

IN-DEPTH REVIEW

Hidradenitis Suppurativa and Down Syndrome: Systematic Review and Meta-Analysis

Niyaz Mostafa, MD^{1,2}, Kevin Phan, MD^{1,2,3}, Tajrian Amin, MD¹, Saxon D. Smith, MBChB, PhD⁴

¹ Faculty of Medicine, University of New South Wales (UNSW), Sydney, Australia

² St. George Dermatology and Skin Cancer Centre, Kogarah, Australia

³ Department of Dermatology, Liverpool Hospital, Sydney, Australia

⁴ The Dermatology and Skin Centre, Gosford, Australia

ABSTRACT

Introduction: Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease, characterized by the presence of painful lesions and recurrent abscesses, and nodules. These lesions can later rupture to form sinus tracts and fistulas. The exact etiology of HS is currently unknown, however a link between genetic, social and environmental factors has been postulated in recent studies. A number of studies have shown a significant association between HS and down syndrome (DS), however the relationship between HS and DS is unclear. We conducted a systematic review and meta-analysis to test for any association between HS and down syndrome.

Methods: A systematic review of existing studies was performed and data was pooled for meta-analysis. Reviews, abstracts and case reports were excluded. Eligible studies were those which investigated HS in cases of down syndrome. Studies that reported DS cases amongst HS patients were not included in the present study.

Results: A total of 6 studies were identified from systematic database searches after applying inclusion and exclusion criteria. Pooled meta-analysis demonstrated a significant association between HS and down syndrome. The pooled proportion of HS cases in the DS group was 10.9% (95% CI, 3.8%-27.6%). The pooled proportion of HS cases in the control group was 0.4% (95% CI, 0.2%-0.8%). This difference was significantly different ($P < 0.001$). The odds ratio is 12.02 (95% CI 10.91-13.23).

Conclusion: The evidence for hidradenitis suppurativa being associated with down syndrome is very limited. The data is promising however, and further prospective studies with larger cohorts are required to reaffirm the findings in the present review.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease that affects 1-4% of the population¹⁻³. It is characterized by the presence of painful lesions and recurrent abscesses, and nodules affecting the skin. These lesions can later rupture to form sinus tracts and fistulas. HS is a progressive disease that is debilitating and can impact an individual across physical, social and

emotional domains, which is worsened in the absence of adequate management. The exact etiology of HS is currently unknown, however a link between genetic, social and environmental factors has been postulated in recent studies¹⁻³.

Down syndrome, also known as trisomy 21, is one of the most common chromosomal disorders affecting chromosome 21. It presents with a number of features in affected patients including, intellectual

May 2022 Volume 6 Issue 3

disability, congenital heart disease as well as other diseases involving different systems of the body⁴. DS affects between 1 in 400-1500 babies born across different populations, which varies according to maternal age and screening schedules in the prenatal period⁵.

There is an increased prevalence of mucocutaneous disorders amongst DS patients in comparison to the general population source ⁶. A number of studies have shown a significant association between HS and Down syndrome (DS)⁷⁻¹², however the relationship between HS and DS is unclear. We conducted a systematic review and meta-analysis to test for any association between HS and Down syndrome.

METHODS

Search strategy

We performed a systematic review and meta-analysis in accordance to the recommended Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search was performed in 2021 and Electronic searches were performed using Ovid Medline, PubMed, Cochrane Central Register of Controlled Trials (CCTR), Cochrane Database of Systematic Reviews (CDSR), ACP Journal Club, and Database of Abstracts of Review of Effectiveness (DARE) from their dates of inception to August 2021. Search terms included: "hidradenitis suppurativa", "hidradenitis suppurative", "acne inversa", "velpeau", "verneuil" combined with "Down syndrome" or "trisomy 21". The resulting articles were assessed systematically by two independent reviewers using the inclusion and exclusion criteria.

Selection Criteria

All eligible studies included those investigating the presence of HS in a population of Down syndrome patients. Studies that reported DS cases amongst HS patients were not included in the present study. All studies must have included either the proportion of patients with HS in each group or the summary effect size for association between HS and DS.

