bbs uk

Bardet-Biedl Syndrome UK

Medical Information Booklet

The Origins of **Bardet-Biedl Syndrome**

The earliest formal description of Bardet-Biedl syndrome was provided in a paper published by John Zachariah Laurence, a 19th century ophthalmic surgeon based in London, and his then house-surgeon, Robert Moon (1845-1914), whose own father, William, invented one of the first raised alphabets for the blind.

There was no further mention of the Syndrome until 1920, when Georges Bardet submitted his MD thesis on hypothalamic obesity.

In 1922, Artur Biedl published a short independent account of two siblings with retinitis pigmentosa and polydactyly. Neither Bardet nor Biedl made any reference to Laurence and Moon's paper previously published in Ophthalmic Review, a publication which by then was no longer in circulation.

John Zachariah Laurence

Robert Moon

Artur Biedl

It was in 1925, when Solis-Cohen and Weiss 'rediscovered' the paper by Laurence and Moon and went on to consider these conditions to be the same. Until the 1980s, the Syndrome was known as LMBS, Laurence-Moon-Biedl syndrome, with no reference to Bardet.

More recently this condition has been split once again on the basis of clinical features, into the Laurence-Moon and Bardet-Biedl syndromes. Bardet-Biedl syndrome represents by far the majority of published cases and is now the more generally recognised term within the medical and scientific community.

Contents

Acknowledgement

This booklet has been funded by NHS England and produced by Bardet-Biedl Syndrome UK, Registered Charity No. 1181244.

It is important to note that there are many symptoms and conditions listed within this booklet that may affect those who have BBS, but they will not necessarily affect everyone and the severity of individual symptoms can vary greatly among those affected.

Our grateful thanks go to the clinicians from the BBS specialist clinics teams at Queen Elizabeth Hospital, Birmingham; Birmingham Children's Hospital; Great Ormond Street Hospital, London and St Thomas' Hospital, London for their contribution to this publication.

Our heartfelt thanks also go to the generous individuals living with BBS who contributed to this booklet; their guidance and personal perspective have been invaluable.

www.bbsuk.org.uk

There's no-one else who knows our child like we do, and we have to take this on board and make ourselves heard. We have to be an equal partner with medical, social and educational teams and believe that we're an equal partner. We have to use the resources available to us to give our children the confidence, courage and self-esteem to know that they have a great deal to contribute to this world.

Parent

Introduction

It is estimated that Bardet-Biedl syndrome (BBS) affects approximately 600 people in the UK. Many GPs, doctors and health professionals will not have come across BBS before and there are many who have not heard of the Syndrome.

BBS is a rare, recessively inherited ciliopathy (see later section explaining the term 'ciliopathy') which affects approximately 1 in 100,000 babies born. Features of the Syndrome include rod-cone dystrophy, a progressive eye disorder that leads to blindness, characterised by tunnel vision and night blindness; obesity; renal abnormalities; developmental delay; speech and language difficulties; extra fingers and/or toes and learning difficulties. Not all the features are always present in those diagnosed as having BBS and each one can vary in severity and appearance. The variability in presentation and severity of the Syndrome, together with the rarity of the condition can lead to delayed diagnosis and a lack of adequate local health care.

This booklet is aimed at the medical and healthcare professionals involved in the care of BBS patients to promote a greater understanding of the Syndrome and the recommended care pathway. The information has been provided and checked by the BBS specialist clinics team and, where possible, is supported by research and published articles. A bibliography of references and useful publications can be found at the back of the booklet. For further information, contact: **admin@bbsuk.org.uk**

Diagnosis and Genetics

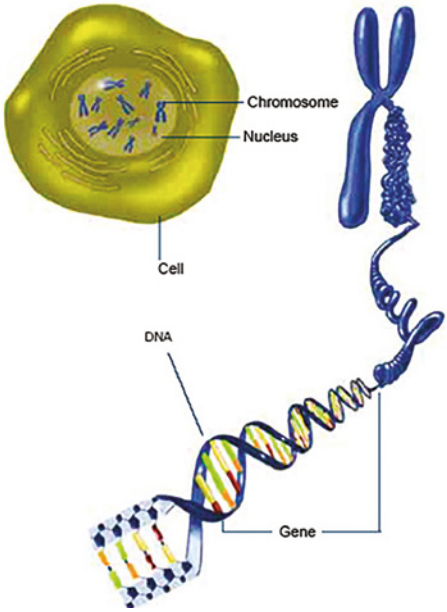
Diagnosis

Beales et al (1999 and 2001) suggest that the presence of four primary features or three primary features plus two secondary features is necessary for a clinical diagnosis of Bardet-Biedl syndrome.

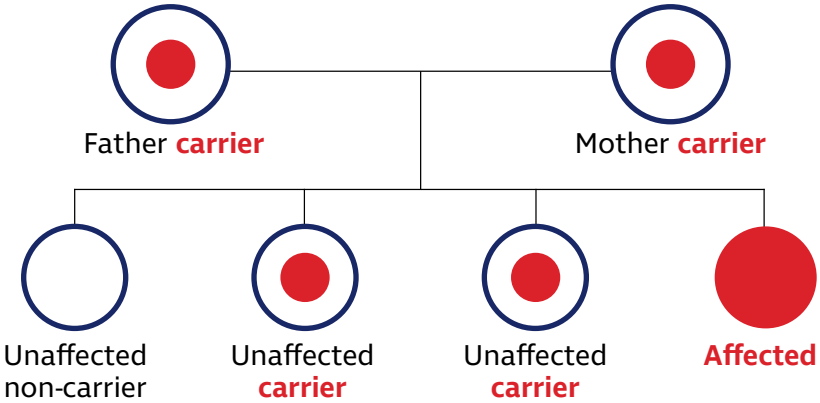
Primary Features	Secondary Features
Rod-cone dystrophy	Speech delay/disorder
Polydactyly	Developmental delay
Obesity	Brachydactyly
Learning disabilities	Polyuria/polydipsia
Hypogonadism in males	Ataxia
Renal anomalies	Poor co-ordination
	Diabetes mellitus
	Left ventricular hypertrophy
	Hepatic fibrosis
	Hypertonia
	Hearing loss

