied the behavioural phenotype.
- Parents of 21 children with BBS seen for a multidisciplinary clinical assessment completed standardised measures of behaviour.
- Children with BBS showed increased levels of internalising problems including feeling withdrawn and anxious/depressed. They also had raised levels of social, thought, and attention problems. A significant minority scored in the clinical range on a measure of autistic symptoms, although none met clinical diagnostic criteria. The children also had increased scores on a measure of repetitive behaviour and the majority was reported to be obsessive by their parents.
- These findings indicated considerable clinical need that had been unmet in many families. Questions for future research include whether behaviour changes with age or differs according to genetic mutation.

notypes is also important for clinical and educational management, and to aid parental understanding of, and adjustment to, their child.

The present paper is the first to attempt to describe systematically the behavioural phenotype of a series of children with BBS using standard behavioural measures.

METHODS

Setting

The children were seen at the neurodisability assessment clinic at Great Ormond Street Hospital for Children NHS Trust, London, UK. Ethical approval was obtained from the joint Research Ethics Committee of Great Ormond Street Hospital for Children NHS Trust and the Institute of Child Health.

Design and participants

Fifty-two children with a diagnosis of BBS were identified through the LMBBS family support group and the clinical genetics department at Guy's Hospital, London, UK. The parents of all children were invited to join the study and 26 agreed to participate (50%). Twenty-one children (11 males, 10 females) were seen within the time frame of the study (40%). No data were available to test the representativeness of the sample seen compared to the sample invited to participate. There were five sib pairs (10 children) in the study group. None of the children in this study was from a consanguineous marriage. At assessment the children were between age 3 years 7 months and 18 years 0 months (mean 9 years 11 months, SD 51 months). In all subjects a diagnosis of BBS was

confirmed by application of diagnostic criteria^{3 18} after having been referred with a tentative diagnosis by their local paediatrician.

Measures

IQ

Nineteen children completed a standardised measure of intelligence (IQ), the Wechsler Intelligence Scale for Children (WISC-III-UK),³⁰ or the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-R-UK),³¹ depending on the age of the child. A short form version of each test was administered and Full Scale, Verbal, and Performance IQ scores were pro-rated. The short form format followed that recommended by Kaufman *et al*³² and included the Similarities and Arithmetic verbal tests and the picture Completion and Block Design performance tests. The youngest child was unable to complete a formal assessment. Three other children only attempted verbal subtests owing to visual acuity impairment.

Behavioural measures

The parents of all 21 children completed the Achenbach Child Behaviour Checklist (CBCL).³³ This well validated scale measures a range of externalising (for example, attention problems, aggression) and internalising (for example, anxiety, social, somatic) behaviour problems. Standardised scores are expressed as T scores (population mean 50, SD 10). The scale provides cut offs for borderline (>67) and clinical levels (>70) of behavioural disturbance.

Parents also completed the Childhood Routines Inventory (CRI).³⁴ This scale measures ritualistic, repetitive, and compulsive-like behaviour. Normative data are only available on typically developing children up to the age of 72 months. However, unpublished data from a large sample of children aged 5 to 18 years with Prader-Willi syndrome (n=75) and childhood autism (n=90) provide appropriate comparison data on children of similar age and IQ to the BBS sample.

Twelve parents also completed the Childhood Autism Rating Scale (CARS).³⁵ This scale measures social, communication, and repetitive impairments characteristic of children with autism. The scale provides cut offs for non-autistic (15-29), mild to moderate (30-36), and severe (>37) levels of autistic behaviour.

Using a structured interview, the parents were also systematically asked about behaviour that they found problematical in terms of management at home or at school.

RESULTS

IQ

The mean Full Scale IQ was 65.7 (n=16, SD 16.2, range 42-108), mean Verbal IQ was 66.3 (n=19, SD 13.5, range 46-93), and mean Performance IQ was 65.7 (n=16, SD 21.6, range 46-127). Only three children (17.6%) had Full Scale IQs within the average range (≥ 80). Eleven children had Full Scale IQs in the mental retardation range (<70), the majority (n=10) in the mild mental retardation range (50-69).

Behavioural measures

The pattern of scores on the CBCL is summarised in table 1. In terms of externalising behaviour, the group mean score was 53.2 (SD 10.8) and only one child fell above the cut off for clinical significance with no additional children falling above the borderline cut off. In terms of internalising behaviour, the mean score was 62.8 (SD 11.2). Five children fell above the cut off for clinical significance and a further two children above the borderline cut off. The difference between internalising and externalising behaviour was significant (paired *t* test, *t* (df=20) = 5.17, *p*<0.001). In terms of pattern of scores on the individual subscales, relatively high scores were also obtained on scales that do not fall into either the externalising or internalising factors (social problems, thought problems, attention

Table 1 Summary of scores on the CBCL

	Mean (SD)	No > clinical cut off (%)	No > borderline cut off (%)
Total problem score	62.6 (10.9)	5 (23.8%)	6 (28.6%)
Internalising score	62.8 (11.2)	5 (28.6%)	7 (33.3%)
Externalising score	53.2 (10.8)	1 (4.8%)	1 (4.8%)
Withdrawn ^l	62.2 (12.1)	3 (14.3%)	7 (33.3%)
Somatic problems ^l	65.2 (8.7)	5 (28.6%)	8 (38.1%)
Anxious/depressed	60.1 (11.8)	4 (19.0%)	6 (28.6%)
Social problems ^l	67.9 (11.3)	8 (38.1%)	12 (57.1%)
Thought problems	64.4 (12.5)	6 (28.6%)	10 (47.6%)
Attention problems	65.6 (12.4)	8 (38.1%)	10 (47.6%)
Delinquency ^e	54.0 (5.2)	0 (-)	0 (-)
Aggressive ^e	56.9 (9.0)	1 (4.8%)	2 (9.5%)

E=externalising subscale, I=internalising subscale.

problems). Notably, very few children scored in the clinical or borderline clinical range on the aggressive and delinquency subscales.

