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Behavioural phenotype in Börjeson-Forssman-Lehmann syndrome

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Abstract

Background Börjeson-Forssman-Lehmann syndrome (BFLs) is an X-linked inherited disorder characterised by unusual facial features, abnormal fat distribution and intellectual disability. As many genetically determined disorders are characterised not only by physical features but also by specific behaviour, we studied whether a specific behavioural phenotype exists in BFLs.
Methods We studied in detail the behaviour of four molecularly proven BFLs patients, and reviewed available literature on BFLs specifically for behavioural characteristics.
Results Behaviour in persons with BFLs is in general friendly, but can be challenging with externalising and thrill-seeking features. Social skills are good. However, variation among patients is wide. Three patients from a single family showed expressed hypersexual behaviour. This was not present in other patients.
Conclusion In BFLs a specific behavioural phenotype exists and in behaviour general is challenging besides a friendly habit. Within single families more problematic behaviour may occur. Further behavioural and molecular analysis of a larger group of patients is warranted to determine whether a genotype-behavioural phenotype correlation exists.

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Keywords behavioural disorder, behavioural phenotype, Börjeson-Forssman-Lehmann syndrome, genotype-phenotype, intellectual disability, *PHF6*

Introduction

Many genetically determined syndromes are characterised not only by their physical phenotype, but also, and sometimes especially, by a typical behavioural pattern. Such behavioural problems can have a major impact on the lives of the patients, families and caretakers. Awareness of specific behaviour can help in early recognition of syndromes. For all involved in the care of the patients, knowledge of the behaviour facilitates acceptation and may enhance the development of management strategies. Furthermore, knowledge regarding specific behaviour provides not only information with respect to the syndrome involved, but may also provide more insight on the origin of behaviour in general.

Börjeson-Forssman-Lehmann syndrome (BFLs, OMIM #301900) is an infrequently reported entity first described in 1962 by Börjeson, Forssman and Lehman in three patients with a cognitive delay and remarkable physical appearance (Börjeson *et al.* 1962). At that time the authors mentioned as the main features of the syndrome severe intellectual disability (ID), obesity, microcephaly, a 'coarse' face with deeply set eyes and large ears with fleshy

lobes, and decreased height (Börjeson *et al.* 1962; Brun *et al.* 1974). Later on it became clear that the clinical picture of the BFLs was much more variable, including mild cognitive delay in stead of an expressed delay and a normal head circumference or macrocephaly in stead of a microcephaly, and that physical features could change over time (Turner *et al.* 2004).

Börjeson *et al.* (1962) already considered the syndrome to follow an X-linked recessive pattern of inheritance. Linkage studies confirmed localisation on the X-chromosome at Xq27 (Mathews *et al.* 1989; Turner *et al.* 1989), and in 2002 mutations were identified in the *PHF6* gene (Lower *et al.* 2002). This is a zinc finger gene that may be involved in transcription (Lower *et al.* 2002) and cell growth and proliferation (Gécz *et al.* 2006). The first cellular expression study of the *PHF6* gene, which lays a base for further functional studies, showed that cell types that express *PHF6* genes strongest during prenatal and postnatal development are found in the central nervous system, anterior pituitary gland, the primordial of facial structures and the limb buds, corresponding to the clinical features of BFLs (Voss *et al.* 2007).

We had the opportunity to study four persons with BFLs. As many (X-linked) ID syndromes are known to be associated with a specific behaviour (Raymond & Tarpey 2006), we studied their behaviour in more detail and compared the results with the pertinent literature on behaviour in BFLs.

Methods

Case studies

We studied four men with BFLs, all diagnosed because of classical physical features.

Three of them belong to one family (Fig. 1). This family was retrieved from an institute specifically dealing with persons with mild IDs and expressed behavioural disorders. The fourth male came to our notice through a call to the Dutch clinical genetics centres. In all patients the diagnosis was confirmed molecularly. Data on exact physical characteristics and molecular results have been published in part elsewhere (Crawford *et al.* 2006: case 1 is present case 3; case 2 is present case 4). From each case medical reports and earlier psychological reports were retrieved, and parents and close caretakers were interviewed, with emphasis on emotional development and behaviour.