Data extraction and quality assessment

The data was extracted by two independent reviewers from articles text, tables and figures. The data of interest included study type, location, demographic data and information related to the proportion of patients with HS in a DS patient population. The quality of the studies was assessed using the Newcastle-Ottawa scale.

Statistical Analysis

Firstly, to establish variance of raw proportions, a logit proportion transformation was applied. To incorporate heterogeneity (anticipated among the included studies), transformed proportions were combined using DerSimonian-Laird random effects models. Finally the pooled estimates were back-transformed. Heterogeneity was evaluated using Cochran Q and I² test. Meta-regression based on subgroup (Down syndrome versus controls) was performed. All analyses were performed using the metafor package for R version 3. P values <0.05 were considered statistically significant.

RESULTS

A total of 30 studies were identified from the electronic database search. After applying inclusion and exclusion criteria, six studies were included for the present systematic review and meta-analysis (Figure 1).

Study Characteristics

Study characteristics and demographic data are summarized in Table 1. Four studies were retrospective and observational in nature^{7,9-11}, whereas the other 2 included studies were case-control studies^{8,12}. Three studies reported age ranges^{8,10,11} and only Garg et al.⁸ adjusted their statistical analysis for confounding factors.

Assessment of study bias

The risk of bias in this study was evaluated using the Newcastle Ottawa scale for cohort and cross-sectional studies. The results are summarized in Table 1. A majority of studies scored 7 or higher, indicating a low level of bias amongst the studies.

Association between HS and DS

Pooled meta-analysis demonstrated a significant association between HS and Down syndrome (Figure 1). The pooled proportion of HS cases in the DS group was 10.9% (95% CI, 3.8%-27.6%). The pooled proportion of HS cases in the control group was 0.4% (95% CI, 0.2%-0.8%). This difference was significantly different ($P < 0.001$). The odds ratio is 12.02 (95% CI 10.91-13.23).

DISCUSSION

From the present meta-analysis and systematic review of observational and case-control studies, we demonstrated a significant association between HS and Down syndrome. Our findings add to the limited, but expanding body of literature that

Table 1. Study Characteristics

HS and other follicular disorders may be associated with DS. Treating clinicians should be aware of the potential link between these 2 conditions in order to institute early intervention in future DS patients.

The exact etiology of HS in DS remains unclear, however our findings suggests that there may be some form of genetic predisposition to HS in Down syndrome patients as postulated in other studies¹³. The link between HS and DS may be related to the increased expression of amyloid precursor protein (APP), normally encoded by a gene located on chromosome 21¹⁴. In DS patients, cleavage of APP by gamma-secretase leads to the formation of beta-amyloid plaques. The presence of the plaques leads to patients developing Alzheimer's disease earlier in life compared to the general population. APP also plays a role in the epidermis, particularly in stimulating the adhesion, migration and proliferation of keratinocytes¹⁵. Increased APP in DS patients may cause the hyperproliferation of keratinocytes and plugging of follicles, which is seen histopathologically as features in HS. Gamma Contributing to this theory, in familial HS, functional mutations of genes encoding the gamma-secretase protein complex have been observed¹⁶. Mutations in gamma-secretase and increased APP in DS may also lead to a defective notch signalling pathway and altered pro-inflammatory effects down the line^{13,17}. This includes inadequate suppression of the innate immune system, causing inflammation, a hallmark of HS, as well as the inhibition of natural killer cell activity. Another potential link between HS and DS is the shared comorbidity of obesity. There are

