Eur J Dermatol 2005; 15 (5): 347-52

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Article accepted on 15/6/2005

Keratitis-ichthyosis-deafness syndrome in association with follicular occlusion triad

Keratitis-Ichthyosis-Deafness syndrome is a rare congenital disorder of the ectoderm caused by mutations in the *connexin-26* gene (*GJB2*) on chromosome 13q11-q12, giving rise to keratitis, erythrokeratoderma and neurosensory deafness. We report the case of a 31-year-old black male diagnosed as having KID syndrome. Sequencing analysis showed a heterozygous missense mutation D50N (148G > A) in the *GJB2* gene. In addition to the classical features of vascularizing keratitis, erythrokeratoderma and congenital deafness, our patient presented a follicular occlusion triad with hidradenitis suppurativa (HS, alias acne inversa), acne conglobata and dissecting cellulitis of the scalp, leading to cicatricial alopecia and disfiguring, inflammatory vegetations of his scalp. Conservative therapy such as a keratolytic, rehydrating and antiseptic external therapy, antibiotic, antimycotic and retinoids were only of moderate benefit, so we finally chose the curative possibility of surgery therapy of the axillar papillomas and of the scalp. The inflammatory papillomatous regions of the axillae and of the scalp were radically debrided. Clean granulation was awaited and covered in a second session with a mesh graft from the thigh, achieving a satisfactory result. To our knowledge, only one case of KID syndrome occurring in association with follicular occlusion triad has been reported before.

Key words: connexin-26, dissecting cellulitis, follicular occlusion triad, GJB2, ichthyosis, KID-syndrome, palmoplantar keratoderma

We report the case of a 31-year-old black male from the Emirates who came to our clinic suffering from cicatricial alopecia, malodorous fistulating papillomas of the scalp *(figures 1A* and *B)*, the axillae *(figures 2A, 2B)* and purulent draining sinus of the groins embedded in keloidal tissue. His skin was dry and scaled since birth. He had congenital deafness and as a consequence never developed speech. At the age of 15 years he developed an acne conglobata of chest, back and face. Although the patient's condition improved, some draining cysts on the face and hyperpigmented scars on the chest and back persisted. At age 22 he developed papillomas of the scalp and both axillae, leading to alopecia and dermal contraction with restricted extension of the arms up to 70 degrees. He had no history of severe systemic infections and no factors aggravating HS such as hyperandrogenism, smoking or obesity. His intelligence was normal. His brother had a history of acne comedonica. Apart from that, his family was phenotypically healthy.

He presented an ichthyosis cutis and a diffuse transgredient palmoplantar keratoderma *(figure 3)*. Due to the hyperkeratosis, his knees and back of his feet showed a pachydermatoglyphia in which dermatoglyphe crests were accentuated in thickness and height *(figure 4)*. His hips and thighs presented fine hyperkeratosis with a slightly erythrodermic aspect *(figures 5A, 5B*). The nails of his feet were dystrophic *(figure 4)*.

Slit lamp examination revealed bilateral vascularizing keratitis *(figure 6A* and *B)* and squamous blepharitis marginalis. In spite of these findings, visual acuity was normal. A hearing test showed complete hearing loss and no response wave in the evocated otoacoustic emissions *(figure 7)*, a sensorineural deafness. Additionally, he suffered from myringitis of the right ear. FACS analysis showed no immunodeficiency. Cultures of the draining abscesses of scalp, axillae and groin yielded no growth or variously grew *Staphylococcus aureus, Corynebacterium* and *Bacteroides*. The histology from skin biopsies of the scalp revealed a scarring folliculitis with rarefication of the adnexes and the follicles embedded in dense connective tissue *(figure 1B)*. Skin biopsies taken from the axillae showed cryptic formation within the epithelium and dense connective tissue with a perifollicular inflammatory infiltration *(figure 2B)*. Skin biopsies from an erythrokeratodermic region showed orthohyperkeratosis and segments of parahyperkeratosis above acanthopapillomatosis (*figure 5*B).