Genetics

In most cases of BBS, both parents carry a normal gene and a faulty, recessive gene. Although the parents have one copy of the faulty gene and are called carriers of the disease, they are unaffected by the presence of the faulty gene. For a recessive disease to occur, a child has to inherit two faulty copies of the gene; one from each parent. The child from each pregnancy has a 1 in 4 chance of being affected. If a new-born child is not affected then there is a 2 in 3 chance that he/she will be a carrier of the faulty gene for BBS. As the Syndrome is rare, a gene carrier is unlikely to have affected children unless their partner is also a carrier.



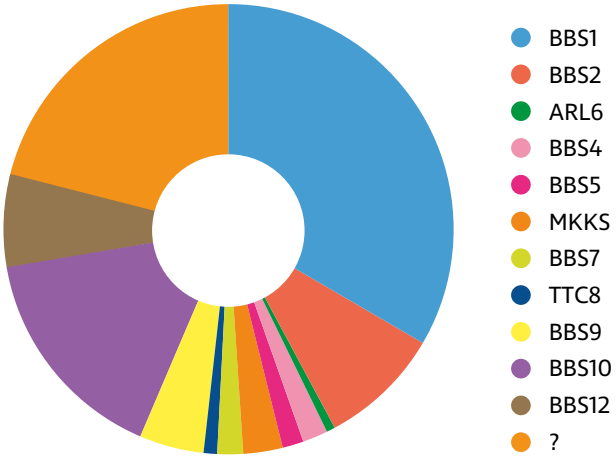
Autosomal Recessive Inheritance



The risk of encountering another carrier increases if couples are close relatives. As some BBS genes are more common than others, there is variation in the frequency with which they are being carried, known or unknown, in the population. For the most common BBS genes, BBS1 and BBS10, the frequency is estimated to be 1 in 250, whereas for a rarer gene such as BBS9, the frequency is closer to 1 in 820.

Pie chart showing relative frequency of mutations in 12 BBS genes tested

(Courtesy of North Thames Regional Genetics Service)



To date, (2020) mutations in 22 BBS genes have been identified in 85% of BBS patients. It is known that there are still more genes to find since not all patients have an identified mutation in any of these identified BBS genes, indicating that these patients must have mutations in other genes. Some genes are more common than others; a quarter of patients have mutations in BBS1 and another quarter have mutations in BBS10. However, patients who carry mutations in the same BBS gene can display quite different symptoms of the Syndrome: one might have extra digits at birth whereas another person with an identical mutation may not have extra digits at all. It is hoped that the comprehensive genetic testing currently available will improve predictions about disease progression in the future.

Cilia

Mutations in BBS genes cause changes in the proteins that are needed for the correct functioning of a particular part of the cell called a 'primary cilium'. For this reason, BBS has been categorised medically as a 'Ciliopathy'.

Ciliopathies are a range of human disease syndromes all caused by defects in primary cilia function. Cilia are long thin, hair-like projections that stick out of the surface of a cell. There are two types of cilium, motile and non-motile or primary cilia (also called sensory cilia). Many cell types in the body rely on having a fully functional primary cilium. Important examples include the retinal photoreceptor in the eye, and cells in the kidney. The scientific community is trying to understand exactly what roles the BBS proteins play in cilia formation and function.

Carrier Testing

Where BBS is confirmed genetically, a simple carrier test is possible in at-risk adult relatives (e.g. siblings) to help determine their own risk of having affected children if their partner is also a carrier. Knowledge of the BBS mutations can also provide the basis for prenatal screening tests, should parents need to know in early pregnancy if the foetus is affected.

> **During the early days of diagnosis, it is important to allow time to come to terms with all that has happened and to give yourself time and space to adjust.**
>
> Parent

Family Planning

Where both parents are carriers of a change in the same BBS gene, every pregnancy has a 1 in 4 risk of the child having Bardet-Biedl syndrome. If the genetic changes are known in the parents, there are several options available to them, should they wish to have more children.

Prenatal Testing

Couples who are already pregnant may consider prenatal testing (e.g. chorionic villus sampling/amniocentesis). It involves testing either the tissue or fluid around the baby in early to mid-pregnancy (11-16 weeks). There is a small risk to the pregnancy with prenatal testing; couples who wish to pursue this option should discuss it with their geneticist and obstetrician.

Pre-implantation Genetic Diagnosis (PGD)

A couple can be referred to be considered for PGD via a clinician provided that they fulfil a number of criteria. Common requirements are that they do not already have a healthy child and that they do not smoke. Couples who wish to pursue this route should contact their GP or geneticist.

Couples who are not interested in either of these options, or do not know the genetic change that has caused BBS, may opt to have a detailed scan throughout pregnancy to assess if there is evidence that the baby is affected. This should be done in a specialist centre by an ultra-sonographer who is familiar with the features associated with BBS. Features of BBS may be difficult to

pick up before 20 weeks gestation and, as already mentioned, may not be present in all babies with BBS.

Some couples may of course choose not to have any form of testing in a pregnancy.

Prospective parents who have Bardet-Biedl syndrome

Those who have BBS, who wish to have children, may also have several options available to them, including the options outlined above. The first step is for the partner of the person who has BBS to be tested for carrier status, to determine whether he or she carries the same change in the same gene.

The children of a BBS affected parent will all be carriers of the affected gene, but will not have the Syndrome provided that the other parent does not have any changes in the same gene. If the other parent is a carrier of a change in the same gene, then each child has a 50% chance of having the Syndrome. If both parents have BBS, then all children will be affected with BBS.

