A Scottish family with Bazex-Dupré-Christol syndrome: follicular atrophoderma, congenital hypotrichosis, and basal cell carcinoma

A Kidd, L Carson, D W Gregory, D de Silva, J Holmes, J C S Dean, N Haites

Abstract

Bazex-Dupré-Christol syndrome (BDCS) is an X linked dominant disorder of the hair follicle characterised by follicular atrophoderma, multiple basal cell carcinomas, hypotrichosis, milia, and localised hypohidrosis. Follicular atrophoderma (FA) are follicular funnel shaped depressions, "ice pick marks", seen most commonly on the dorsum of the hands.

We describe the first known Scottish family with this syndrome, five affected members spanning three generations. They have hypohidrosis confined to the face, coarse hair, dry skin, milia, and follicular atrophoderma. All the adults have a history of multiple basal cell carcinomas. None of them has any skeletal feature suggestive of Gorlin's syndrome. The clinical features, skin histology, and scanning electron microscopic (SEM) examination of the hair are described and illustrated. The features are compared with 15 previous reports of BDCS and four reports in which this is a possible diagnosis are also reviewed.

BDCS should be considered as a differential diagnosis in patients with early onset or familial basal cell carcinomas. 

Key words: BCC; follicular atrophoderma; hypotrichosis; hypohidrosis.

In 1964 Bazex et al. described a new syndrome characterised by multiple basal cell carcinomas (BCCs), hypotrichosis, hypohidrosis confined to the face, and follicular atrophoderma. In subsequent reports it became apparent that milia and hair shaft dystrophies were also major features and that the hypohidrosis was sometimes generalised. It is thought to be a disorder of the hair follicle.

The term "follicular atrophoderma" (FA) is used to describe discrete areas of dilated hair follicles, giving the appearance of funnel shaped depressions in the skin. They are seen most commonly on the dorsum of the hands but also occur on the face, elbows, and knees, and on the dorsum of the feet; they are sometimes referred to as "ice pick marks".

Fifteen other families have been reported with convincing evidence of BDCS, containing about 120 cases between them. Two of the families were from the USA, the others were European, the majority being French or Belgian. Two further large families reported by Parish et al. and Oley et al. exhibit many features of BDCS and are probably variants of the same condition.

BDCS is inherited as an X linked dominant trait (McKusick No 301845). X linked inheritance had been suspected for some time. One case of male to male transmission was reported in 1967; in 1995 this family was re-examined and a key male previously reported as affected was found not to be so. There are now no cases of male to male transmission, despite at least 12 opportunities. Almost all daughters of affected males are affected and the female to male ratio is almost 2:1. In one large pedigree, males were more severely affected. In 1995 Vabres et al. reported linkage of all three families they studied to Xq24–q27. We report the first Scottish family with this disorder and review previously published reports.

Case reports (figs 1–6)

III.3

The proband, now aged 36, developed milia on her face as a toddler. They became more numerous during puberty and then much less

Figure 1 The pedigree.
obvious in adulthood. She had five BCCs excised from her face, the first when she was 28 years old. She felt that some of the BCCs had developed within milia. Ice pick marks had been present on the dorsum of her hands and elbows for as long as she could remember. She had dry skin and reported that she never sweated on her face but did perspire a little elsewhere. Heat exhaustion had never oc-
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Figure 7  Scanning electron micrographs of (left) normal hair and (right) hair from IV-2 showing complete absence of cuticular scales. Bar lines = 20 μm.

curred. She had lived in Gibraltar for two years and had had one severe episode of sunburn, causing blistering on her face. She had very wispy hair which “stuck our straight” as a child. The hair thickened as she got older but remained very dry and coarse. Her eyelashes and eyebrows were not affected and body hair elsewhere was normal. She had a long, thin nose with hypoplastic nasal alae and a prominent columella but no other unusual facial or skeletal features.

III-2

The proband’s 44 year old sister also had all five main features of the disorder. She has had milia on her face, neck, and hands since she was a toddler. They were most obvious during puberty. BCCs first developed when she was 21 years old and occurred below her eyes and on her nose. She has had four more BCCs and a small haemangioma excised recently. Hypohidrosis and hypotrichosis followed the same pattern as in her sister. Ice pick marks first appeared on the dorsum of her hands and on her elbows and big toes in early childhood. She had a similar nose to her sister, III-3. As an infant she had surgery for a large haemangioma of the scalp. She had not lived abroad. She reported that her skin was very sensitive to the sun but it had never blistered.

II-1

The proband’s mother died of a myocardial infarct when aged 58 years, but her family remembered that she also had very dry, coarse hair. Records confirmed that she had five histologically proven BCCs removed from her face. The first was excised when she was 53 years old. Her daughters could not remember whether she had the ice pick marks or milia.