Study	Location	Design	Cases/Controls	Females % (cases/control)	Age in years (cases/control)	Adjustment	NOS
Firsovicz et al., <i>Pediatr Dermatol</i> , 2020	USA	Retrospective observational	243/0	NA	NA	NA	7
Garg et al., <i>Br J Dermatol</i> , 2018	USA	Case-control	11936/16813290	60/44	18-29 ¹ 36/18 30-39 23/16 ≥ 40 41/66	Down syndrome, age, sex, race, obesity	7
Hamadah et al., <i>Pediatr Dermatol</i> , 2017	Saudi Arabia	Retrospective observational	29/0	NA	NA	NA	7
Poizeau et al., <i>Acta Derm Venerol</i> , 2019	France	Retrospective observational	783/0	46/0	HS 23 (10-53)/0 ² Non-HS 31(9-67)/0	NA	7
Rork et al., <i>Pediatr Dermatol</i> , 2020	USA	Retrospective observational	101/0	39/0	19.7 (15.9)/0 ³	NA	8
Sechi et al., <i>Dermatol Pract Concept</i> , 2019	Italy	Case-control	131/12351	42/38	NA	NA	6

NA, not reported; NOS, Newcastle-Ottawa scale for study quality; 1, age reported as means in different age groups; 2, age reported as median and range; 3, age reported as mean and standard deviation