> **It is not the end of the world when it comes to being diagnosed with a medical condition. Everybody is their own unique person. It doesn't matter how fast or slow they are at achieving their goals in life, as long as they've enjoyed trying, they will get there at their own pace.**
>
> Parent

Sign Post

Bardet-Biedl Syndrome UK
www.bbsuk.org.uk

Genetic Alliance UK
www.geneticalliance.org.uk
020 7704 3141

Contact
www.contact.org.uk
0808 808 3555

Clinical Features and Presentation

There are many aspects to BBS and it is important to remember that there is great variation among those affected, even between siblings. The following section looks at each aspect in turn and includes recommended tests and assessments.

Eyes

Upon examination of the retina in those with BBS, pigment changes are often seen, making the condition similar in clinical appearance to retinitis pigmentosa. The correct term for the retinal findings in BBS is rod-cone dystrophy. The rods and cones are the names of the light-sensitive cells (called photoreceptor cells) found in the retina, which in BBS, degenerate over time because of defective cilia.

The rods provide night vision and peripheral vision and therefore, as the rods degenerate, the BBS individual will experience poor night vision and loss of peripheral vision. The cones provide colour vision and central vision, so if a patient has damage to their cones, colour and detailed vision will be impaired.

Onset of these problems is usually during primary school years and is initially experienced as difficulty with seeing in poor light conditions and at night. In some cases however, visual symptoms can be delayed into the late teens or beyond. As the retina degenerates and the condition progresses, the affected individual may lose some ability to see through the whole visual field. Loss of peripheral vision is frequently referred to as tunnel vision; as the visual fields `close in', the young person may begin to appear clumsy, especially at night-time. Functional vision will also be affected by changes in lighting and low lighting, dark evenings will

make it much more difficult to use residual sight and daytime glare will affect central vision.

A study found rod-cone dystrophy present in almost all patients who have a genetic diagnosis of BBS. A significant number of people with BBS have retinal signs that are seen on examination of the retina, however, in some the retina can appear normal and electro-diagnostic testing is needed to provide evidence of the retinopathy.

A study found that the average age at which symptoms or signs of visual loss are reported is twelve years of age, although night blindness was often noted earlier. The study also found that the average age of registration of blindness is at approximately fifteen years. Other eye conditions associated with BBS include wobbly eyes (nystagmus), an irregularly shaped cornea (astigmatism), squints (strabismus), glaucoma and cataracts.

Treatment

Gene therapy may one day be used to treat rod-cone dystrophy in BBS, but in the meantime, ophthalmic advice and support should be offered to maximise the quality of life of patients with low vision.

Correction of short or long sightedness and astigmatism and the provision of tinted glasses (for light sensitivity) can assist in maximising useable vision. Cataract surgery should be offered where appropriate and where it will be of actual visual benefit. Low vision aids and mobility training can improve independence and confidence. Magnifying glasses, digital systems and voice systems may also be helpful.

> **No one should ever put limitations on what they think someone will be able to accomplish just because of a diagnosis of BBS.**
>
> Patient

Consideration should be given to educational planning and if there are disrupted sleep patterns and difficulties with breathing at night (nocturnal apnoea), sleep studies should be considered. Referrals to local low-vision clinics and organisations assisting the visually impaired are recommended. Partial sight and blind registration (certificate of visual impairment) should be carried out in the first instance where any visual impairment is diagnosed.

Visual Assessment

At diagnosis:

- Visual acuity assessment and refraction
- Visual field testing
- Examination of the back of the eyes
- Electro-diagnostic testing
- OCT scanning

Follow-Up
Yearly eye examination:

- Visual acuity
- Visual field testing (where possible)
- Examination of the back of the eyes
- Electrodiagnostic testing if indicated
- Screening for cataract, glaucoma and diabetic retinopathy as appropriate
- General eye health check (by local optician between hospital appointments)

Sign Post

RNIB
www.rnib.org.uk
0303 123 9999

VICTA
www.victa.org.uk
01908 240831

Look
www.look-uk.org
07464 351958

Sense
www.sense.org.uk
0300 330 9250

Obesity

Obesity is reported to occur in 92% of affected individuals. Weight issues usually begin in childhood and increase in severity with age. Many children exhibit rapid weight gain within the first year of life, with one third of babies developing obesity by their first birthday. Controlling rates of weight gain during the first years of life can be challenging, especially when crawling and/or walking is delayed. However, some children may not present with weight concerns until puberty and final adult height is achieved.

The majority of adults who have BBS, have a BMI greater than 30 which is often accompanied by other health issues, for example, high blood pressure, dyslipidaemia (an abnormal amount of lipids, such as cholesterol and/or fat in the blood) and type 2 diabetes mellitus. Fat tends to be deposited within the abdomen, which can be a cause for concern as it has been linked to high blood pressure and elevated triglycerides (a type of fat found in the blood).

The cause of the obesity associated with BBS is unknown but is the subject of current research. There is certainly a dysfunction of appetite regulation which can lead to hyperphagia (excessive appetite) and energy intake exceeding requirement, which makes dietary management challenging.

Treatment

BBS symptoms cover a wide spectrum and vary significantly between individuals and therefore an individual assessment of weight and/or dietary concerns should be arranged.

Understandably, diet and weight concerns are a major source of stress for patients and their families. The knowledge that untreated obesity can lead to multiple health problems, for example, metabolic syndrome, diabetes mellitus and cardiovascular disease, adds to this stress.

Unfortunately, there is no single treatment approach for obesity in BBS, just as for obesity in general but those with BBS can successfully lose weight. In younger children, care should focus on controlling the rate of weight gain, without compromising growth. A healthy well-balanced diet and active lifestyle approach is advocated and for some, considering the glycaemic index of foods may also be useful. Portion control strategies are important, because of the excessive appetite that can be associated with BBS. Very low-calorie diets, as used to manage Prader Willi syndrome are not warranted, as this is an over restriction of energy intake.

