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Hidradenitis suppurativa

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THE POSSIBLE ASSOCIATION OF HIDRADENITIS SUPPURATIVA AND DOWN SYNDROME:

ARE IMPAIRED NOTCH SIGNALING AND
IMMUNOLOGICAL ABNORMALITIES THE MISSING
LINKS?

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ABSTRACT

Hidradenitis suppurativa (HS) is an inflammatory skin disease of unknown origin. Recently, it has been demonstrated that mutations in several genes encoding for the protease γ -secretase (GS), including presenilin-1 (*PSEN1*), probably play a major role in the pathogenesis through impairment of the Notch signaling pathway. Mutations in *PSEN1* are also associated with Alzheimer's disease (AD), a condition that is strongly related to Down syndrome (DS). HS occurring in patients with DS has been described in only five patients so far. Here we describe five new cases. An association between HS and DS is reasonable since trisomy of chromosome 21 leads to overexpression of the amyloid precursor protein (APP) resulting in a change of the substrate pool for GS processing at the expense of the Notch receptors. Consequently, Notch signaling is impaired in DS predisposing these individuals to HS. APP itself may also directly influence keratinocytes resulting in the typical histopathological features seen in HS. Finally, the relatively high prevalence of obesity amongst DS patients as well as alterations in their immune system could underlie the possible association between both conditions. To confirm our hypothesis, further studies are needed investigating the expression of Notch receptors and APP in the epidermis of DS patients.

Hidradenitis suppurativa (HS) is an inflammatory skin disease that usually arises after puberty and severely impairs quality of life. Smoking, obesity, genetics and abnormalities of the immune system are important risk factors for the development of HS.⁽¹⁾ The latter makes that the disease is generally responsive to immunosuppressive agents, including to tumor-necrosis-factor (TNF)- α inhibitors.¹ Our knowledge regarding the pathogenesis, risk factors and treatment may be further enhanced by studying conditions that tend to co-occur with HS. Here, we describe five cases where HS occurred in Down syndrome (DS). The cases are summarized in table 1 and figure 1. The disease characteristics and course of patients 1-3 have several similarities: they have therapy resistant disease located at the (ano)genital area and a pre-pubertal onset. Patients 4 and 5 are monozygotic twins whose other family members were not affected by HS.

DS is caused by trisomy of chromosome 21 and occurs in approximately 1 of 1000 newborns. The co-occurrence of HS and DS has previously been described in three men and two women.²⁻⁴ The phenotype of DS is complex and includes a broad range of cognitive and neurological deficits. Two hypotheses have been proposed regarding the cause of the DS phenotype: the “developmental instability hypothesis” states that developmental pathways are disrupted through a general genetic imbalance whereas the “gene-dosage theory” implies that increased expression of certain genes on chromosome 21 is responsible. We think that the genetic abnormalities of DS might also predispose these individuals to the development of HS. Previously, loss-of-function mutations in the genes encoding for the γ -secretase (GS) complex have been identified in familial HS, including nicastrin (*NCSTN*), presenilin-1 (*PSEN1*) and presenilin enhancer 2 (*PSENEN*).⁵ GS is a transmembranous enzyme complex that enhances intracellular Notch signaling by cleavage of the Notch receptor (figure. 2). Humans have four Notch receptors of which Notch-1 and Notch-2 are predominantly expressed in the epidermis.⁶ GS-deficiency and inhibition of Notch-1 and -2 in mice causes replacement of hair follicles by epidermal cysts and diminished sebaceous gland differentiation, which are typical features of HS.⁵ Impaired Notch signaling also inhibits the generation of natural killer cells and causes an insufficient suppression of the innate immune system once it is activated, resulting in a compromised defense mechanism and continuing inflammatory activity, respectively.⁵ GS is also a key player in the development of Alzheimer's disease (AD). By the fourth decade of life characteristic β -amyloid ($A\beta$) brain plaques start to develop in DS that eventually give rise to AD. $A\beta$ is a product resulting from GS-cleavage of the amyloid precursor protein (APP). APP is also strongly expressed in the human epidermis.⁷ The gene encoding for APP has shown to be located on chromosome 21 and its expression is therefore, in accordance with the “gene dosage hypothesis,” probably increased in DS. APP and one of its other cleavage products sAPP α (secretory N-terminal ectodomain of APP) stimulate keratinocyte adhesion, migration

and proliferation.⁷ This makes DS patients prone to keratinocyte hyperproliferation and follicular plugging, which are major histopathological features of HS. Furthermore, Berezovska *et al.*⁸ demonstrated that APP and the Notch receptor are competitive substrates for GS and that Notch-1 signaling was diminished in primary neurons overexpressing APP. The increased amounts of APP that need to be processed by GS in DS might therefore occur at the expense of Notch processing. The genes encoding for the Notch receptors and GS are in contrast to APP not located on chromosome 21. Thus, increased APP expression might represent the missing link between HS and DS by enhancing keratinocyte activity as well as by being a competitive substrate for Notch receptors, leading to impairment of Notch-1 and -2 signaling (figure. 2).