IV-2

The proband’s 11 year old daughter has had milia on her face since early infancy. They have recently become much more obvious. Ice pick marks were first noticed when she was 10 and were present on her hands, elbows, and knees. She had hypotrichosis and hypohidrosis, following a pattern similar to her mother’s. She had not yet developed any BCCs. She too had a narrow, “pinched” nose.

IV-3

The proband’s 9 year old daughter had almost no scalp hair until she was 2 years old. Her hair now looks and feels entirely normal. She has no milia or BCCs, but on careful inspection we found two discrete patches of ice pick marks on the dorsum of her hands.

OTHER RELATIVES

III-1, an older sister of the proband, and IV-1, the son of III-2, have no history or clinical signs of BDCS. The proband’s maternal grandmother died of adenocarcinoma of the cervix aged 45 years. The proband’s maternal aunt, II-4, died of a sarcomatous malignancy thought to have been renal in origin aged 38 years. We do not know if these two women had features of BDCS.

None of the six members of the family examined personally had any palmar or plantar pits, increased pigmentation, or skeletal abnormalities. Their nails and teeth were normal (except for III-2 who had dental abscesses and then dental clearance at the age of 21 years) and they had little or no past history of eczema. They were of normal intelligence.

Scanning electron microscopic examination of the hair

Three or four hairs from each affected case were examined by scanning electron microscope (fig 7). All except IV-2 had a mixture of normal and abnormal hairs. The most common abnormalities were jagged scales and lifted scale edges. All IV-2’s hairs were abnormal. Some were kinked and some of them had no scale at all. IV-3 had no scales on the tips of some of her hairs. Hair from III-1 and IV-1, unaffected members of the family, had no abnormal features.

No pili torti or trichorhexis nodosa were seen on any of the hairs. The diameters of the hair shafts were normal.

Histological findings

Resected skin lesions from III-3, III-2, and II-1 were re-examined. Five specimens from II-2’s face were confirmed to be BCCs. One of them also contained a trichoepithelioma and a milial cyst. The proband had five histologically confirmed BCCs and three milial cysts. III-2 had four confirmed BCCs; a fifth specimen contained a milial cyst and a trichoepithelioma.

Hair follicles from perilesional skin were abnormally wide, plugged, and surrounded by an
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>No of cases</th>
<th>FA</th>
<th>BCC</th>
<th>Milia</th>
<th>Hypertrichosis</th>
<th>Hypohidrosis</th>
<th>Other features</th>
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<tr>
<td>2*22</td>
<td>1966</td>
<td>6</td>
<td>6</td>
<td>4</td>
<td>6</td>
<td>5</td>
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<td>2</td>
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<td>MH x 1</td>
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<td>'70/'94</td>
<td>20</td>
<td>8/8</td>
<td>4/8</td>
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<td>7</td>
<td>7/7</td>
<td>5/7</td>
<td>1/2</td>
<td>0/7</td>
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<td>16</td>
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<td>+</td>
<td>+</td>
<td>+</td>
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<td>1993</td>
<td>3</td>
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<tr>
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<td>8/8</td>
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<td>1995</td>
<td>5</td>
<td>4/4</td>
<td>3/5</td>
<td>4/5</td>
<td>4/5</td>
<td>3/4</td>
<td></td>
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<tr>
<td>% families &gt;1 affected</td>
<td>100</td>
<td>75</td>
<td>87</td>
<td>94</td>
<td>62</td>
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</table>

+ Present in some or all. NR = not recorded. – Not present. * Linked to Xq24–27.

Inflammatory cell infiltrate. Sweat glands were absent in nine out of 11 specimens.

**Laboratory and radiological findings**

* X rays of the skull, jaw, spine, chest, and hand in III.2, III.3, IV.2, and IV.3 were all normal. Chromosome analysis was normal in III.2 and serum zinc, copper, and thyroid function levels were normal in III.3. Linkage studies are under way and will be published separately in a collaborative study.

**Discussion**

The clinical features of our family are very similar to those reported in the original paper of Bazex et al.1 Our family had no features suggestive of Gorlin's syndrome23 apart from the milia and BCCs which are common to both syndromes. They also had no evidence of peripheral dilatation with cyanosis or vermicular atrophyderma, both of which are characteristic of Rombo's syndrome.24 This disorder is otherwise very similar to BDCS but has only been reported in one family and appears to be autosomal dominant. We originally thought that the proband's younger daughter, IV.3, was unaffected. But the SEM findings, the history of very sparse scalp hair until she was 2 years old, and the two discrete patches of FA suggest that she is mildly affected. The histological findings also support the diagnosis of BDCS in the dead grandmother, II.1.