It is important to intervene and educate with dietary strategies to control weight gain in childhood as these are more likely to have a lasting effect into adulthood. A multi-disciplinary approach is needed and should include dietary advice, behavioural management and exercise. Early referral to a registered dietitian with experience of BBS is important and attendance at the multi-disciplinary BBS clinics is strongly advised.

Research continues into therapies to target the obesity associated with BBS. The latest research developments are discussed at the BBS UK annual conference and are made available via a Conference Report which can be downloaded from the BBS UK website. At present the available pharmacological and surgical management approaches for obesity are the same as for the general population and the associated risks and benefits of these options need to be carefully considered.

Bariatric surgery is considered only for life-threatening obesity and its use in young patients with genetic syndromes of obesity is rare, with a limited number of cases reported in the literature. However, bariatric surgery may offer an alternative treatment option, when traditional non-invasive methods of weight control fail. It is important to note that specialist dietary advice and support is needed post-surgery and compliance with these dietary restrictions is imperative. It is not an easy option and is not suitable for all individuals.

Polydactyly and Brachydactyly

84% of patients are reported to have extra digits (polydactyly), most commonly appearing next to the little finger or toe; presentation ranges from a single skin tag to a fully formed digit on all four limbs.

Shortness of the fingers and toes (brachydactyly) is common, affecting 46%-100% of patients and is more frequently found in the feet than in the hands. When present in the hands, it may affect dexterity and the ability to use keyboards or Braille.

Webbing (syndactyly) is less frequently seen and is usually partial and generally confined to the feet.

Treatment

Skin tags can be tied off at birth after documentation by a medical practitioner. Fully formed digits are often non-functional and should be removed, where possible, within the first year of life by either an orthopaedic or plastic surgeon. Bony malformation in wide feet can lead to ill-fitting shoes and it is important to seek podiatric/orthotic advice and special fitting.

Renal

BBS can affect the kidneys in a number of ways, although significant kidney problems and kidney failure are seen in only a small proportion of patients. Nevertheless, it is important to monitor all patients regularly.

Most patients with BBS do not have any kidney involvement at all. Some patients with BBS have kidneys that are an abnormal shape or size, or they may have kidney cysts. These abnormalities do not usually cause any problems but can be seen on a kidney ultrasound scan. When kidney problems do occur, they usually cause mildly impaired kidney function, protein in the urine and high blood pressure. For these reasons blood and urine tests and ultrasound scanning of the kidneys should be a routine aspect of renal management in BBS.

A minority of patients with BBS experience more severe kidney problems that may lead to a significant reduction in kidney function or kidney failure, requiring dialysis or a kidney transplant. Fortunately, this is uncommon. A recent review of kidney involvement in 219 BBS patients seen in the specialised BBS clinics in the UK noted that only 12 (6%) of these patients had developed kidney failure requiring dialysis treatment or kidney transplantation. It was also noted that 5 out of the 12 patients with kidney failure developed it in the first year of life, and these were all patients that were born with severe abnormalities of their kidneys. The remaining 7 developed kidney failure later in childhood, probably reflecting less severe congenital abnormalities of the kidney.

The encouraging news from this review is that patients who do not have any evidence of kidney abnormalities in early childhood are very unlikely to develop severe kidney problems later in life. It is important to understand however, that with advancing age, other factors, such as obesity, diabetes, hardening of the arteries and high blood pressure may also contribute to a decline in kidney function. Those patients who do develop kidney failure seem to do well with dialysis and kidney transplantation, so even if kidney failure does develop there are very good treatments to support patients.

Other kidney problems may occur in BBS, including a reduced capacity to concentrate the urine. This leads to higher than average urine output and sometimes excessive thirst, although few patients notice this. Infections of the bladder (cystitis) and, occasionally, of the kidneys themselves can also occur and are treated in the conventional way with antibiotics.

High blood pressure may be evident in patients with kidney disease of any type and in BBS is often present and should therefore be regularly checked and treated if necessary. High blood pressure can also put further strain on the kidneys, so in BBS patients, where there is known kidney involvement, it is particularly important to monitor and treat this.

> **When I was 16, I went to the West of England College in Exeter. At the college I learnt how to be independent, doing such things as cooking, cleaning, and shopping. I also completed courses in further education, including an NVQ in administration. I also did work experience placements. I love living independently and being able to see my friends and go where I want to. I feel that I have achieved a lot so far in my life, and I look forward to enjoying life to the full.**
>
> Patient

Renal Assessment

At diagnosis:

- Check symptoms of anaemia, polyuria and polydipsia
- Baseline blood pressure assessment: 24-hour blood pressure monitoring, if there are concerns and if possible
- Measure plasma creatinine, urea, electrolytes, GFR
- Bladder and renal ultrasound examination

Follow-Up:

- Yearly for symptoms, baseline blood pressure
- Yearly early morning urine analysis for albumin creatinine ratio and dipstick testing for microscopic haematuria
- Yearly monitoring of plasma creatinine, urea and electrolytes, GFR

Obesity is a very common problem in people with BBS and excessive body weight can put additional strain on the kidneys and make high blood pressure worse. This can exacerbate any underlying kidney problems or can even occasionally cause kidney damage on its own. The reasons for managing weight in BBS therefore extends to protecting the kidneys from damage.

Sign Post

National Kidney Federation
www.kidney.org.uk
0800 169 0936

Kidney Care UK
www.kidneycareuk.org
01420 541424

Development, Learning and Emotional Needs

BBS is a condition that has a wide spectrum and so each person will be affected differently. Some children and adults will have few developmental or learning needs, whereas others may need ongoing support throughout their lives. Like all children, those with BBS will generally continue to progress and learn throughout their childhood. Each individual child will have their own strengths and personality and follow their own unique path in learning and development.