We diagnosed a Keratitis-Ichthyosis-Deafneass (KID)-Syndrome with vascularizing keratitis, ichthyosis cutis, erythrokeratoderma, palmoplantarkeratoderma and congenital neurosensory deafness. Additionally the patient fulfilled all the criteria of a follicular occlusion triad, presenting acne conglobata, hidradenitis suppurativa (HS) and dissecting cellulitis of the scalp. Under therapeutic mea-

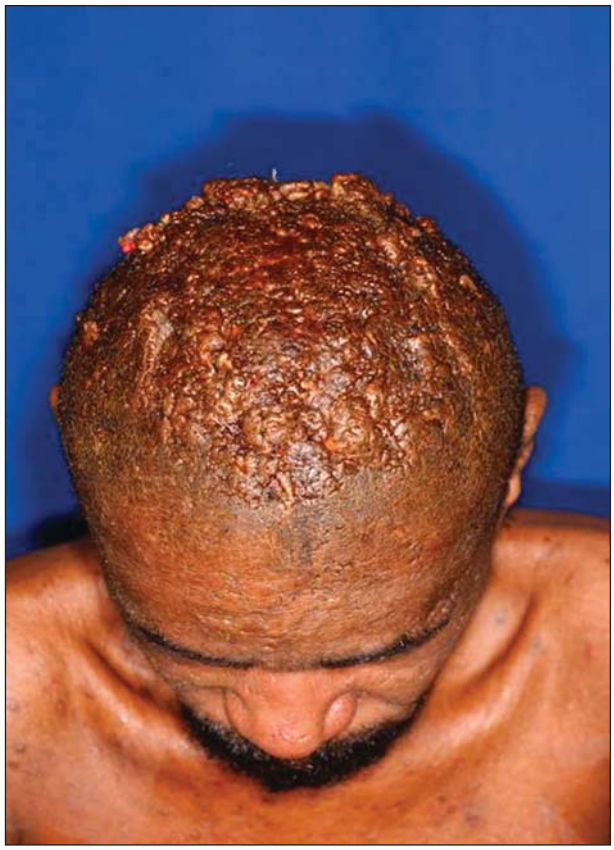

Figure 1A. Characteristic features of dissecting cellulitis of the scalp.

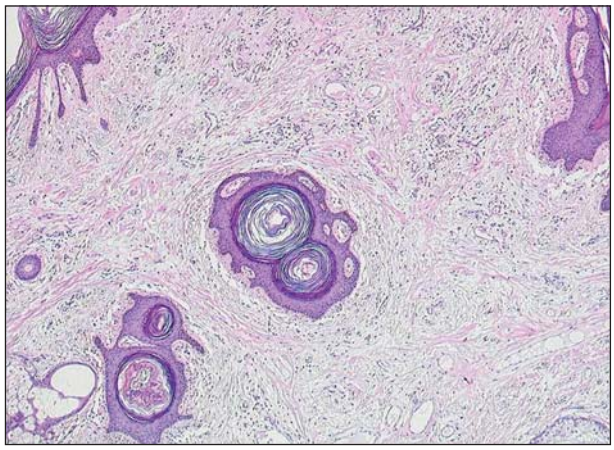

Figure 1B. Histology of dissecting cellulitis of the scalp revealing a scarring folliculitis with rarefication of the adnexes and the follicles embedded in dense connective tissue.

sures such as a keratolytic, rehydrating and antiseptic external therapy, antibiotic and antimycotic treatment, the clinical symptoms and infectious parameters were reduced. Therapy with isotretinoin, started some years previously, was without success. At admission of the patient to our department, we began an acitretin therapy but finally chose the curative possibility of surgery therapy of the axillar papillomas and of the scalp, as conservative therapy of the follicular occlusion triad shows a high rate of recurrence.