Only 12 parents completed the CARS measure. The mean score was 28.3 (SD 8.2). Two of the 12 children (16.7%) scored in the mild-moderate autism range and a further two children (16.7%) scored in the severe autism range.

The parents of all 21 children completed the CRI. The mean score was 8.7 (SD 4.8). This compares to the mean score (SD) of 7.0 (4.6) for typically developing 72 month old children,³⁴ 13.1 (5.1) for children with Prader-Willi syndrome, and 14.0 (4.1) for children with autism (Charman *et al*, unpublished data).

The structured parental interviews showed further behavioural characteristics of the sample. The parents of 19 of the 21 children (90.5%) reported that their child was socially and emotionally immature. Seventeen children (80.9%) were reported to have obsessions, 12 (57.1%) to prefer routines, 12 (57.1%) to like playing the same game over and over, nine (42.9%) to like collecting things, and 13 (61.9%) to talk to themselves.

DISCUSSION

In terms of whether a distinctive behavioural phenotype was seen in BBS, a number of potentially important findings emerged. The overall level of behavioural disturbance as measured by the CBCL was relatively high, with between one quarter and one half of the sample showing clinical or borderline clinical levels of disturbance across the subscales. Notably, clinical levels of externalising behaviour including aggression and delinquency were rarely reported. In contrast, internalising problems including withdrawn, somatic, and anxious/depressed mood were frequent, as were problems with social behaviour, thought disturbance, and attention. Thus, the behavioural difficulties evidenced by children with BBS is different from that seen in the more common neuropsychiatric disorders ADHD and conduct disorder.³³ Although many groups of children with mild mental retardation show increased levels of disturbed behaviour on the CBCL, neither the internalising nor the externalising was correlated with IQ in the present sample (*r*=-0.20 and *r*=-0.31, respectively, both *p*>0.10). The absolute levels of disturbance on the CBCL are similar to that found in samples of children with other genetic disorders (for example, Prader-Willi syndrome),³⁶ although in other genetic syndromes behavioural disturbance on the CBCL appears to be less common (for example, VCFS).³⁷ The identification of a relatively specific profile of behavioural disturbance on the CBCL (a picture dominated by high internalising, social and thought problems, but low levels of externalising problems) is important for the clinical issue of management and advice to parents. In the present sample

much of this clinical need was unmet and few families had received expert help about behavioural management.

Data on the CARS was available on only half the sample, but four of 12 parents who completed the measure indicated a significant level of autistic-like symptoms. One child scored 45.5 on the CARS, well into the "severe autism" range of the scale. However, clinical assessment of this child, including the use of the structured diagnostic instrument, the Autism Diagnostic Interview-Revised (ADI-R),³⁸ showed that they did not meet clinical criteria for autism. This child scored above the cut off on the social reciprocity and repetitive behaviours and stereotyped patterns dimensions but not on the communication dimension. No consistent pattern emerged in terms of CARS items that were endorsed more frequently in the sample. That is, while some children scored very low on social items and high on repetitive behaviour items, others showed the opposite pattern.

On the CRI, the present sample showed increased levels of routines and rituals compared to typically developing children (in whom by the age of 72 months CRI are beginning to decline), albeit lower than that seen in samples of children with Prader-Willi syndrome and autism (Charman *et al*, unpublished data). This corroborates published reports of obsessive, compulsive ritualistic behaviour in some patients with BBS.¹⁸ Parents also reported high levels of preference for routines and similar activities and these did impact on family life in some cases. For example, one boy was obsessed with anything to do with wrestling. He compulsively collected toys, posters, pictures, or anything to do with the subject. Another was rigid about timing of meals and was obsessively neat and tidy. He cannot cope if anything is out of place and will only do a small selective number of puzzles over and over again. However, the social impairments and repetitive behaviours reported from the CARS and the CRI were not associated with IQ or language ability within the sample.

Atypical behaviours are associated in general with IQ, and are found more commonly in genetic syndromes, particularly those in which mental retardation is common.³⁹⁻⁴⁰ However, there is increasing evidence that genetic syndromes can show specific behavioural phenotypes, alongside their primary medical and developmental features.^{26-29 37} The present findings suggest that further examination of the behaviour seen in patients with BBS is warranted. Particular questions of interest include how such behaviours change with age (the current sample included children only) and IQ, and whether they differ according to genetic mutation.² Understanding the behavioural phenotype of BBS is also important for a comprehensive approach to management and service provision for these patients and their families.

The present paper is a first step towards the elucidation of the behavioural phenotype in children with BBS.

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