Several authors have reported their SEM findings of hair in cases of BDCS.4,11,12,17 Pili torti and trichorexis nodosa were the most frequently described features, but we did not see them in our family. The lack of scale seen in two of the affected cases has not been reported before in BDCS. It is very rarely seen in the normal population, but can occur in extreme weathering.23

The histological findings of milia, BCCs, and trichoepitheliomas were similar to previous reports.25 A paucity of sweat glands seen in our specimens has also been reported before.2 However, our samples were all perilesional, so our result could be a sampling error. It is clear from published reports that follicular atrophyderma is a misnomer as there does not appear to be any atrophy of the hair follicles.2 Several authors have reported a number of different features ranging from completely normal follicles to widened, plugged, or lax follicles.25-27 FA is also seen in chondrodysplasia punctata (Conradi-Hunerman syndrome), another X linked dominant disorder, and in association with keratosis pilaris palmaris, keratosis follicularis, and hyperhidrosis palmaris.26

The clinical details of the 15 previously reported families are summarised in the table. There is marked intra- and interfamilial variability. FA has been documented as present from birth in two families10,16 and was present in early childhood in most cases. It occurs mainly on the dorsum of the hands and feet and on the knees, elbows, and face. Milia were present from birth in some reports,25 but definitely appeared later in infancy or childhood in others. They occurred mainly on the face and were most numerous during puberty. Goeteyn et al reported that the milia occurred in association with the BCCs and, interestingly, our proband had noticed that the BCCs sometimes evolved from the milia. The BCCs seem to be confined mainly to the face. The age of onset of the BCCs varied from 9 to 50 years.2 In most cases they started in the second or third decade. The degree of penetrance of BCCs is not yet clear and is likely to be influenced by environmental factors. BCCs do not appear to be more numerous in males. Goeteyn et al1 reported that the males had uniformly severe hypotrichosis, whereas the females had intermingled normal and abnormal hairs. Hypohidrosis could be generalised or be confined to the face. Posiloa et al confirmed local hypohidrosis by measuring water evaporation rates from forehead skin. Several authors reported papules, some of which were hyperpigmented.

None of the authors commented on a characteristic facial appearance, but on reviewing the facial photographs of nine cases from eight families we felt that six of them had a rather "pinched" appearance to their noses, similar to our own cases.25-27,11,15,17,18 Our cases had long, thin noses with hypoplastic nasal alae and prominent columella somewhat reminiscent of the nasal appearance in Ehlers-Danlos type IV syndrome.
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The only report7 of BDCS occurring in association with other malignancies described a 10 year old girl who was diagnosed as having BDCS at the age of 5 and who developed prolymphocytic leukaemia at the age of 10. In our family, the sister of II-2 died of a sarcoma at the age of 38 and the mother of II-2 died of cancer of the cervix at the age of 45, but we do not know if these women also had BDCS.

Two further families, of Italian extraction, described by Parrish et al23 and Oley et al20 had milia and hypotrichosis. The family of Oley et al also had multiple BCCs. The authors did not mention ice pick marks. Both of the pedigrees are compatible with X linked inheritance. We and other authors29 suspect that these families also have variants of BDCS.

Two cases from India were reported as “Bazex syndrome” but they were very atypical and we now believe that the diagnosis of BDCS is in some doubt: Mehta and Potdac28 described a 22 year old man from Bombay with multiple, dark, fibroepithelial papules interspersed with pits on his trunk. The man’s father and sister were said to have similar features. Somasundaram et al29 reported an isolated case of a 12 year old boy from Madras with multiple skin coloured papules on his face, ears, forearms, and scrotum. Lichenification of the skin had occurred. The papules were trichoepitheliomas, kerototic BCCs, or both. Ice pick marks were present on his forehead and he had patchy scalp alopecia. His hands and feet were short and stubby.

Reduced DNA repair capacities have been reported in some families with early onset of BCCs. This has not yet been studied in BDCS. Vabres et al23 have proposed a candidate gene for BDCS, UBE2A; its yeast homologue is involved in the repair of ultraviolet induced DNA damage and has been mapped to Xq24–q25.31 Fifty percent of the reported families originate from France or Belgium and we suspect that BDCS is underdiagnosed elsewhere. The ice pick marks can easily be overlooked and most of the early reports were in French. Identification of families with this disorder would be of considerable benefit to the affected subjects, as the condition can usually be recognised at an early age and exposure to UV light could be minimised in the hope that this would reduce the incidence of BCCs. Further studies are required to see if BDCS is associated with radiation sensitivity.

Finally, we feel that the term “Bazex syndrome” should be avoided as it can easily be confused with another unrelated syndrome of the same name, also known as “paraneoplastic acrokeratosis of Bazex”.32

We would like to thank the members of the affected family, Mrs D Marshall for her help with the SEM micrographs, Jon Campbell for his help in preparing the manuscript, Maureen Crompton for her help in translating French and German papers, and Professor Donnai for first suggesting that BDCS may be associated with a characteristic facial appearance.

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doi: 10.1136/jmg.33.6.493

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