This section will talk about the range of difficulties that can occur for children and adults with BBS. This does not mean that each person will experience all of these difficulties. It will be important however for parents, carers, school staff and others around them to understand their strengths and needs in order to help them achieve their potential, to be themselves, and to enjoy life together as a family.

Learning and academic ability

Children with BBS show a wide range of developmental and learning abilities. Studies to date show that 75% of children with BBS perform below average for their age on intelligence tests and may need additional support in school. Some of these children will meet criteria for a diagnosis of an intellectual/learning disability. Whilst children with an intellectual/learning disability learn and develop throughout their childhood, they do so more slowly than other children of their age. Many children with BBS attend mainstream school and some attend specialist schools.

Visual needs and learning

Regardless of the school setting that a child or young person is in, if they have any visual needs, these will influence how they need to access learning in the school setting. Regular vision assessments and timely support from vision specialists is needed; as the young person's visual needs change over time, so the support they receive will need to be adapted. As these visual changes occur, consideration of learning new skills will be important especially as the young person becomes more independent. Information about supporting children and young people in a learning environment can be found in the BBS UK Booklet for Schools and Colleges.

Social communication and autism spectrum

It is known that children with BBS often show differences in how they communicate and understand social situations. Children may also behave in a way that appears obsessive and rigid. Recent studies suggest that around 75% of children with BBS will show autistic tendencies, with an overall estimate of 33% identified as being on the autism spectrum. Therefore social communication needs will be important to consider during childhood, adolescence and into adulthood.

Emotional and behavioural needs

As can be expected for children with learning, language, visual and social communication needs, children with BBS are more likely to show emotional and behavioural challenges. For young children with BBS, it is important to be mindful of their emotional wellbeing and consider what may be behind any behavioural challenges they show. Typical behaviour management strategies may not be effective and specialist support from local health services may be required. Setting clear boundaries around food and eating at an early stage may help to prevent future difficulties in this area.

Towards the later years of primary school, some children with BBS may show an increasing awareness of their needs which can lead to the feeling of being different, particularly in the school setting. At this age, young people may experience difficulties with friendships and bullying which, alongside weight issues, can result in low self-esteem. Helping children and young people to recognise and appreciate their own strengths as well as developing their interests can be protective for such difficulties.

As the young person gets older, they and their family often experience fears and worries, relating to the daily management of any behaviour difficulties, education, living an independent life and relationships. Fitting in socially is very important and the teenage years are when relationships and sexuality are important issues that young people may explore. This stage of development involves the young person exploring their identity as being separate from their parents, and so they may want to spend more time away from parents. As with the general population, hormonal changes can also contribute to developing emotional difficulties, with people feeling lonely and unhappy.

In adulthood, anxiety is commonly reported which can significantly impact on the individual's ability to cope with their condition. Common concerns include worrying about health and medical needs, not feeling in control of emotions, apathy, social skills problems and finding employment. Individuals with autism or autistic traits may have difficulty understanding other people's emotions and difficulty reading social cues, which makes it harder to relate to others. Independence is an issue for some, but not for others. Some people will find employment, whereas others find themselves understandably frustrated about the limitations that come with BBS. Specialist support will continue to be needed for adults with visual, learning and social communication needs.

Low mood, panic attacks, obsessions and compulsions, anger and poor emotional control also commonly affect adults and young people with BBS. It is unclear whether this is a part of the Syndrome or an indirect result of it. Most likely, it is a combination of both. A small number of patients experience delusional thoughts and some develop periods of psychosis. If this is suspected, prompt referral for a psychiatric opinion and therapy is warranted.

Support and management

For young children of pre-school age, an Education, Health and Care Plan (EHCP) will ensure the child is fully supported. Parents or carers should contact the school or pre-school and request an assessment be commenced. The school or pre-school's SENCo (Special Educational Needs Co-ordinator) will co-ordinate the process and arrange for educational psychologist and sensory team involvement. Possible interventions for children would include:

- Assistance with school integration
- Behaviour support
- Speech and language therapy
- Qualified Teacher of Children with Visual Impairment
- Family support
- Management of symptoms
- Sensory support
- Exploring emotional needs

It is important to get any intellectual/learning disability and autism spectrum needs diagnosed, as this could then lead to help from other areas.

For adults, isolation can lead to or exacerbate anxiety and depression and it is vital that appropriate support is in place. There are many ways to access support:

- Ask GP to arrange a social services assessment and occupational therapy assessment
- Ask GP or Social Worker about local support groups for the disabled or visually impaired
- Ask GP about counselling or psychological intervention if more support is needed for low mood or anxiety
- Talk to staff at a local disability centre or Social Worker about activities in the area
- Contact BBS UK for advice or support. It may help to talk to others in the same situation
- Exercise is vitally important for emotional and physical wellbeing
- Local Disabilities Team or Social Worker will be able to help with claiming benefits, arranging support workers, carers or respite, and linking individuals into local services in the area

Endocrine

Male Reproductive System

Hypogonadism (lack of production of sex hormones) is common amongst males, affecting up to 30% of BBS patients; a small, buried penis with reduced volume testes is common. 10% have undescended testes at birth. In most cases this is due to a partial failure of the hypothalamus/pituitary gland with low or inappropriately normal luteinizing hormone (LH) and follicle stimulating hormone (FSH), with low circulating testosterone levels. In a small number of individuals there may be primary gonadal failure. There is usually enough testosterone production to permit normal pubertal development. The timing of male puberty is often slightly delayed but with normal progression and secondary sexual characteristics. Puberty is a particularly stressful time for those with BBS, regardless of their sex, and, where possible, referral to a counsellor with experience in this field can be of help.

Adult male patients with hypogonadism may be prescribed testosterone replacement by an endocrinologist. This may take the form of either injections or daily gel preparations. While this may help with sexual function and libido, an important benefit is likely to be in the preservation of bone mineral density and reducing the risk of fractures. Although affected males are likely to be infertile, several have fathered children.

