REVIEW ARTICLE

Hornstein–Knickenberg syndrome vs. Birt–Hogg–Dubé syndrome: a critical review of an unjustified designation

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Abstract

The disorder that is presently called ‘Birt–Hogg–Dubé syndrome’ was in reality delineated in 1975 by Otto P. Hornstein and Monika Knickenberg from Erlangen (Germany) who emphasized that the occurrence of multiple ‘perifollicular fibromas’ represented a distinct autosomal dominant trait heralding extracutaneous cancer proneness. By contrast, Arthur R. Birt, Georgina R. Hogg and W. James Dubé from Winnipeg, Manitoba, Canada, claimed in 1977 that they had discovered ‘a previously unrecognized hereditary pilar hamartoma’ for which they proposed the name ‘fibrofolliculoma’, to be distinguished from the perifollicular fibromas as reported by Hornstein and Knickenberg. Today, many authors believe that ‘fibrofolliculoma’ is identical with ‘perifollicular fibroma’, but for the purpose of the present article this question can be left open. More importantly, the Canadian authors did not mention any association with extracutaneous cancer proneness within the large family examined in Winnipeg, nor when discussing the report from Erlangen, which means that they have neither described nor redescribed the syndrome that presently bears their names. Hence, the autosomal dominant disorder of multiple perifollicular fibromas heralding proclivity to extracutaneous cancer should be called after the original authors, Hornstein–Knickenberg syndrome.

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Conflicts of interest

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Pereant qui ante nos nostra dixerunt
May they perish who have expressed our bright ideas before us

In 1975, Otto P. Hornstein and Monika Knickenberg from Erlangen, Germany (Fig. 1) described a new autosomal dominant trait characterized by ‘perifollicular fibromatosis cutis’, multiple skin tags and multiple colonic polyps with proneness to cancer.1 They emphasized that this disorder was most likely ‘a cutaneo-intestinal syndrome sui generis’, which means of its own kind. In 1977, Arthur R. Birt, Georgina R. Hogg and W. James Dubé from Winnipeg, Manitoba, Canada (Fig. 2) described similar hereditary skin lesions as representing ‘a previously unrecognized hereditary pilar hamartoma’.2 Their publication resulted in an unwarranted eponymic designation.

The story how the syndrome was discovered

At the University Hospital of Erlangen, Germany, a 47-year-old woman was referred in April 1974 by the Department of Surgery to the Dermatological Outpatient Clinic for evaluation of numberless benign-looking skin tumours. She had undergone surgical removal of multiple bleeding polyps of the colon, including one colon carcinoma. The head of department, Otto Paul Hornstein, and the senior physician Monika Knickenberg had the immediate feeling of a highly unusual disorder, all the more because the patient reported that her father and one of her brothers had similar skin changes. The woman had countless skin tags preponderantly involving her neck and axillary areas. Moreover, ‘innumerable solid, skin-coloured nodules varying in diameter from 2 to 4 mm, most flat-topped, some rather prominent, are in profusion scattered over the face, the nape and both sides of the neck, as well as over the entire breadth of the back...As a typical feature, the nodules are arranged perifollicularly, as most of them show a small central pore or a minute keratotic plug’.1 Histopathological examination revealed ‘fibroma-like proliferations surrounding atrophic sebaceous glands and elongated strands of follicular epithelium some of them with an obliterating keratin plug. The connective tissue fibres are arranged in marked and whorl-shaped cords supplied with only a few fibroblasts and fibrocytes, some nodules extending to the subcutis and being rather sharply defined from the texture of the
normal corium’. In specimens from a skin tag, neither follicles nor sebaceous glands were found. Similar skin lesions were noted in the patient’s brother. Their father ‘who died of bilateral kidney cysts (and unilateral lung cysts), hypertension and cardiac insufficiency, was reported to have had skin nodules resembling his children’s on his face, neck and back’.1

The two dermatologists realized that this might be a new genodermatosis heralding extracutaneous cancer proneness. In May 1974, Hornstein took some vacation days and, equipped with his typewriter and an English dictionary, he went by car to a guesthouse in a nearby village where he prepared a draft delineating the novel ‘cutaneo-intestinal syndrome sui generis’.1 In 1976, the group from Erlangen specifically informed the gastroenterologists3 and medical geneticists4 on this ‘apparent autosomal dominant trait’.

