Dermatological manifestations of Down’s syndrome

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Summary
Down’s syndrome (DS) is associated with rare dermatological disorders and increased frequency of some common dermatoses. Owing to advances in medical care and changes in attitude, the median age of death in this population has increased to 49 years, and the life expectancy of a 1-year-old person with DS today is more than 60 years and is likely to improve. With the increase in the number of individuals with DS in the population and an increased life span, dermatologists are more likely to encounter the wide spectrum of dermatological disorders that occurs in these patients. Furthermore, new reports of possible associations are frequent in the literature. The purpose of this article is to discuss the various dermatological conditions that affect DS individuals. A brief overview is given of the new information on genetics and the immunology of DS. We also discuss the molecular mechanisms of premature ageing, to which DS individuals are prone. We review the literature and discuss the known dermatological manifestations, concentrating on recent reports.

Introduction

Down’s syndrome (DS) is associated with rare dermatological disorders and increased frequency of some common dermatoses. Owing to recent advances, the median age of death in this population has increased to 49 years,1 and the life expectancy of a 1-year-old person with DS today is more than 60 years. Thus, dermatologists are more likely to encounter the wide spectrum of dermatological disorders that occurs in these patients, and new reports of possible associations are frequent in the literature.

We performed a literature search using the terms Down’s syndrome; trisomy 21; skin; immunology; premature ageing; and genetics and dermatology. Particular relevance was given to newer papers, although most studies on dermatological aspects of DS were conducted on institutionalized patients. Our previous experience was also used to choose which papers to include in this review.

Genetics of Down’s syndrome

In 1866, John Langdon Down published Observations on an Ethnic Classification of Idiots, his description of DS.2 It was in 1959 that Jerome Lejeune and Patricia Jacobs showed that DS is caused by trisomy of HSA21.3,4 In about 5% of all cases of DS, the extra chromosomal material derives from the presence of a Robertsonian translocation of the long arm of chromosome 21 to another acrocentric chromosome (usually 22 or 14). Approximately 1% of DS patients are mosaics, usually having a mixture of cells with 46 and 47 chromosomes.5

Immunity and autoimmunity

Individuals with DS have high mortality due to infections and a high risk of developing malignancies.6 Furthermore, the frequent occurrence of hyperthyroidism, chronic hepatitis, and alopecia areata in DS strengthens the hypothesis that autoimmunity may
play a role in some clinical manifestations of DS, and also reflects an unbalanced immune control. The immunological disturbances in DS are shown in Table 1.

**Premature ageing**

DS is a disorder of accelerated ageing. There is premature onset of age-dependent changes including greying of hair, hair loss, skin wrinkling, menopause, osteoporosis, osteoarthritis, hypogonadism, immunological changes and senile cataracts in patients with DS. The DNA repair theory offers one explanation for accelerated ageing in DS. A positive correlation has been postulated between maximum life span and the capacity to repair UV-induced DNA damage. The basal levels of many DNA repair enzymes are significantly lower in DS and deteriorate with ageing.

An alteration in free-radical metabolism, which is known to exist in DS, is another possible explanation. Effects of chronic sun exposure and those of intrinsic skin ageing lead to free radical generation. The genetic locus for superoxide dismutase (SOD), a key enzyme in free radical metabolism, is located on chromosome 21. Overexpression of Cu–Zn SOD leads to overproduction of \( \text{H}_2\text{O}_2 \), and thereby to increased production of cytotoxic hydroxyl radicals and singlet oxygen species. These in turn cause cell membrane lipid oxidation, altering the structure and function of the involved tissues.

**Cutaneous phenotype**

Schepis *et al.* have rightly separated the features observed in the skin into two main groups; the phenotype and the dermatological diseases. The cutaneous phenotype in DS is the skin involvement of the whole clinical phenotype. Features considered to be part of the cutaneous phenotype include single transverse palmar crease, scrotal tongue, or macroglossia and xerosis.

**Dermatological disorders**

The dermatological disorders associated with DS are detailed in Table 2.