Female Reproductive System

Hypogonadism is much less frequent in women, however, structural anomalies of the female genitourinary tract are documented, including vaginal atresia (abnormally closed or absent vagina), hydrometrocolpos (collection of watery fluid in the uterus and vagina), ectopic urethra (urethra that terminates somewhere other than the bladder), hypoplasia (underdevelopment) of the

uterus, ovaries and fallopian tubes, and septate vagina (vagina that is divided). Women with BBS tend to have a normally timed puberty, and although there is little evidence to suggest secondary hypogonadism, polycystic ovary syndrome (PCOS) may be present in up to 20% of women with BBS. This can lead to problems with menstrual irregularity, acne and excessive hair. For those patients who are considering fertility, polycystic ovary syndrome needs to be considered should there be a delay in conception. Several females with BBS have given birth successfully to healthy children.

Thyroid function

Thyroid function tests are normal in most patients with BBS, however, approximately 25% of patients may have thyroid test abnormalities. Most commonly, this is an underactive thyroid gland (hypothyroidism) which can cause tiredness, lack of energy, feeling cold, constipation and difficulty in losing weight. In the majority of cases, this is a very mild abnormality (often termed 'sub-clinical hypothyroidism') and may not require any treatment. In some individuals however, thyroid hormone replacement treatment is needed. Patients with BBS should have an annual blood test to measure thyroid function.

Sign Post

Patients affected by any of these issues should speak to their GP for a referral to an endocrinologist and/or counsellor where appropriate.

Patients of the BBS multi-disciplinary clinics should speak with their endocrinologist or BBS Clinical Psychologist.

Diabetes

Diabetes is reported as being present in 26% of adult patients with BBS. It rarely presents before adolescence and in this age group occurs in those with the highest BMI scores. A higher proportion of patients may have abnormalities of glucose tolerance and regular screening for the development of diabetes is recommended.

The underlying BBS ciliopathy and high BMI scores contribute increased risk factors for diabetes mellitus. This can be controlled with combinations of diet and medicine including insulin. Newer therapies, for example, GLP-1 analogues, DPP-IV inhibitors and SGLT2 inhibitors are also potentially useful to try to optimise glycaemic control. Regular diabetes assessments are important and should be carried out at least annually. Preventable diabetic retinopathy can lead to rapid deterioration of vision already compromised by rod-cone dystrophy.

Alongside monitoring for complications of diabetes, it is important to control blood pressure adequately and all patients with diabetes over the age of 40 should be on lipid lowering therapy. Both measures are aimed at decreasing long-term cardiovascular risk.

Endocrine Assessment

At diagnosis:

- Measure height and weight- calculate BMI
- Hormone levels: including testosterone, gonadotropins FSH and LH
- Consider pelvic ultrasound examination (females)
- Liver chemistry (including AST and ALT)
- Fasting lipid profile, including triglycerides
- Fasting plasma glucose (FPG)
- Glycated haemoglobin
- Thyroid function tests

Follow-Up: (at least annual, but may be more frequent)

- Measurement of weight, height and calculation of BMI
- Annual thyroid function test
- Liver chemistry (including AST and ALT)
- Fasting lipid profile, including triglycerides
- Fasting plasma glucose or Glycated haemoglobin

Sign Post

Diabetes UK can offer information and support to those affected by diabetes:
www.diabetes.org.uk
0345 123 2399

Additional Features

Speech and Language

Many children with BBS present with speech and language difficulties and it is very common for first words to emerge late. The difficulties may range from mild to severe and there can be problems across a range of communication skills or just in one area. Below are some examples of the types of difficulties that can occur:

- Expressive language impairment including slow acquisition of new words, difficulties putting sentences together and difficulties describing a sequence of events or telling a story.
- Difficulties with receptive language including difficulties with understanding words and sentences; difficulties following stories and more abstract language within the classroom and at home.
- Difficulties with social communication and play. In addition, restricted or repetitive interests and behaviours and possible sensory difficulties may be present. Some children may have a diagnosis of autism.
- Speech sound development can be very delayed. Some children do not babble when they are young, other children do not develop speech sounds in the expected pattern or they have unusual speech patterns (disordered speech and/or dyspraxic speech patterns).
- Voice can be high pitched.
- Resonance can be hypernasal.

Treatment

A referral to speech and language therapy should be made at the first signs of speech and language difficulties. An assessment of the child's difficulties can then be made and specialist advice and treatment be provided early.

Hearing impairment, if present, will contribute to speech and language difficulties. For example, if conductive hearing loss is present during the pre-school years and is left untreated, this will have a negative impact on speech and language development. Hearing difficulties should be actively managed as soon as they are detected.

Useful Links:

www.ican.org.uk

www.talkingpoint.org.uk

www.afasic.org.uk

www.autism.org.uk

www.dyspraxiauk.com

www.makaton.org

> **Of course the two things which inspire me the most to carry on with strength and determination are my children, two bright, funny, intelligent, kind and loving young people who have enriched our lives and made us proud parents.**
>
> Parent

Seizures/Epilepsy

The prevalence of seizures and epilepsy in BBS is reported as being much higher than previously recognised and significantly higher than in the general population, however the reason behind this is still unclear. In the majority of cases, seizures stop before adulthood.

Seizures can affect people in different ways including a loss of awareness, unusual sensations and jerking and shaking of the body. Seizures can occur when awake or asleep and sometimes there are triggers such as tiredness.

Patients/parents should seek urgent medical help if they suspect they or their child has had a seizure. A referral to a neurologist would be appropriate for investigations/tests.

Neurological Abnormalities

Ataxia is the term for a group of disorders that affect co-ordination, balance and speech and is reported in a significant number of individuals with BBS. Hypertonia is a condition marked by an abnormal increase in muscle tension and a reduced ability of a muscle to stretch and is also commonly reported, as is low muscle tone.