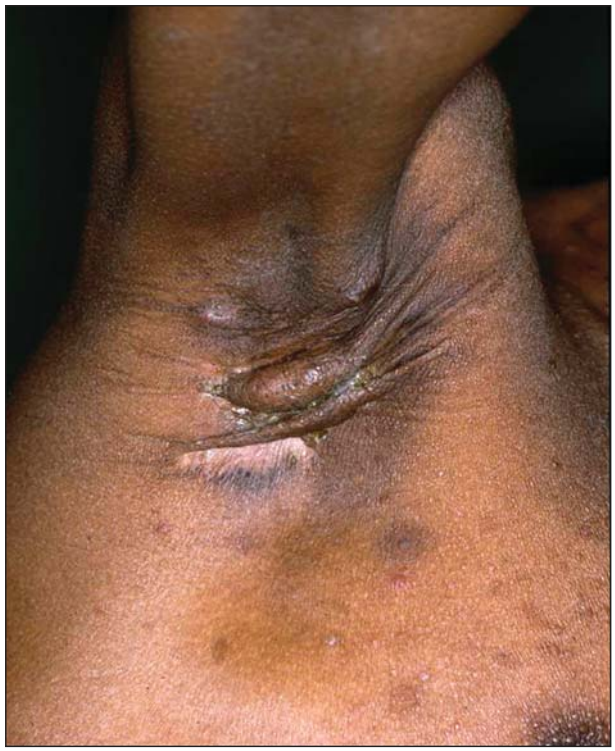

Figure 2A. Clinical picture of acne inversa of the axilla.

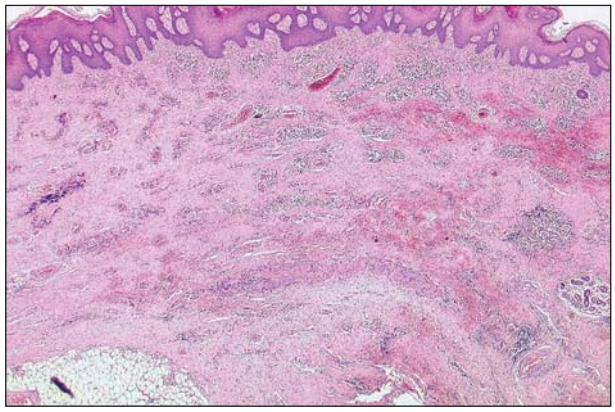

Figure 2B. Histology of acne inversa lesions of the axilla showing cryptic formation within the epithelium and dense connective tissue with a perifollicular inflammatory infiltration.

The inflammatory papillomatous regions of the axillae (department of Dermatology) and of the scalp (department of Oral and Maxillofacial Surgery) were radically debrided. Clean granulation was waited upon and covered in a second session with a mesh graft from the thigh, achieving a satisfactory result. With regard to the increased carcinogenic potential in both KID syndrome and follicular occlusion triad, periodical follow-up controls were scheduled.

Mutation analysis of the GJB2 gene

We used genomic DNA of the patient extracted from paraffin-embedded tissue samples for mutation analysis of the *GJB2* gene. The DNA was extracted using Quiagen Kit.

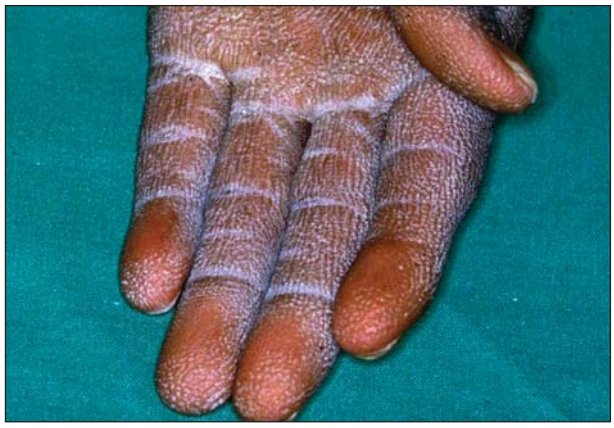

Figure 3. Transgredient palmarkeratoderma.

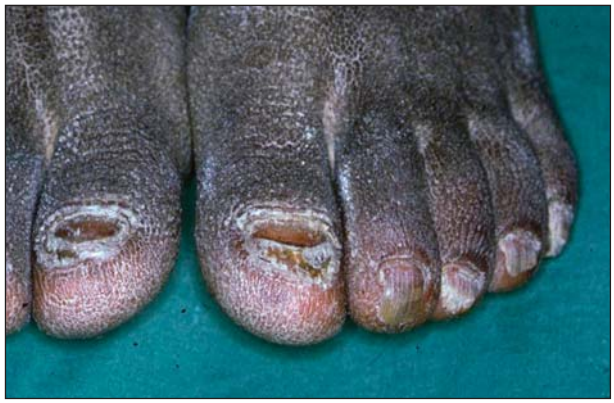

Figure 4. Pachydermatoglyphia of the back of his feet and nail dystrophy.