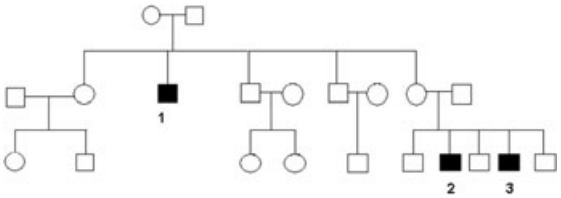

Figure 1 Pedigree of family 1 with cases 1, 2 and 3 indicated.

We used the 'Adult Behavioural Checklist' (ABCL) as this instrument evaluates adaptive functioning, substance use and behavioural problems, expressed in both an ABCL problem scale and a Diagnostic and Statistical Manual of Mental Disorder (DSM) oriented problem scale scored on a checklist of 134 items. The ABCL problem scale scores on a range of internalising to externalising problems (anxious, depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behaviour, rule-breaking behaviour, intrusiveness). The DSM-oriented problem scale indicates DSM disorders (somatic problems, personality problems and other problems) (Achenbach & Rescorla 2003). This corresponds to the DSM-IV axis I disorders (Tenneij & Koot 2007). Scores are expressed in being normal, in the borderline clinical range or in the clinical (high) range of psychopathology. The ABCL has been validated for use in intellectually disabled persons with severe challenging behaviour (Tenneij & Koot 2007).

Written informed consent for the testing and publication was obtained from each of the parents or legal representative. The procedure was explained verbally to the patients, and each patient gave verbal consent. As a family with three affected members might be easily identifiable in a rare condition like BFLs the exact information published in this reports and the implications of publication were discussed in detail with this family, and they provided consent to publish this.

Literature review

A literature search was undertaken by using the search terms 'Börjeson-Forssman-Lehmann

syndrome' and 'PHF6' in the Pubmed database. Limitations used were accepting studies in the languages Dutch, English, French and German only. No other exclusion criteria were used. All literature obtained was systematically and independently evaluated by two authors (C.D.W. and F.V.D.). All references provided in the literature were hand searched for other articles not retrieved in the Pubmed search. Articles were reviewed with specific attention to descriptions of behaviour, and also data on cognitive development and institutionalisation were gathered. Two papers of which has been suggested that the diagnosis BFLs was wrongly made (Veall *et al.* 1979) or very uncertain (Baar & Galindo 1965) were not included (Ardinger *et al.* 1984; Preus 1984). In total data on 51 patients were gathered.

Case studies

Case 1

This male was born in 1947 after a normal pregnancy. He developed slowly from early on and needed special education. He was institutionalised at the age of 25 years because of his abnormal behaviour. He had a mild to moderate ID (IQ 55).

As a child he was said to be a friendly boy, who was no burden for the family. In his adolescence he started to behave sexually aberrant with exhibitionism. Furthermore, he was very hyperactive. He liked to destroy objects, like his glasses. At age 28 years he was prescribed libido inhibitors because of exhibitionism. However, impulsive aggression and hypersexual behaviour continued throughout his life despite him being hypogonadal. His behaviour showed a relation with discomfort elsewhere, such as stress at work or changing staff at the institution. At the age of 50 he was found masturbating publically. During his life he has been treated with a combination of antidepressants (clomipramine), antipsychotics (pipamperon, haloperidol) and benzodiazepines (alprazolam). At age 53 he was admitted to a psychiatric hospital because of a psychosis with regressive behaviour and self-injurious behaviour. Since then periods of severe behavioural problems alternated with periods in which he was well tempered and friendly. He could be compassionate and had a nice sense of humour, but had a low self-esteem. He never had a (sexual) relation, and neither seemed to long for it.