Some limited brain MRI studies have shown that some patients with BBS have smaller, unusually formed hippocampi and that there is a tendency towards decreased overall white matter. However, it is not clear if or how this affects neurocognition. A number of patients with BBS report difficulties with memory function.

Hearing

Conductive hearing loss, almost always caused by glue ear, affects many children with BBS. This often resolves spontaneously or, with treatment, by adulthood. A minority of patients with BBS have sensori-neural deafness.

Hearing Assessment

At diagnosis:

- Audiogram, audiometry, tympanogram
- Auditory evoked potentials

Follow-up:

- Yearly examination: audiometry
- Detect glue ear (acute and chronic otitis media) which can lead to conductive hearing loss

Treatment

Glue ear management: myringotomy tubes and/or hearing aids.

Digestive System

A survey undertaken by BBS UK indicates that gastrointestinal problems are a common issue in BBS and this is backed up by anecdotal evidence from patients attending the BBS multi-disciplinary clinics. Commonly reported symptoms include constipation, diarrhoea, bloating and cramping and further research is needed in this area. Individuals who are experiencing difficulties should consult their GP who may wish to refer for investigations or dietetic support. Patients attending BBS clinics should discuss their symptoms with a member of their clinic team.

Hirschsprung's disease occurs more frequently in Bardet-Biedl syndrome than in the general population, but the incidence is unknown. The condition is present at birth (congenital) as a result of missing nerve cells in the muscles of the baby's colon. A new-born who has Hirschsprung's disease usually can't have a bowel movement in the days after birth. In mild cases, the condition might not be detected until later in childhood or rarely as an adult, presenting as a swollen abdomen, poor appetite and constipation that does not respond to any of the usual treatments.

Orthopaedic Abnormalities

Examination and early identification of scoliosis (curvature of the spine), genu valga (knock-knee), genu vara (bow-leg) and pes planus (flat-foot) will allow for early intervention/treatment and may avoid unnecessary discomfort.

Physiotherapy and orthotic referral should be considered; early orthotic intervention and supportive footwear/insoles will ease discomfort and protect feet against further damage.

Liver

Fibrocystic and fibrotic liver diseases have been reported in a very small number of cases of BBS. More recently, there is an awareness of the likelihood of co-existent non-alcoholic fatty liver disease (NAFLD) that is driven by obesity and type 2 diabetes. This is a chronic condition that can evolve over many years. It can manifest within a spectrum of disease that ranges from simple fat accumulation (hepatic steatosis) that has few, if any clinical consequences, to inflammation (steatohepatitis) and in some cases scarring that can lead to liver cirrhosis. It is progressive in some, but not all, patients. Managing the condition relies on staging the severity of NAFLD and treating the conditions that predispose to it, namely reducing weight and optimising blood sugar control in patients with diabetes.

Liver Assessment

- Measurement of plasma ALT, AST and GGT concentration
- Liver ultrasonography

Cardiovascular

Hypertension is a common feature of Bardet-Biedl syndrome and often presents in childhood or early adulthood. It may occur as a result of other features contributing to metabolic syndrome in Bardet-Biedl syndrome, in particular obesity. It is imperative that hypertension is treated, since it can contribute to renal deterioration. Both lifestyle modification and pharmacological intervention are encouraged.

Congenital heart disease has been reported in a minority of BBS patients. Dextrocardia (heart points to the right instead of the left), and occasionally complete situs inversus (where organs are positioned opposite to normal position) have been reported but these are rare.

Cardio Assessment

- Blood pressure monitoring
- Auscultation
- ECG
- Echocardiography

Joints

Many patients with BBS report pain in weight-bearing joints, probably because of osteoarthritis. However, a small proportion also have abnormally hypermobile or lax joints, the cause of which is unknown, but may be associated with hypotonia (decreased muscle tone).

Dental

Several people with BBS have unusually short tooth roots, especially of the front lower teeth. Crowding of the teeth necessitating extraction is common. Many patients have a high-arched palate and occasionally enamel dysplasia is evident. These abnormalities can increase susceptibility to tooth decay and loss and regular dental supervision is advisable.

Respiratory System

Asthma commonly affects individuals with BBS with prevalence reported at around 25%.

Obstructive sleep apnoea (OSA) is common and related to excess weight, particularly around the neck. This may be compounded by low muscle tone and soft palate dyscoordination. All patients should be questioned about their quality of sleep and the presence of daytime somnolence (excess sleepiness). Evidence suggesting obstructive sleep apnoea should lead to referral for sleep studies and lung function assessments as many BBS patients report that treatment (e.g. nocturnal CPAP devices) results in major benefits such as increased activity, weight loss and lower blood pressure.

Parents and Carers

For parents and carers of children with BBS, the diagnosis brings with it many questions and worries about what this means for them and their family. This can understandably cause stress and anxiety and adjusting emotionally can take time. Having a child with BBS can be hugely rewarding and frequently takes people's lives in unexpected directions. It can be helpful to take the journey one step at a time, take pleasure in the joyful moments and seek support when it is needed.

BBS is a complicated and lifelong condition that impacts in many ways, and so parents and carers can find it stressful to coordinate with the many health and support services involved. The child or adult with BBS may have significant needs that may impact on parents, carers and their family. Siblings frequently have a large role in supporting people with BBS during childhood and into their adult lives. Therefore of paramount importance is the need for parents and other family carers to receive support as well.