**Atopic dermatitis**

Atopic dermatitis (AD) affects 5% of western populations. There is conflicting evidence regarding the prevalence of AD in patients with DS. In a study of 214 institutionalized patients with DS, Carter and Jegasothy diagnosed AD in 56.5%, and a prevalence of more than 50% was noted by Scherbenske *et al.* Baccichetti *et al.* similarly found AD in 35 of 102 patients with DS living in northeast Italy. However, in 1997, Schepis *et al.* challenged this association. Using the diagnostic criteria of Hanifin and Rajka, they found a 3% prevalence of AD in 100 DS patients. These results were reproduced in another study by the same authors on 203 DS patients, where the reported prevalence of AD was 4.9%. Similar results were also reported by Ercis *et al.*, who found a prevalence of 1.4%. The high reported prevalence of AD in previous studies could be an overestimate, as in the absence of concrete diagnostic criteria, isolated signs such as facial dermatitis and generalized xerosis could easily be misinterpreted as AD. AD can be severe and difficult to manage in DS, as it is often complicated by lichenification and impetiginization caused by an increased susceptibility to infections.

**Seborrhoeic dermatitis**

Carter and Jegasothy found a 36% prevalence of seborrhoeic dermatitis in their study. This was similar to the 31% prevalence found by Ercis *et al.* A high prevalence of pityrosporum folliculitis in DS patients could have a pathogenic role.

**Alopecia areata**

A well-recognized association of alopecia areata (AA) with DS exists. Carter and Jegasothy reported an 8.9%
prevalence of AA in their study group of 214 patients with DS.\textsuperscript{12} Females were more frequently affected than were males (17.4\% vs. 3.1\%), but this observation has not been confirmed by others.\textsuperscript{10} Du Vivier \textit{et al}. diagnosed AA in 60 (6\%) of 1000 patients with DS.\textsuperscript{7} Wunderlich and Braun-Falco, however, found only 13 cases (0.13\%) of AA in their study on 1000 children with DS.\textsuperscript{17}

\textit{MxA}, the product of the \textit{MX1} gene, is an interferon-inducible protein, which is strongly expressed in lesional anagen hair-bulbs from patients with AA but not in normal follicles. The \textit{MX1} gene maps to the distal part of the DS critical region. Tazi-Ahnini \textit{et al}. have shown an association of a marker within the \textit{MX1} gene with increased susceptibility of AA in a non-DS population, which supports the hypothesis that the \textit{MX1} gene is a new candidate gene in AA.\textsuperscript{18}

AA in patients with DS tends to be more severe, and alopecia totalis and universalis have been seen in up to 2.5\% of patients with DS. AA in DS has been known to occur in association with vitiligo, thyroiditis, hypothyroidism and trachyonychia.\textsuperscript{7,12,19} AA associated with DS can be refractory to standard treatment, although some authors have successfully used intralesional triamcinolone or dinitrochlorobenzene.\textsuperscript{20}

\textbf{Vitiligo}

Vitiligo is a common skin condition affecting 1\% of the general population. Several cases of vitiligo associated with AA in DS have been reported. Carter and Jegasothy, in their series, found a 1.9\% prevalence of vitiligo.\textsuperscript{12} Three of their four patients with vitiligo also had AA.

\textbf{Milia-like calcinosis cutis}

Milia-like calcinosis cutis (MICC; Fig. 1a) is a distinct subtype of idiopathic calcinosis cutis, with characteristic clinical and histological features. Clinically, these are small, discrete, white papules resembling milia, but have firm consistency and chalky appearance. These are asymptomatic and are most common on the hands and feet. There is no evidence of abnormal calcium metabolism or preceding tissue injury in these patients. Histologically, well-defined, round, papillary dermal calcific deposits with a fibrous rim are seen. Transdermal elimination associated with calcium deposits may occasionally be seen.

The pathogenesis of MICC in association with DS is unclear. Higher concentrations of calcium in sweat have been found in DS, which may lead to sweat-duct calcification.\textsuperscript{21} Increased calcium levels have also been found in fibroblast cultures from DS patients.\textsuperscript{22} This high calcium state may be a predisposing factor for development of these lesions. As many of these lesions eventually heal without scarring, no treatment is necessary.