Finally, obesity and a dysregulated immune system might also contribute to an association between DS and HS. The majority of the patients in our case series were overweight or obese (four out of five patients). Indeed, the prevalence of obesity is higher in children with DS compared to healthy children, making them more prone for the development of HS as well as to a more severe course of the disease. Additionally, DS patients are more susceptible to the development of infections and autoimmune disorders, like celiac disease, due to intrinsic immunological defects.⁹ With five new cases we strengthen the thought that DS and HS are associated. We hypothesize that this results from increased APP expression, an altered immune system and increased prevalence of obesity in DS. Further studies comparing the expression of Notch receptors and APP in the epidermis of DS patients and controls are needed to confirm our hypothesis.

	Patient 1	Patient 2	Patient 3	Patient 4 ^a	Patient 5 ^a
Seks	Female	Female	Male	Female	Female
Age (years)	14	16	13	24	24
Age at disease onset (years)	9	10	13	20	20
BMI (kg m ⁻²)	33.1	22.9	27.1	35.2	37.2
Family history	Negative	Negative	Negative	Negative ^b	Negative ^b
Location affected by HS	Genital area	Anogenital area	Genital area and upper legs	Armpits and groins	Armpits and groins
Treatment history	SA, anti-androgens, prednisone, etanercept, infliximab, surgery	SA, i.l. Corticosteroids, surgery	TA, SA	SA, surgery	SA, surgery
Current treatment	infliximab 5 mg kg ⁻² every 4 weeks	i.l. Corticosteroids	Doxycycline 100 mg daily	None	None

^aMonozygotic twin sisters; ^bexcept for the monozygotic twin sister no other family members were affected. BMI, body mass index; HS, hidradenitis suppurativa; i.l., intralesional; SA, systemic antibiotics; TA, topical antibiotics.

Table 1. Characteristics of the patients with Down syndrome

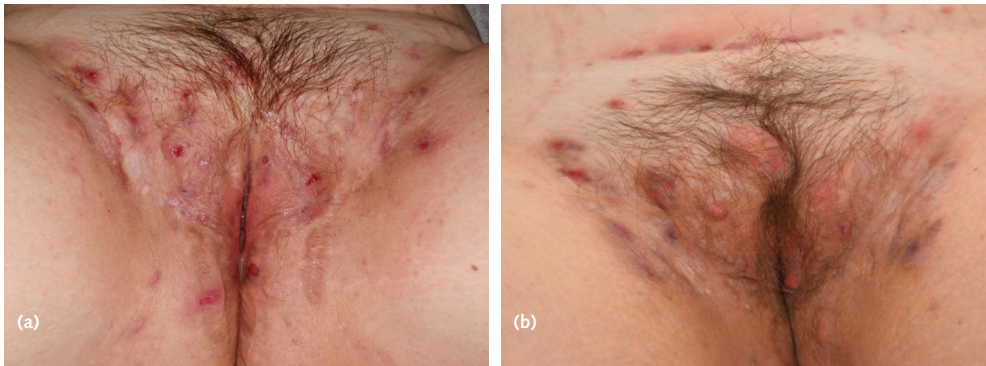


Figure 1. (a) Patient 1 with erythematous nodules, fistulae and scarring located on the genital area, before treatment with infliximab. (b) Four months later after four infusions of infliximab; the hidradenitis suppurativa has improved to some extent but there are still multiple active nodules and fistulae present.

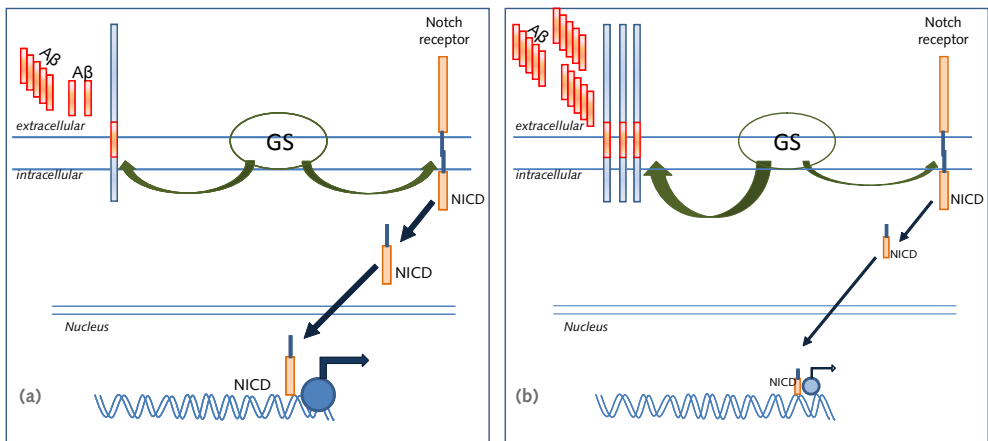


Figure 2. (a) Normal situation: amyloid precursor protein (APP) and the Notch receptor are both processed by *g*-secretase (GS). APP is cleaved by GS whereupon β -amyloid ($A\beta$) is released. The Notch receptor is also cleaved by GS leading to the release of the nuclear intracellular domain (NICD). NICD enters the nucleus where it activates the transcription factor for the Notch target genes that enhance epidermal differentiation and immune regulation. (b) patients with Down syndrome: increased expression of APP changes the substrate pool of GS. Increased amounts of GS are required for APP processing occurring at the expense of the Notch receptor. This leads to a “functional GS deficiency” for Notch processing whereupon the release of the NICD is prevented resulting in impaired intracellular Notch signaling.

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