PCR was performed using standard conditions with primer pairs covering the coding region of the *GJB2* gene (primer sequences and PCR conditions are available on request). The PCR products were purified with the GFX™ PCR DNA Purification Kit (Amersham Biosciences) and directly sequenced using the BigDye® Terminator v1.1 Cycle Sequencing Kit (Applied Biosystems) on an ABI 3100 genetic analyser (Applied Biosystems). The sequencing analysis showed in addition to a known polymorphism (– 34C→T; NCBI ref SNP ID: 15 9578260) a heterozygous 148G→A transition in connexin 26 (Cx26) resulting in substitution of aspartic acid with asparagine in codon 50 (D50N).

Discussion

KID syndrome (MIM 148210) was first reported 1915 by Burns as a generalized congenital keratoderma with ocular and mucosal involvement, but the acronym KID syndrome was coined 1981 by Skinner *et al*. to highlight the main features of the syndrome [1]. Caceres-Rios *et al*. stated 1996 that approximately seventy cases, most of them sporadic, had been reported [2]. All of them showed cutaneous and auditory abnormalities, 90% sensorineural deafness, 89% erythrokeratoderma, 79% alopecia, 41% reticulated hyperkeratosis of the palms and soles and 95% had ophthalmologic defects, most of them (79%) had vascularizing keratitis. Caceres-Rios proposed the name keratoderatous ectodermal dysplasia, as the KID acronym does not accurately define this entity and the skin condition does not always show ichthyosis, but rather keratodermatous skin. However, a change in terminology has not been accepted yet.

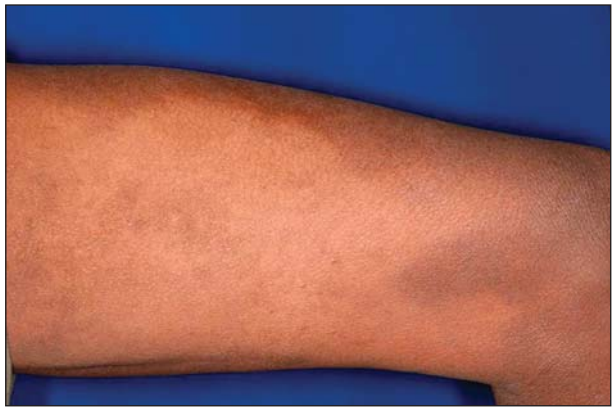

Figure 5A. Fine hyperkeratosis and erythrokeratoderma of his thighs.

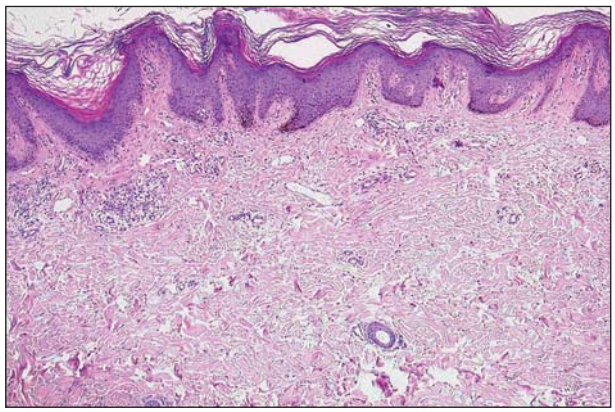

Figure 5B. Histology of erythrokeratoderma showing orthohyperkeratosis, segments of parahyperkeratosis above acanthopapillomatosis.

Both an autosomal dominant form [3] and an autosomal recessive form [4] have been described, but numerous sporadic cases [5] have also been reported. Heterozygous missense mutations in the *GJB2* gene localized on chromosome 13q11-q12 encoding a gap junction protein called connexin-26 were found to be associated with the KID-syndrome [6-8]. Connexines are universal integral membrane proteins forming inter- and intracellular channels for ion and molecule transfer, aqueous gap junction channels, thus influencing a wide range of cellular activity [9]. Intercellular signalling through gap junctions is essential for tissue homeostasis, tissue growth and development, and cellular response to external stimuli [10]. KID and Hystrix Ichthyosis Deafness (HID) syndrome share the same connexin-26 mutation [8]. Chronic cutaneous bacterial and mycotic infections may develop and contribute to alopecia, nail dystrophy and body odour. Death in infancy from overwhelming infection has been reported in several patients with KID syndrome [11, 12]. The susceptibility of