\textbf{Syringomas}

The incidence of syringomas in DS has been reported to be approximately 30 times greater than in the general population.\textsuperscript{23} Syringomas of the eyelids are almost

\begin{table}[h]
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 & Schepis \textit{et al}.\textsuperscript{10} & Ercis \textit{et al}.\textsuperscript{16} & Polenghi \textit{et al}.\textsuperscript{29} & Carter & Jegasothy,\textsuperscript{12} \\
\hline
Atopic eczema & 4.9 & 1.4 & 8 & 56.5 \\
Seborrhoeic eczema & 8 & 30.9 & NI & 36.0 \\
Alopecia areata & 2.9 & 1.4 & 20 & 8.9 \\
Vitiligo & NI & NI & NI & 1.9 \\
MICC & 2.9 & NI & NI & NI \\
Syringomas & 12.3 & NI & NI & 39.2 \\
Elastosis perforans serpiginosa & 0.49 & NI & NI & NI \\
Onychomycosis & 4.4 & NI & 8 & 67.8 \\
Tinea corporis & 1.9 & NI & NI & NI \\
Anetoderma & 3.9 & NI & NI & NI \\
Folliculitis & 21.1 & NI & 26 & 10.3 \\
Chelitis & 2.4 & 5.6 & NI & NI \\
Keratosis pilaris & 2.3 & 2.8 & NI & 3.2 \\
Psoriasis & 1.4 & NI & 8 & 0.5 \\
Cutis marmorata/livedo reticularis & 8.8 & 12.6 & NI & 8.4 \\
Xerosis & NI & 9.8 & NI & 85.0 \\
Palmar and/or plantar hyperkeratosis & NI & 40.8 & NI & NI \\
\hline
\end{tabular}
\caption{Frequency of dermatological disorders in Down's syndrome (\%).}
\end{table}
exclusive to DS patients. Butterworth et al. described syringomas in 18.5% of 200 institutionalized DS patients, with a prevalence of 26% among female and 13% among male patients. Schepis et al. studied 30 male and 31 female patients with DS and found palpebral syringomas in 13 females and 1 male, confirming the high incidence of these lesions in DS and a clear female preponderance. The same authors have also noted MICC in association with syringomas in DS, thus supporting the hypothesis that syringal structures may play an important role in the pathogenesis of MICC in DS.

Therapeutic options include electrocoagulation or cryotherapy. Topical retinoic acid and atropine have been used to treat eruptive syringomas.

**Elastosis perforans serpiginosa**

Elastosis perforans serpiginosa (EPS; Fig. 1b) is a rare skin disorder of unknown aetiology characterized by transpidermal elimination of abnormal elastic tissue. Disseminated EPS has been described in association with DS. These patients seem to be predisposed to developing a generalized form of the disease. The reason for this association is not clear, but premature ageing, joint hyperlaxity and acrocyanosis in DS, which indicate connective tissue dysplasia, could be a potential explanation. Although EPS has been reported to occur in 1% of patients with trisomy 21, this has not been confirmed in other studies. Collagenomas have also been described in patients with DS.

**Leukaemia cutis**

Infants with DS have an increased risk of haematological abnormalities, including leukaemoid reaction, transient myeloproliferative disorder and congenital leukaemia. Leukaemia cutis is often associated with congenital leukaemia. Clinically this manifests as blue, firm, infiltrated papules and nodules and histopathologically

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**Figure 1** Some dermatological manifestations of Down’s syndrome. (a) Milia-like idiopathic calcinoïd cutis (courtesy of Dr Carmelo Schepis). (b) Elastosis perforans serpiginosa. (c) Anetoderma (reprinted from: Structural disorders of the skin and diseases of subcutaneous tissue. In: Diseases of the skin (White G, Cox N), 2006; 474, with permission from Elsevier). (d) Cutis marmorata (reprinted from: Venous malformations. In Diseases of the skin (White G, Cox N), 2006; 295, with permission from Elsevier).
as a nodular or perivascular dermal infiltrate of leukaemic cells. Unusual pustular or vesiculopustular eruptions have been described in children with DS in association with leukaemoid reaction and myeloproliferative disorders.28

Onychomycosis

There is a higher frequency of onychomycosis in DS patients. Of the 214 patients examined by Carter and Jegasothy, 145 had onychomycosis (67.8%) while 164 had tinea pedis (76.6%).12 Schepis et al. diagnosed onychomycosis in 9 (4%) and tinea corporis in 4 (2%) of their 203 patients with DS.10 These prevalence figures were similar to those found by Polenghi et al.29 The authors hypothesized that fungal infections may have been overdiagnosed in the past or may have been sustained by poor hygiene conditions and communal living.