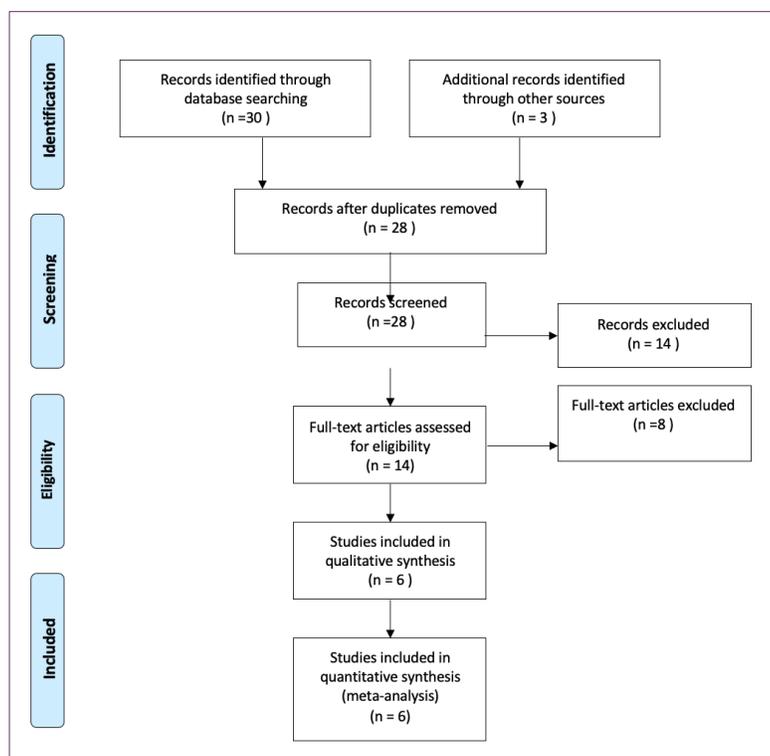


Figure 1. PRISMA flowchart

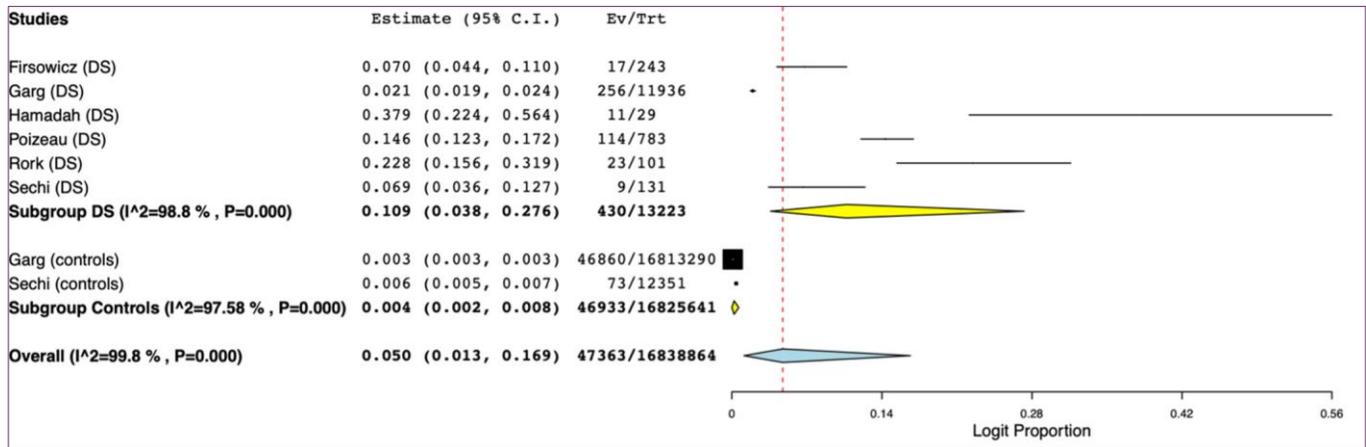


Figure 2. Forest plot assessing the relationship between hidradenitis suppurativa and Down syndrome compared to controls.

increased frequencies of obesity in children with DS in comparison to healthy children¹⁸. This common comorbidity between both diseases may mean that obesity in patients with DS may predispose them to HS^{19,20}

HS is also associated with several other comorbidities including smoking, dyslipidaemia, diabetes mellitus and metabolic syndrome³ as well as those associated with the integumentary system such as acne and pilonidal disease²¹. Recent evidence based recommendations from the US and Canadian HS foundations suggest regular screening for such comorbidities as well as screening DS patients for HS²². The decision to screen for certain diseases should vary based on patient risk factors.

The present review has several limitations. The studies included were composed of both case-control and observational studies, which were mostly retrospective, making them susceptible to selection and assessment bias. Confounder variables may have influenced the analysed effect sizes, which were unadjusted. Data for a majority of studies was obtained from large databases which may have errors in coding disease parameters, and there is likely heterogeneity between the criteria used for

HS and Down syndrome diagnosis. Prospective studies with larger cohorts are required to reaffirm the findings in the present review.

DISCUSSION

Pooled analysis of existing studies reveals that patients with DS are associated with an increased risk of HS in comparison to controls. Dermatologists and other clinicians involved in the care of patients with DS should be aware of this association and implement early screening and intervention based on risk factors in this cohort.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:

Niyaz Mostafa
University of New South Wales
Faculty of Medicine
Sydney, Australia, 2052
Email: nmostafa.research@gmail.com

References:

1. Vekic DA, Frew J, Cains GD. Hidradenitis suppurativa, a review of pathogenesis, associations

- and management. Part 1. *Australas J Dermatol*. 2018;59(4):267-277. doi:10.1111/ajd.12770
2. Fimmel S, Zouboulis CC. Comorbidities of hidradenitis suppurativa (acne inversa). *Dermatoendocrinol*. 2010;2(1):9-16. doi:10.4161/derm.2.1.12490
 3. Garg A, Kirby JS, Lavian J, Lin G, Strunk A. Sex- and Age-Adjusted Population Analysis of Prevalence Estimates for Hidradenitis Suppurativa in the United States. *JAMA Dermatology*. 2017;153(8):760-764. doi:10.1001/jamadermatol.2017.0201
 4. Roizen NJ, Patterson D. Down's syndrome. *Lancet*. 2003;361(9365):1281-1289. doi:10.1016/S0140-6736(03)12987-X
 5. Kazemi M, Salehi M, Kheirollahi M. Down Syndrome: Current Status, Challenges and Future Perspectives. *Int J Mol Cell Med*. 2016;5(3):125-133.
 6. Daneshpazhooh M, Nazemi TMJ, Bigdeloo L, Yoosefi M. Mucocutaneous findings in 100 children with Down syndrome. *Pediatr Dermatol*. 2007;24(3):317-320. doi:10.1111/j.1525-1470.2007.00412.x
 7. Firsowicz M, Boyd M, Jacks SK. Follicular occlusion disorders in Down syndrome patients. *Pediatr Dermatol*. 2020;37(1):219-221. doi:10.1111/pde.14012
 8. Garg A, Strunk A, Midura M, Papagermanos V, Pomerantz H. Prevalence of hidradenitis suppurativa among patients with Down syndrome: a population-based cross-sectional analysis. *Br J Dermatol*. 2018;178(3):697-703. doi:10.1111/bjd.15770
 9. Hamadah I, Haider M, Chisti M, Binamer Y. Hidradenitis Suppurativa in Down Syndrome: A Case Series. *Pediatr Dermatol*. 2017;34(4):461-464. doi:10.1111/pde.13188
 10. Poizeau F, Sbidian E, Mircher C, et al. Prevalence and Description of Hidradenitis Suppurativa in Down Syndrome: A Cross-sectional Study of 783 Subjects. *Acta Derm Venereol*. 2019;99(3):351-352. doi:10.2340/00015555-3095
 11. Rork JF, McCormack L, Lal K, Wiss K, Belazarian L. Dermatologic conditions in Down syndrome: A single-center retrospective chart review. *Pediatr Dermatol*. Published online June 10, 2020. doi:10.1111/pde.14214
 12. Sechi A, Guglielmo A, Patrizi A, et al. Disseminate Recurrent Folliculitis and Hidradenitis Suppurativa Are Associated Conditions: Results From a Retrospective Study of 131 Patients With Down Syndrome and a Cohort of 12,351 Pediatric Controls. *Dermatol Pract Concept*. 2019;9(3):187-194. doi:10.5826/dpc.0903a03
 13. Blok J, Jonkman M, Horváth B. The possible association of hidradenitis suppurativa and Down syndrome: is increased amyloid precursor protein expression resulting in impaired Notch signalling the missing link? *Br J Dermatol*. 2014;170(6):1375-1377. doi:10.1111/bjd.12887
 14. Jenkins EC, Devine-Gage EA, Robakis NK, et al. Fine mapping of an Alzheimer disease-associated gene encoding beta-amyloid protein. *Biochem Biophys Res Commun*. 1988;151(1):1-8. doi:10.1016/0006-291x(88)90551-7
 15. Herzog V, Kirfel G, Siemes C, Schmitz A. Biological roles of APP in the epidermis. *Eur J Cell Biol*. 2004;83(11-12):613-624. doi:10.1078/0171-9335-00401
 16. Wang B, Yang W, Wen W, et al. Gamma-secretase gene mutations in familial acne inversa. *Science*. 2010;330(6007):1065. doi:10.1126/science.1196284
 17. Melnik BC, Plewig G. Impaired Notch-MKP-1 signalling in hidradenitis suppurativa: an approach to pathogenesis by evidence from translational biology. *Exp Dermatol*. 2013;22(3):172-177. doi:10.1111/exd.12098
 18. Rubin SS, Rimmer JH, Chicoine B, Braddock D, McGuire DE. Overweight prevalence in persons with Down syndrome. *Ment Retard*. 1998;36(3):175-181. doi:10.1352/0047-6765(1998)036<0175:OPIPWD>2.0.CO;2
 19. Gold DA, Reeder VJ, Mahan MG, Hamzavi IH. The prevalence of metabolic syndrome in patients with hidradenitis suppurativa. *J Am Acad Dermatol*. 2014;70(4):699-703. doi:10.1016/j.jaad.2013.11.014
 20. Miller IM, Ellervik C, Vinding GR, et al. Association of metabolic syndrome and hidradenitis suppurativa. *JAMA Dermatol*. 2014;150(12):1273-1280. doi:10.1001/jamadermatol.2014.1165
 21. Reddy S, Strunk A, Garg A. Comparative Overall Comorbidity Burden Among Patients With Hidradenitis Suppurativa. *JAMA Dermatol*. 2019;155(7):797-802. doi:10.1001/jamadermatol.2019.0164
 22. Garg A, Malviya N, Strunk A, et al. Comorbidity screening in hidradenitis suppurativa: Evidence-based recommendations from the US and Canadian Hidradenitis Suppurativa Foundations. *J Am Acad Dermatol*. Published online January 23, 2021;S0190-9622(21)00213-9. doi:10.1016/j.jaad.2021.01.059