Syndrome of the month

Journal of Medical Genetics 1989, 26, 45-48

Johanson-Blizzard syndrome

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In 1971 Johanson and Blizzard reported a new syndrome in three unrelated girls characterised by congenital aplasia of the alae nasi, deafness, hypothyroidism, dwarfism, absent permanent teeth, and malabsorption. Children with this syndrome had been described earlier by Morris and Fisher in 1967 and Townes in 1969 as examples of trypsinogen deficiency disease. Townes and White subsequently reviewed the patient reported in 1969 and described the presence of additional features which confirmed the diagnosis of the Johanson-Blizzard syndrome. There have since been 22 patients reported with Johanson-Blizzard syndrome, and a further seven children related to these. The spectrum of associated features is now well documented and the inheritance of the syndrome is autosomal recessive. However, there remain many problems which make counselling difficult, in particular the degree of mental handicap and the observation that some children die from complications of the severe malabsorption despite intensive treatment. This article reviews the 22 patients previously reported and also includes details of a previously unreported boy.

Clinical features

The main features are shown in the table. The most constant signs necessary to make a diagnosis are aplasia of the alae nasi, an exocrine pancreatic defect, and unusual hair growth pattern.

In the absence of major structural abnormalities, the affected infant usually comes to medical attention because of failure to thrive. On presentation, the infant is malnourished, hypotonic, and often oedematous because of hypoproteinaemia.

The face

The diagnosis should be made easily in the neonatal period. Indeed the 'gestalt' of the Johanson-Blizzard syndrome is so distinct that seen once it should not be missed (figs 1 and 2). The picture is determined by the unusual nasal configuration. The severe aplasia of the alae nasi leads to the appearance of a

<table>
<thead>
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<th>TABLE Frequency of features in the Johanson-Blizzard syndrome</th>
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<tr>
<td>Reported cases (n=22)</td>
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</tr>
<tr>
<td>Hypoplastic alae nasi</td>
</tr>
<tr>
<td>Pancreatic insufficiency/failure to thrive</td>
</tr>
<tr>
<td>Aplasia cutis congenita</td>
</tr>
<tr>
<td>Short stature</td>
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<tr>
<td>Mental retardation</td>
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<tr>
<td>Dental anomalies</td>
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<tr>
<td>Deafness</td>
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<tr>
<td>Anorectal anomalies</td>
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<tr>
<td>Microcephaly</td>
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<td>Genitourinary abnormalities</td>
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<tr>
<td>Hypothyroidism</td>
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<td>Cardiac malformation</td>
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FIG. 1 Our patient, a boy, aged two months. Note the small nose with aplasia of the alae nasi and the abnormal hair growth pattern, also shown in fig 3.
thin, torpedo shaped nose with large nostrils. In addition, the hair is swept up, especially frontally (fig 3), and has a patchy distribution over the scalp. Closer inspection shows areas of alopecia (fig 4) with underlying aplasia cutis congenita, which are characteristically in the midline and in the occipital region. They heal to form atrophic scars.

MALABSORPTION
An exocrine pancreatic defect is a constant feature of this condition. Townes3 and Townes and White4 described the abnormalities of pancreatic function. They reported an absence of trypsin, chymotrypsin, and their proenzymes, as well as carboxypeptidase and lipase, but they thought the amylase activity was normal. This was subsequently found to be a spurious result as isoenzyme studies showed that amylase was from the salivary gland. When the contribution from saliva is excluded, pancreatic amylase activity is absent. At necropsy the parenchyma of the pancreatic gland is replaced by fatty tissue.5 6 There are fewer islets of Langerhans but clinically there are no reports of impaired glucose tolerance.

The severe malabsorption caused by these enzyme deficiencies leads to hypoproteinaemia, oedema, anaemia, and failure to thrive. The treatment of the pancreatic failure is by pancreatic enzyme replacement, as in cystic fibrosis. It is a life threatening condition and several of the children reported have died despite full medical treatment.

SHORT STATURE
The short stature has been attributed to hypothyroidism and malabsorption. There have been su
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Efficient cases of short children with normal thyroid function
to know that hypothyroidism is not the
case. A poor nutritional state contributes to the
short stature and the child will not grow well unless
the pancreatic enzyme deficiency is treated.

Our patient had pituitary hypothyroidism, but as
yet has not had further pituitary function tests. It is
interesting to speculate that growth hormone de-
iciency may be the cause of the short stature in this
syndrome. In the two necropsy reports, there is
no mention of pituitary gland pathology.

Hypothyroidism
All three girls in the original report of Johanson and
Blizzard were hypothyroid. They stated that the
hypothyroidism may be aquired rather than con-
genital, as one of their patients had a normal bone
age at birth and her thyroid function was not as
depressed as in the older patients. Subsequently six
out of the 22 reported cases have been found to
have reduced thyroid function. The results may be
difficult to interpret because in severely mal-
nourished children there will be depression of the
thyroid binding globulin. The additional patient
with the Johanson-Blizzard syndrome we present
here had normal thyroid function, including a TRH
test at the age of eight weeks. By the age of six
months he had a low T4 (29 nmol/l) and low TSH
(1.5 mU/l) indicating pituitary hypothyroidism.