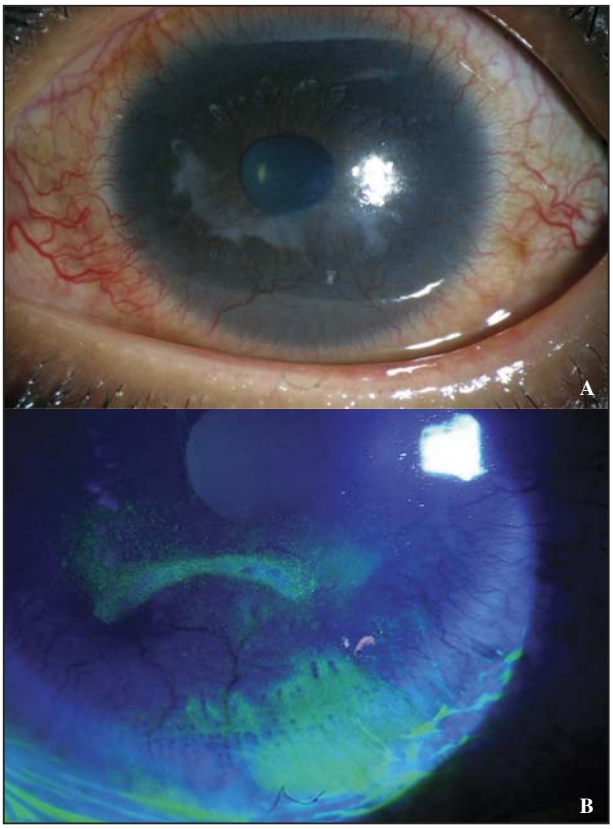

Figure 6. Vascularizing keratitis; differently shaped corneal paracentral opacities of the cornea accompanied by superficial punctuated keratopathia as well as epithelial and stromal vascularisation (A) native, (B) fluorescein staining.

KID to viral, bacterial and mycotic infections and the severity of infections (septicemia) suggest a primary immunodeficiency in addition to an imperfect cutaneous barrier to micoorganisms. An increased oncogenic potential with invasive squamous cell carcinoma arising within the hyperkeratotic lesions has been reported in several KID patients [6, 13]. Other disorders as hypohidrosis, dermoskeleton dystrophies, cerebellar hypoplasia, Hutchinson's triad

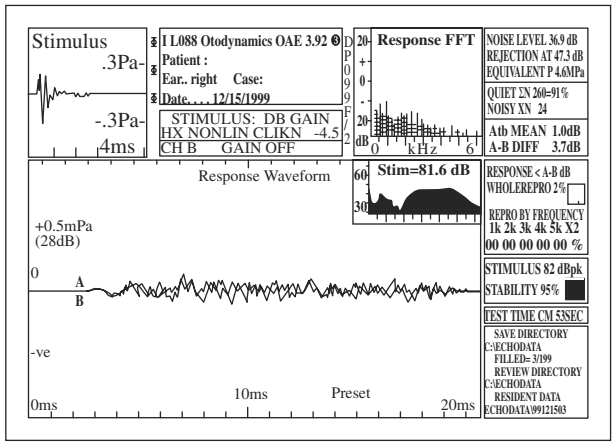

Figure 7. Sensorineural deafness without response in the evocated otoacustic emissions.

symptoms, cryptorchidisma and peripheral neuropathy may be associated. Cases of Carotenaemia, generalized cytomegalia infection, malignant histiocytoma and hair follicle tumours have been described. Congenital sensorineural deafness is evident during infancy in most patients. In typical KID syndrome, progressive corneal vascularization occurs in childhood, often after a febrile illness, and leads to blindness by adolescence. Delayed onset of the keratitis has been reported. Intellect is unaffected but the combined disabilities of deafness, blindness and disfigurement impose severe limitations and hardship on the individual. The major differential diagnosis of KID is Keratosis palmoplantaris mutilans Vohwinkel with or without deafness [14], but, unlike KID, without ophthalmological changes (details shown in *table 1*). The treatment consists of a keratolytic, rehydrating and antiseptic external therapy, antibiotic and antimycotic treatment and systemic retinoids.