ABCL

The scale indicated anxiety and depression problems, withdrawn behaviour, somatic complaints, attention problems and problems with aggression. There was no substance abuse. On the DSM-oriented scales, the scores for somatic problems and avoidant personality problems were in the high range. He showed especially high scores for hyperactivity-impulsivity (Table 1).

Table 1 Adult Behavioural Checklist (ABCL) scores in the presently studied patients

Case	ABCL internalising problems	ABCL externalising problems	Somatic problems	Aspects of personality problems	Other problems
I	C	C	C	Avoidant (C)	Depressive (C), attention deficit and hyperactive (C)
II	N	B	N	Antisocial (C)	N
III	C	C	B	Avoidant, antisocial (C)	Depressive, anxious, attention deficit and hyperactive (C)
IV	C	C	B	Antisocial (B)	Depressive, attention deficit and hyperactive (C)

C, clinical range (pathological): scores above 97th percentile; B, borderline clinical range: scores in 93rd to 97th percentile; N, normal range: scores below 93rd percentile.

Case 2

This male, a nephew of case 1 (Fig. 1) was born in 1977 after an uneventful pregnancy. His behavioural problems started at age 2 with biting and kicking his brother. At the age of 3, he was noted to have a developmental delay. He became hyperactive and did not obey his parents. He went to a special children's day care centre at 4 years, where he showed the same behaviour but was also noted to have good social skills. Because of his behaviour he was admitted in an institution for children with ID when he was 6 years old. He remained hyperactive and longed for attention from staff continuously. Between age 10 and 19 behavioural problems included arson, mistreating animals and stealing.

At age 20, he moved to a closed institution because he needed continuous supervision and extremely strict rules to prevent him from progressive unacceptable behaviour (especially stealing and hurting animals). He suffered from paraphilia, as he became sexually stimulated by children's feet, hairy legs and woollen socks. He worked in a special work provision centre, performing easy tasks. He was friendly and liked social contacts, although sometimes this was inappropriately expressed. He was found to have a moderate ID (IQ 48).

ABCL

On the ABCL problem scale he scored high on rule-breaking behaviour. His total scores on externalising behaviour were in the borderline clinical range. He did not have a partner, and there was no substance abuse. The DSM-oriented scales showed aspects of an antisocial personality disorder (Table 1).

Case 3

This male is the proband in his family (mutation c.940A→G/p.I314V). He is the brother of case 2 (Fig. 1) and was born in 1983 after a normal full-term pregnancy. Initially he suffered from expressed feeding problems including forceful vomiting for which he was hospitalised in the first week after birth. His motor development was slow and he started walking at age 2.3 years and talking at the age of 4. He was small for his age (<P3) and struggled with obesity from early on. He was described as an overactive, hyperkinetic toddler, who was not able to play on his own. At a very young age he started to show challenging behaviour, including stealing, pyromania and aggression towards his brothers. Because of this he was institutionalised when he was 8 years old.

In the institution the problems of kleptomania and pyromania remained. He also suffered from sexual disinhibition. He continuously kept seeking attention from the staff in both positive and negative ways. He experienced problems in keeping friends. At age 18 he had small genitalia and normal pubic hair. His testosterone and sex hormone binding globulin levels were in the borderline normal and normal range (3.85 and 17.4 nmol/L respectively). At this age he was convicted because of illicit sexual acts with other more vulnerable residents including exhibitionism, lying naked on undressed victims and touching genitals or buttocks with his genitals, but without intercourse. He suffered from paraphilia, becoming sexually stimulated by wet napkins, towels, children's feet and pictures of children. At age 20 he was admitted to a closed psychiatric hospital for treatment. Here it was concluded that he lacked the capacity to develop compassion for victims and to restrict his own impulses. Libido inhibition by cyproteron had no effect, but triptoreline diminished his urge for sexual activities. Except for his frequent rule-breaking behaviour he was a very open, friendly and easy-going boy, and speaking about his unacceptable behaviour with little shame and regrets. At present he lives in a closed ward, which is part of an institution for people with IDs. He has a mild ID (IQ 61).