The true aetiology of the hypothyroidism has not
been determined. Thyroid autoantibodies are not
present. At necropsy the thyroid gland was
atrophic with colloid distension in a child known to
be hypothyroid, but normal in a euthyroid child.
The growth failure, deafness, and mental retarda-
tion have also been considered in terms of the
hypothyroidism. However, there are sufficient chil-
dren with normal thyroid function to know that
hypothyroidism is unlikely to be the cause, though
it can contribute if allowed to go untreated.

Mental Retardation
Thirteen out of the 22 children reported have been
developmentally delayed. This is an underestimate
as infants have died in the neonatal period.
The cause is obscure. Daentl et al.6,7 showed focal migra-
tional defects in the brain at necropsy but this was
not confirmed by Moeschler et al.,8 who found the
brain to be small but structurally normal. There is
also no clear relationship between mental retarda-
tion and hypothyroidism. As pointed out by Moes-
chler and Lubinsky,8 the patients of Schussheim et
al.9 and Sismansis et al.10 were severely retarded but
neither microcephalic nor hypothyroid. The degree
of retardation cannot be predicted. The patient of
Day and Israel10 showed mild developmental delay
and that of Townes11 was reported as "relatively
normal" at three and a half years, although by 12½
years she needed special education. The brother and
sister reported by Moeschler and Lubinsky8 were
normal at two and a half and two years. Severe
retardation was found in the patients of Daentl et
al.,5 Baraitser and Hodgson,12 and Mardini et al.13

Anorectal Anomalies
As shown in the table, 11 of the reported children
with the Johanson-Blizzard syndrome had anorectal
abnormalities. In the majority of cases this was an
imperforate anus. These children come to medical
attention early and the initial surgical management is
the fashioning of a transverse colostomy. It is
important that poor weight gain in these infants is
not attributed to the surgery but that malabsorption
is recognised and treated.

Deafness
Hearing loss has been reported in 12 out of 22
patients. The case of Sismansis et al.12 was investi-
gated in detail. There was a severe sensorineural
ing loss with associated absent vestibular func-
tion, but the inner ears were structurally normal on
polytomograms. There have been no further reports
of more detailed radiological investigations. At
necropsy the temporal bones were not studied.
Our patient has a symmetrical, moderately severe
sensorineural hearing loss.

Other Features
Additional features listed in the table are abnormali-
ties of dentition, genitourinary anomalies, and
cardiac malformations. The dental findings have
been well reviewed by Zerres and Holtgrave.14 The
children have delayed eruption of teeth, which are
small but normal in shape. The genitourinary
anomalies were striking in the three girls originally
reported,1 two of whom had a single urogenital
orifice, but other children have not had major
structural problems. A congenital heart defect has
been reported in only three of the children, two of
whom were sibs reported by Helin and Jodal15 with
situs inversus. Minor abnormalities of the lacrimal
duct have also been recorded.

Differential Diagnosis
The diagnosis of the Johanson-Blizzard syndrome is
not difficult when all the features are present.
Hypoplasia of the alae nasi occurs in the ocu-
dentodigital syndrome,16 aplasia cutis congenita of
the scalp in the Adams-Oliver syndrome,17 and
pancreatic malabsorption in the Shwachman-
Diamond syndrome, but these should not prove to
be diagnostic problems.
Counselling

There is strong evidence for autosomal recessive inheritance. Affected sibs have been described by Moeschler and Lubinsky,8 Day and Israel,10 Heln and Jodal,15 and Bresson et al.18 Parental consanguinity has been reported by Schussheim et al.,9 Sismansis et al.,7 Mardini et al.,13 and Bresson et al.18

A more difficult problem in counselling is that of predicting the degree of mental retardation, the presence of severe structural lesions, and the success in treating the pancreatic exocrine defect. There have been no reports of prenatal diagnosis to date. At present one could offer a high resolution ultrasound scan in the hope of detecting the distinctive facial features and any structural abnormalities, such as the cardiac or urogenital lesions.

Prognosis

In the family of Mardini et al.13 all three patients died in infancy from complications of malabsorption and failure to thrive. The girl reported by Townes3 and Townes and White4 was still alive at the age of 12 years nine months. She had short stature, no permanent teeth, a sigmoidostomy because of an imperforate anus, and she required pancreatic enzyme supplements with her meals. She had mild mental retardation. If the pancreatic malabsorption problems are overcome the child can survive infancy, but is likely to require prolonged medical supervision. Even when given the best medical attention these children may develop severe problems associated with hypoproteinaemia, namely infections and oedema, which can lead to death in childhood.

References

17 Adams FH, Oliver CP. Hereditary deformities in man due to arrested development. J Hered 1945;36:3-7.