Velthuis and Nijenhuis found terbinafine an effective treatment, with a mycological cure rate of 94% in 32 patients with DS with onychomycosis.30

Scabies

Outbreaks of scabies occurring in institutional settings are not uncommon. Patients with DS seem predisposed to crusted (Norwegian) scabies.13 Immunological dysfunction has been proposed as one factor for this propensity. Poor cutaneous sensation leading to increased infestation rates and diminished likelihood of mites being mechanically removed may be another factor.13

Anetoderma

Anetoderma (Fig. 1c) secondary to chronic folliculitis has been described in Down’s syndrome patients.31 It has been hypothesized that a congenital malformation of elastic fibres in this population may be responsible for anetoderma. Treatment of folliculitis with systemic antibiotics could, however, prevent the development of anetoderma in this population.31

Cutaneous infections

Cutaneous infections including folliculitis, furuncles, abscesses and secondary impetigo in atopic individuals are common in DS. Schepis et al., in their study population, found folliculitis to be the commonest dermatological manifestation.10 Pityrosporum folliculitis affecting the preterminal and infrascapular region was found to occur in about 50% of affected men between the ages of 20 and 40 years.32 Kavanagh et al., in their study, found a follicular rash consistent with Malassezia folliculitis in 50% of male and 1% of female patients with DS.33 Treatment with oral itraconazole produced a significant improvement in the folliculitis.

Oral manifestations

Patients with DS have many distinctive oral manifestations. Macroglossia, fissured tongue and geographical tongue occur in up to 80% of patients. The oral cavity appears to be smaller; prognathism and dental malocclusion are common. The prevalence of periodontal disease tends to be high.34 Scully et al. found lip fissures in 27% and angular chelitis in 25% of 77 patients with DS compared with 0.6% in the general population. These patients also have an increased tendency to orofacial candidal infections.35

Keratodermatoses

Of the 71 children with DS examined by Ercis et al., 29 had palmoplantar hyperkeratosis (40.8%) and 7 had xerosis (9.9%).18 Keratosis pilaris also has a well-known association with DS, with 24 of 203 patients affected in one series.10 Carter and Jegasothy recorded keratosis pilaris in 7 of 86 female patients examined, while none of their 128 male patients showed this feature.13 Although cases of pityriasis rubra pilaris and the hyperkeratotic form of psoriasis have been reported in association with DS, it appears that these disorders run a normal course in DS and there is no evidence of an increased association.

Vascular instability

Acrocyanosis and cutis marmorata occur with a greater frequency in DS patients. Nine of the 71 patients examined in one survey had cutis marmorata16 (Fig. 1d), and livedo reticularis was seen in 24 of the 204 DS patients examined by Schepis et al.10 Congenital cardiac malformations such as ventricular and atrial septal defects also occur more frequently in this population, and a reduction in the peripheral perfusion may account for these signs.

Carotenaemia

Carotenaemia occurs with increased incidence in individuals with learning difficulties, including DS. This is attributed in part to the high level of carotene products in institutional diets.13
Conclusion

With the increasing life span and number of DS patients in the population, dermatologists are more likely to encounter skin manifestations associated with DS. While premature ageing and the cutaneous phenotype are almost universal in DS patients, atopic and seborrhoeic dermatitis and alopecia areata are common and can be a challenge to treat. These patients have a high incidence of syringomas, and MICC occurs almost exclusively in association with DS. There are many isolated case reports linking various skin disorders to DS, but further epidemiological studies would be needed to confirm an association.

Learning points

- Immunological disturbances are common in DS, hence a higher prevalence of certain dermatological disorders such as alopecia areata.
- DS is associated with premature ageing. However, life expectancy of DS patients is increasing.
- Atopic dermatitis does not seem to occur with an increased prevalence in DS patients, although it may prove difficult to treat.
- DS patients do not seem to have a high incidence of bacterial or fungal skin infections, although these patients are at increased risk of development of anetoderma secondary to folliculitis.
- MICC and syringomas are common in DS.

References

8 Hart RW, Setlow RB. Correlation between deoxyribonucleic acid excision-repair and life-span in a number of mammalian species. Proc Natl Acad Sci USA 1974; 71: 2169–73.