ABCL

On the ABCL problem scales he scored high on thought problems, withdrawn, somatic complaints, attention problems, aggressive behaviour and rule-breaking behaviour. Furthermore, there were symptoms of anxiety, depression and intrusive behaviour. He did not have a partner, and there was no substance abuse. He scored high on multiple problems on the DSM-oriented scales. Especially his inattention and antisocial personality problems were of concern (Table 1).

Case 4

This male is the proband and only affected male in his family (mutation c.2T→C/p.M1T). He was born in 1989 after an uneventful pregnancy. At the age of 6 months he was found to be hypotonic and to have a slow motor development. At 1 year he suffered form viral meningitis, with slight paresis of the left side of his body, which disappeared after recuperation. His delayed development urged for special education. His behaviour became increasingly difficult, which led to admission in a psychiatric hospital at the age of 10 years. Observation showed him to be a friendly and cheerful boy, who made contacts easily, but had inappropriate contact to strangers. He could also become verbally and physically aggressive, showing impulsive behaviour, and lack of attention and motivation. He suffered from stereotypical behaviour. He was diagnosed as having a pervasive developmental disorder. He was found to be vulnerable and attentive. On physical examination he had the characteristic features of BFLs (short stature, deep-set eyes, large ears, lower abdominal obesity) and a small penis and testes. At age 18 formal psychological testing showed a moderate ID (IQ 49).

ABCL

He experienced anxiety and depression problems, somatic complaints, thought problems, attention problems, aggression, rule-breaking behaviour and intrusiveness. His total problems, internalising and externalising scores were all in the clinical range. He did not have a partner, and there was no substance abuse. On the DSM-oriented scales the scores on depressive symptoms and attention deficit hyperactivity (both inattention and hyperactivity-impulsivity) were in the clinical rang; the scores on somatic problems and antisocial personality problems were in the borderline clinical range (Table 1).

Literature review

Cognition

In 40 of the 51 patients with BFLs comments were made on cognitive functioning. Four had profound ID and 14 had severe ID. Most patients ($n = 23$) were in the mild to moderate ID range (Table 2). In one study (Turner *et al.* 2004), ID was described in childhood and remained present as learning difficulties during adolescence. Adults all required some degree of supervision (Weber *et al.* 1978; Ardinger *et al.* 1984; Turner *et al.* 2004). Institutionalisation usually occurred at a young age (Ardinger *et al.* 1984).

Intellectual functioning in heterozygous females has been described from normal to moderate ID (Börjeson *et al.* 1962; Robinson *et al.* 1983; Ardinger *et al.* 1984; Dereymaeker *et al.* 1986; Petridou *et al.* 1997; Kubota *et al.* 1999; Baumstark *et al.* 2003; Turner *et al.* 2004; Valleé *et al.* 2004; Crawford *et al.* 2006). The frequency of significant learning problems was estimated to occur in 20% (Turner *et al.* 2004).

Behaviour

The various reported behavioural characteristics are tabulated in Table 2. Most patients were studied at the time of referral for genetic counselling. This may explain why most papers focussed on physical appearance and less attention was paid to behaviour. In general, behaviour varied from hyperactivity, expressed aggression, self-injury and difficulties to control behaviour, to friendly, pleasant and cooperative (Dereymaeker *et al.* 1986; Turner *et al.* 1989; Kubota *et al.* 1999; Turner *et al.* 2004; Valleé *et al.* 2004; Visootsak *et al.* 2004). In two studies sexual behaviour was mentioned: Robinson *et al.* (1983) reported absence of erections and ejaculations, and Turner *et al.* (2004) mentioned absence of sexual activity in men, although one had a relationship.

One study compared the behaviour in BFLs with the behaviour in Prader–Willi and Klinefelter syndrome. Compared with these entities, men with BFLs showed significantly fewer maladaptive internalising and externalising behaviour, and scored low on anxiety, attention-seeking behaviour, frustration and vengeance. The BFLs group scored higher than Prader–Willi and Klinefelter syndrome patients on motivations for helping others, social contacts and sexuality (Visootsak *et al.* 2004).