Key support is likely to come from family members and friends who may also need to learn about BBS. Parents and carers often find it useful to link with others who are in a similar situation. At times, parents and carers may struggle with their own mental health and so additional input may be warranted. There are many ways parents and carers can seek support:

- Ask GP to arrange a social services assessment and occupational therapy assessment
- Ask GP about individual or couples counselling if more support is needed for low mood or anxiety or conflict arising in the family
- Talk to staff at a local children's centre or child development centre about activities in the area for parents and carers

- Contact BBS UK, it can sometimes help to talk to other parents and carers in the same situation
- Keeping physically active and healthy is important for emotional and physical wellbeing
- Parents and carers should try to find some time for themselves, it is important to have 'me' time, whether alone, with friends or each other. Relationships often suffer when caring for someone with a health condition
- The local Children with Disabilities Team or Social Worker will be able to help with claiming benefits, arranging support workers, carers or respite, and linking families with local services in the area

> **We sometimes need to find a little time for ourselves. This normally involves a bike ride, a swim, a run or simply relaxing over a drink with friends. This time is important because it makes us function better as parents and my advice to any parents of newly-diagnosed Bardet-Biedl children, is to allow yourselves this time too, in whatever form it takes.**
>
> Parent

BBS Specialist Clinics

BBS UK, together with Great Ormond Street Children's Hospital, Guys and St Thomas' Hospital, London, Birmingham Children's Hospital and Queen Elizabeth Hospital, Birmingham are commissioned by NHS England to provide multi-disciplinary clinics for Bardet-Biedl syndrome patients. At each clinic, patients are seen by an ophthalmologist, nephrologist, dietitian, clinical psychologist, geneticist, speech and language therapist and endocrinologist; the aim is to provide a 'one stop' annual visit to ensure patients receive specialised and expert attention and management with a focus on diagnosis, early intervention and good health management. Telemedicine clinics are also available across the four centres and will be offered where appropriate.

BBS UK is an integral member of this valued multi-disciplinary team (MDT) and provides information and support to patients and their families and carers before, during and after clinics. Its involvement pre-clinic ensures that patients, their families and carers are well informed about the Syndrome and service and feel well supported to attend. BBS UK Patient Liaison Officers attend each clinic, offering emotional and practical support to patients and

> **I have met so many children, young people and adults who have BBS at conference and clinics over the years, and their bravery, courage and determination in the face of disability and illness is inspiring. I have also seen so much achievement within our group, whatever their passion; we have successes in business, sport, in the workplace, music, art, as well as academic, and there is a great deal that can be achieved.**
>
> BBS UK Service Manager

their families. Post clinic they provide ongoing support and liaise between patient and hospital where required and generally provide an ongoing point of contact.

It is recommended that all patients with a suspected diagnosis of BBS should be referred to one of these centres. All referrals should be addressed to:

Professor Phil Beales
Consultant Clinical Geneticist
Great Ormond Street Children's Hospital
Great Ormond Street
London
WC1N 3JH

For more information,

contact: **admin@bbsuk.org.uk**

Or visit: **www.bbsuk.org.uk**

Bardet-Biedl Syndrome UK

BBS UK is the only charity in the UK providing information and support to those diagnosed with BBS, their families and carers, from diagnosis and beyond; the Charity is a lifeline to over 500 individuals, their families and carers, providing essential support, literature and advocacy services. BBS UK also focusses on raising awareness of the Syndrome amongst medical professionals and wider society and supporting the medical and scientific community with research.

I got in touch with two wonderful people from the BBS charity. They were a huge source of support to me and put me in contact with even more families. Sometimes I think the hardest thing for people is thinking that you are alone and that is where the charity comes into its own.

Parent

The whole Conference Weekend has been very instructive and we have gained a lot of knowledge relating to the condition. Thank you for a wonderful weekend, it has been brilliant.

Parent

BBS UK organises annual events including a family conference, bringing members together to learn about the latest research and meet others living with the Syndrome and maintains a web site and Facebook page. Through these it has developed a community which self supports, with members helping each other through the challenges often faced. For more information, go to **www.bbsuk.org.uk**

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Summary of recommended assessments

Visual Assessment

At diagnosis:

- Visual acuity assessment and refraction
- Visual field testing
- Examination of the back of the eyes
- Electro-diagnostic testing
- OCT scanning

Follow-Up
Yearly eye examination:

- Visual acuity
- Visual field testing (where possible)
- Examination of the back of the eyes
- Electrodiagnostic testing if indicated
- Screening for cataract, glaucoma and diabetic retinopathy as appropriate
- General eye health check (by local optician between hospital appointments)

Renal Assessment

At diagnosis:

- Check symptoms of anaemia, polyuria and polydipsia
- Baseline blood pressure assessment: 24-hour blood pressure monitoring, if there are concerns and if possible
- Measure plasma creatinine, urea, electrolytes, GFR
- Bladder and renal ultrasound examination

Follow-Up:

- Yearly for symptoms, baseline blood pressure
- Yearly early morning urine analysis for albumin creatinine ratio and dipstick testing for microscopic haematuria
- Yearly monitoring of plasma creatinine, urea and electrolytes, GFR

Endocrine Assessment

At diagnosis:

- Measure height and weight- calculate BMI
- Hormone levels: including testosterone, gonadotropins FSH and LH
- Consider pelvic ultrasound examination (females)
- Liver chemistry (including AST and ALT)
- Fasting lipid profile, including triglycerides
- Fasting plasma glucose (FPG)
- Glycated haemoglobin
- Thyroid function tests

Follow-Up: (at least annual, but may be more frequent)

- Measurement of weight, height and calculation of BMI
- Annual thyroid function test
- Liver chemistry (including AST and ALT)
- Fasting lipid profile, including triglycerides
- Fasting plasma glucose or Glycated haemoglobin

Hearing Assessment

At diagnosis:

- Audiogram, audiometry, tympanogram
- Auditory evoked potentials

Follow-up:

- Yearly examination: audiometry
- Detect glue ear (acute and chronic otitis media) which can lead to conductive hearing loss

Liver Assessment

- Measurement of plasma ALT, AST and GGT concentration
- Liver ultrasonography

Cardio Assessment

- Blood pressure monitoring
- Auscultation
- ECG
- Echocardiography

bbs uk
Bardet-Biedl Syndrome UK

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