A list of unjustified statements
1 In 2019, the home page of the ‘BHD Foundation’5 is informing interested families in the following way: ‘Birt–Hogg–Dubé syndrome (also known as BHD) is a hereditary condition named after the three Canadian doctors who first described it in 1977—Arthur R. Birt, Georgina R. Hogg and William J. Dubé. At first, BHD syndrome was thought to be a skin condition after skin lesions were found on the faces and necks of several members of an extended family’. This statement is untrue because initially the syndrome was not identified as a sole skin condition. In fact, the feature of extracutaneous cancer proneness was emphasized in 1975,1 that is, 2 years prior to the publication of Birt et al.2
2 In a review of the ‘BHD Foundation’ for researchers,3 we read that ‘BHD syndrome was described in 1977 by three Canadian doctors—Birt, Hogg and Dubé. Hornstein and Knickenberg had also identified the syndrome in 1975, and it has been suggested that the syndrome be renamed ‘Hornstein–Birt–Hogg–Dubé’.4 This statement is false in two ways. There is no syndrome of hereditary cancer proneness that has ever been described by the Canadian physicians. Hence, it is untrue that Hornstein and Knickenberg had also identified the syndrome in 1975. In fact, they were the only ones who delineated the phenotype characterized by extracutaneous cancer proclivity, whereas Birt et al.2 did not describe the syndrome that unduly bears their names.
3 Moreover, we read on the homepage of the BHD Foundation5:
‘Early studies suggested an association between BHD syndrome and colorectal neoplasia (Hornstein et al.3; Birt et al.2; Schachtschabel et al.7; Schulz and Hartschuh8).’ In reality, we cannot find in the text of Birt et al.2 any word about colon polyps or colorectal neoplasia. Admittedly, they cited the paper of Hornstein and Knickenberg2 that they had thoroughly studied, but they prudently and incorrectly amputated the title by eliminating the significant words ‘a cutaneo-intestinal syndrome sui generis’. Meanwhile, numerous authors have corroborated the nosological association between multiple perifollicular fibromas and colonic polyps/cancer,9–15 as advocated by the authors from Erlangen.1

Perifollicular fibromas or fibrofolliculomas?
The authors from Winnipeg2 claimed that the multiple ‘fibrofolliculoma’ of their patients represented ‘a previously
unrecognized hereditary pilar hamartoma involving both epithelial and fibrous tissues. By contrast, Hornstein and Knickenberg\(^1\) emphasized that the skin tumours of their patients had previously been described as ‘peripilar fibromas’ in France\(^6\) and subsequently as ‘perifollicular fibromas’ by other authors.\(^{17,18}\) Civatte and Le Tréguilly\(^19\) had even reported a familial occurrence of that trait. A comparison of these publications with the skin tumour described by Birt et al.\(^2\) shows that there are two possibilities. Firstly, the authors’ assumption of a new pilar hamartoma may have been right,\(^20\) which means that they claimed to delineate a skin tumour that was quite different from the ‘perifollicular fibroma’ as described by Hornstein and Knickenberg\(^1\) in an article that had meticulously been scrutinized by the authors from Winnipeg.\(^2\) If so, the Canadian authors were dealing with a heritable skin disorder that has nothing to do, as far as we know, with extracutaneous cancer proneness. Secondly, they may erroneously have described a skin tumour being identical with ‘perifollicular fibroma’.\(^{1,3,4,6}\) In either case, it is obvious that Birt et al.\(^2\) did neither discover nor describe any new cutaneous disorder heralding proclivity to extracutaneous cancer. Hence, the term ‘Birt–Hogg–Dubé syndrome’ represents a bold distortion of history and should no longer be used to describe the disorder specified by Hornstein and Knickenberg.\(^1\)

### A false diplomatic estimation of the present author

In 2012, I explained why the term ‘BHD syndrome’ does not make sense and proposed, as a compromise, the eponymous designation ‘Hornstein–Birt–Hogg–Dubé syndrome’.\(^6\) In 2019, however, I’m glad to see that nobody has adopted my proposal. Meanwhile, I’ve realized that it is not justified to combine the names of the discoverers of a new genodermatosis heralding extracutaneous cancer proneness with those claiming that they had detected a quite different hereditary skin disorder characterized by ‘fibrofolliculomas’, without any proclivity to extracutaneous cancer.

### Conclusion

Today, time has come to put this right. The syndrome should be named after the original authors, Hornstein and Knickenberg.\(^1\)

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