In females some characteristics of the male BFLs behavioural phenotype can occur (Crawford *et al.* 2006). Some females were reported with bad temper, easy agitation, anxious, hyperkinetic,

Table 2 Behaviour and cognitive functioning in males with Börjeson-Forssman-Lehmann syndrome described in literature

Study	Case	Mutation	Age (years)	Cognitive functioning	Behaviour	Institutionalisation (age and reason of institutionalisation)
Börjeson *et al.* 1962	III-3	c.1024C→T/p.R324X	37	SID,AS	Challenging	Yes (at 'young age')
	IV-2		20	PID,AS	Challenging	Yes (at 'young age')
	IV-3		16	SID	Challenging	Yes (infant)
Weber *et al.* 1978	I		28			Yes (11)
Robinson *et al.* 1983	III-3		27			
Ardinger *et al.* 1984	A1		23	PID		Yes (8, because of PID)
	A2		15	SID		Yes (5)
	B3		24	SID		
	B4		40			Yes
	B5		27	PID		
Dereymaeker *et al.* 1986	I		11	SID	Challenging	Yes
Mathews *et al.* 1989 (also described in Lower *et al.* 2002 and Turner *et al.* 2004)	3	c.686A→G/p.H229R	40, 24, 27	2 SID–PID, 1 PID		
Turner *et al.* 1989 (also described in Lower *et al.* 2002 and Turner *et al.* 2004)	III-14	c.1024C→T/p.R324X	42		Challenging	Yes ('late teens', because of behaviour)
	III-17		18		Friendly	
	III-19		(Died at 2 8/12 years)			
	IV-10		15	MilD	Friendly, social	
	IV-4		14			
	V-2		2			
	V-3		1			
Kaplinsky *et al.* 2001	I		19		Challenging	
Lower *et al.* 2002	F1	c.1024C→T/p.R324X				
	F2	c.296G→T/p.C99F				
	F3	c.700A→G/p.K234E				
	F4, F8	c.134G→A/p.C45Y				
	F5	c.686A→G/p.H229R				
	F6	c.2T→C/p.M1T				
	F7	c.IVS2-8A→G/p.M46fs				
	F9	c.22A→T/p.K8X				
Lower *et al.* 2004	1, 2	c.1024C→T/p.R324X	15	SID		
	3	c.1024C→T/p.R324X	16			

Birrell 2003 (also described in Lower *et al.* 2002 and Turner *et al.* 2004)	sib A	c.22A→T/p.K8X	Infant					
	sib B		Infant					
Baumstark *et al.* 2003	4	c.999_1001delTGA/p.D333del	16–18	SID		Yes		
Valleé *et al.* 2004	I (family 1)	c.769A→G/p.R257G	19	SID	Challenging			
	III-1 (family 2)	c.IVS2-8A→G/p.M46fs		MilD–MoID				
	III-2							
Turner *et al.* 2004 (included patients described previously by Turner *et al.* 1989, Mathews *et al.* 1989 and Lower *et al.* 2002)	25		Childhood to adolescence	MilD–MoID	Most friendly, social			
	25		Adult		4: challenging	4 institutionalised (behaviour), others in group homes or parents home (because of ID)		
Visootsak *et al.* 2004 (same as Lower *et al.* 2002)	10 (2 families)	c.134G→A/p.C45Y and c.IVS2-8A→G/p.M46fs	Adult	MilD–SID	Friendly, social			
De Winter	I	c.940A→G/p.I314V	60	MoID	Challenging, friendly	Yes (25, behaviour)		
	2		30	MoID	Challenging, friendly	Yes (6, behaviour)		
	3		24	MilD	Challenging, friendly	Yes (8, behaviour)		
	4	c.2T→C/p.M1T	18	MoID	Challenging, pervasive developmental disorder	Yes (10, behaviour)		

Spaces in this table are left empty when no information was available.
MilD, mild intellectual disability (IQ 50–69); MoID, moderate intellectual disability (IQ 35–49); SID, severe intellectual disability (IQ 20–34); PID, profound intellectual disability (IQ below 20); AS, absent speech.

emotionally labile and hypersensitive to sensory input (Börjeson *et al.* 1962; Petridou *et al.* 1997; Crawford *et al.* 2006). However, most functioned well and independently in society (Turner *et al.* 2004; Valleé *et al.* 2004).