The follicular occlusion triad is constituted by acne conglobata, hidradenitis suppurativa and dissecting cellulitis of the scalp [15]. The assumed pathophysiology of these disorders is occlusion of the follicular pores and a subsequent granulomatous response to the ruptured duct contents [16]. HS is a recurrent disease manifested by abscesses, sinus

Table 1. Differential diagnosis of KID syndrome

Keratoderma	Eponyms	Encoding	Special features
Keratoderma with prelingual deafness (MIM 148210)	KID-syndrome Erythokeratoderma progressiva Burns	Connexin-26	•Vascularizing keratitis, •Erythrokeratoderma, •Palmoplantar Keratosis, •Deafness
Cicatrizing keratoderma with hearing loss (MIM 124500)	Vohwinkel, Keratoma hereditarum mutilans	Connexin-26	•Papular lesions becoming confluent, •Starfish keratosis, •Pseudo-ainhum, •mild hearing impairment
Loricrin keratoderma (MIM 604117)	Camisa Variant Vohwinkel	Loricrin	•Mild Ichthyosis, •Honeycomb pattern •Keratoderma, •Pseudo-ainhum (cicatricial bands around digits) •No deafness

Table 2. Differential diagnosis of Dissecting cellulitis

Chronic scarring bacterial scalp conditions acquired scalp alopecia	Characteristics
Dissecting cellulitis	Painful nodules, purulent drainage, burrowing interconnecting abscesses and cicatricial alopecia
Acne keloidalis nuchae	Keloidal plaques on the back of the neck
Tufted hair folliculitis	Multiple hair tufts emerge from dilated follicular orifices
Folliculitis decalvans	Central scarred patches of alopecia and atrophy without nodules or sinuses
Pseudopelade of Brocq	Atrophy
Tinea capitis	Positive fungal culture and palpable lymph nodes
Follicotropic mycosis fungoides	Large-cell transformation

tracts and scarring, with a predilection for intertriginous areas. It affects an estimated 4.1% of the population with a female preponderance, except for patients with axillary lesions [17]. There is often a family history with autosomal dominant inheritance [18] and the onset is usually in late adolescence. Aetiological factors such as hyperandrogenism, obesity, smoking [19] and chemical irritants are not consistently associated with the affection, but in some patients may be relevant aggravating factors. Potential complications include dermal contractions, local or systemic infection due to the spread of microorganisms, systemic amyloidosis, arthropathy, and squamous cell carcinoma.

Dissecting cellulitis (also called Hoffmann's disease or perifolliculitis capitis abscedens et suffodiens) manifests with perifollicular pustules, nodules, abscesses and sinuses that evolve into scarring alopecia. It occurs predominantly in African American men between 20-40 years of age [20], but can occasionally affect other races [21] and women [22], too. Associated musculoskeletal findings are sometimes reported. Dissecting cellulitis must be distinguished from several other chronic scarring bacterial scalp conditions summarized in *table 2*. The course of both dissecting cellulitis and HS is chronic and relapsing, and treatment is often difficult. Medical therapies include an external antiseptic treatment, retinoids, antibiotics, oral zinc and steroids. Destructive therapies include surgical excision with skin grafting for both, X-ray therapy and laser epilation in patients with dissecting cellulitis of the scalp [23-25].

Montgomery *et al*. found a novel heterozygous point mutation (C119T) in *GJB2* in a patient with features of KID syndrome and the follicular occlusion triad [26]. Though our patient showed the same clinical features, we only identified the pathogenic mutation D50N found in the majority of KID patients [6-8, 12, 27-29]. The follicular occlusion triad was more severe than in the white patient described by Montgomery, which might be due to his ethnic group. Darker-skinned persons have higher incidence rates of dissecting cellulitis of the scalp [20] and complications of acne such as postinflammatory hyperpigmentation and keloidal scarring [20, 30]. Features of the follicular occlusion triad in patients with KID syndrome might result from the hyperproliferative epidermis leading to obstruction of follicular orifices, cyst formation, rupture and secondary inflammatory response to the extruded keratin and secretions [26]. Cx26 is expressed in the skin most commonly on the palms and soles and there is a high expression of Cx26 in hair follicles and eccrine sweat glands [10]. Whether Cx26 mutations are associated with disorders of the sebaceous glands besides hyperkeratotic skin diseases, hearing loss, ophthalmological and neurological changes, remains to be elucidated. ■

Acknowledgements. *We thank Jana Pforr for excellent technical assistance. RCB is supported by an Emmy Noether research grant from the Deutsche Forschungsgemeinschaft (DFG).*

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