Discussion

We studied the behaviour in BFLs. Four own mild to moderate intellectual disabled patients showed a broad spectrum of severe externalising behaviour of which sexually deviant behaviour was extremely disturbing and lead to legal consequences. Internalising problems included anxiety and depression. All four males presented as otherwise friendly and sociable persons. The present family with three affected persons was retrieved from an institute specifically dealing with persons with mild IDs and expressed behavioural disorders. This may have biased our findings towards more severe problem behaviour, as well as the fact that three out of four patients came from one family.

Affected males from literature showed in general a mild, moderate or severe ID, and rarely a profound delay with absence of speech. All men required some degree of supervision: some lived with their parents, but most lived in institutions already from early age on. Early institutionalisation usually occurred because of the challenging behaviour, with a few exceptions where the severity of ID was the reason for institutionalisation. This indicates that the behaviour problems arose because of the syndrome, and not as a consequence of the institutionalisation. The most commonly noted behaviour trait was challenging behaviour, which was usually expressed in aggression towards others. On the other hand, a considerable number of patients were noted to be remarkably friendly and exhibit a social behaviour. The information about behaviour described in published papers is too limited to allow any conclusion on age trend. Furthermore, although there is a tendency for an intra-familiar resemblance of behavioural patterns and more variable behaviour between various families, data are insufficient for a firm conclusion in this respect as well. It may be that the nature of the behavioural problems correlates here with the localisation and type of mutation. It would be interesting to know whether such a correlation would exist between the hypersexual behaviour and the mutation found in case 1, 2 and 3 (Crawford *et al.* 2006). However, no other patients are published with this mutation, and in general only few patients with a molecularly proven diagnosis are available.

The four patients in this study all had characteristics fitting hypogonadism, although measured testosterone level in one patient was normal. This means that if a hypopituitarism is present, this can only be partial in this patient. A hypersexual behaviour might also be explained as obsessive in nature but the patients did not have high scores for such obsessive behaviour on the ABCL problem scale. Treatment with libido-inhibiting medication, in combination with increased supervision, suppressed the sexual needs in one of them, but not completely. Which may point to a both biological and behavioural origin.

The mutation in the *PHF6* gene in BFLs is expressed in the central nervous system during prenatal and postnatal development (Voss *et al.* 2007), which may lead to a specific behavioural phenotype. However, the exact function of the *PHF6* gene remains unknown. The hypogonadism might contribute to the problem behaviour as other entities that go along with ID and hypogonadism, such as Klinefelter syndrome, are known to be associated with specific behavioural traits. These range from impulsivity, frontal executive problems, attention deficit and socially inappropriate behaviour to marked shyness (Geschwind *et al.* 2000) and autistic traits (Van Rijn *et al.* 2008). In part this resembles the presently reported behaviour in BFLs, but differences exist: especially men with Klinefelter syndrome are more likely to have problems with social contact, whereas men with BFLs have much better social skills (Visootsak *et al.* 2004).

We conclude that behaviour in persons with BFLs is in general challenging besides a friendly habit, and within single families more problematic behaviour such as hypersexuality may occur. This may point to a specific genotype-behavioural phenotype correlation, but currently insufficient information in this respect is available. It is important that persons with BFLs are studied both with respect to their behaviour as to the genotype, as this may have important consequences for adequate

counselling of future families and might provide further insight in causes of hypersexual behaviour in general.

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