Key Points for Clinical Practice

Dermatological Pathologies Often Associated With Trisomy 21 : Part 2

Alopecia Areata (AA)

- Alopecia Areata, or AA, is a non-scarring, autoimmune alopecia with a prevalence in the general population estimated at 0.1 to 0.2%.
- In 95% of cases, it presents as the common patchy form, with the rapid onset of one or more well-defined, variable-sized, non-pruritic alopecic patches on the scalp. The patches can also appear on the beard, eyelashes, eyebrows, and all other hair-bearing areas of the body.
- In about 5% of cases, the patches can coalesce to affect the entire scalp (Alopecia Totalis) or even the entire body (Alopecia Universalis). Nail involvement occurs in 10 to 20% of cases.
- The diagnosis is clinical, with an unpredictable course: spontaneous regrowth within a few months in about 30 to 50% of cases for the common patchy form; regrowth is unlikely in severe forms.
- AA is estimated to be 15 to 30 times more frequent in Trisomy 21 than in the general population.
- The association between Trisomy 21 and AA is primarily attributed to the predisposition of individuals with T21 to autoimmune diseases and autoinflammation. The role of family heredity is still a matter of debate.
- Individuals with T21 and AA also have a significantly higher risk of thyroid disease, and association with vitiligo is common.
- In terms of severity and progression, AA associated with Trisomy 21 may occur at a younger age and be more severe compared to the general population.
- Treatment in Trisomy 21 is similar to that in the general population: conservative management in mild to moderate forms; topical and/or systemic treatments may be attempted in severe forms.
- The use of biologics such as JAK inhibitors in severe forms of AA associated with Trisomy 21 is still anecdotal and cannot be recommended.

Vitiligo :

- Vitiligo is an autoimmune condition targeting melanocytes and characterized by the gradual appearance of white patches on the skin, which can occur at any age but most commonly before 30 years old.
- In the general population, vitiligo prevalence ranges from 0.5 to 2%.
- Non-segmental vitiligo accounts for 90-95% of cases, with bilateral and symmetrical lesions affecting the face, hands, feet, and friction areas of the upper and lower limbs.
- Segmental vitiligo is much rarer, with unilateral lesions limited to a well-defined skin area.
- The diagnosis is clinical, and can be supported by Wood's lamp examination.
- In Trisomy 21, the prevalence of vitiligo in observational cohorts ranges from 0.7% to 9.1%. Both segmental and non-segmental forms have been described in this population.
- In Trisomy 21, as in the general population, vitiligo is associated with other autoimmune conditions such as Hashimoto's thyroiditis and alopecia areata.

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- Vitiligo is medically benign but has a significant psychosocial impact.
- Vitiligo progresses in outbreaks, and its course is unpredictable.
- Treatment in individuals with T21 is similar to that of the general population, typically combining topical treatments: corticosteroids, Tacrolimus, JAK1/2 inhibitors (ruxolitinib), along with UVB phototherapy.

Elastosis perforans serpiginosa (EPS):

- EPS is a rare condition that belongs to the group of primary perforating dermatoses, characterized by transepidermal elimination of abnormal elastic fibers. Its prevalence is unknown.
- EPS presents as small, keratotic, erythematous, or normochromic papules arranged in an arcuate, serpiginous, or annular pattern. The lesions are often multiple, located on the nape, neck, cheeks, or limbs. The diagnosis of EPS is histopathological.
- EPS can be associated with genetic disorders affecting the elastic fibers (e.g., Marfan, Ehlers-Danlos) or, more rarely, iatrogenic (D-Penicillamine). It typically affects adolescents or young adults.
- The association of EPS with Trisomy 21 is well established and may result from alterations in elastic fibers and/or the extracellular matrix due to mechanisms involving the triplication of the Cystathionine β-synthase (CBS) gene and the basal hyperactivation of INF-ɤ expression.
- The age of onset is around 20 years old. The lesions are typically multiple, located on the neck and arms but can also be found on the legs and thighs and tend to be generalized.
- EPS may spontaneously resolve within a few months, sometimes leaving an atrophic scar, but in the majority of cases, it is chronic and there is currently no standardized treatment.

Milia-like Idiopathic Calcinosis Cutis (MICC):

- MICC is a rare benign dermatological condition with more than half of the cases (58%) reported in individuals with T21. Histologically, it corresponds to a sub-epidermal calcified nodule.
- MICC presents as multiple small, white, painless, non-pruritic papules measuring 1-3 mm, typically located on the back and the palms of the hands and soles of the feet.
- The etiology of MICC is unknown, and no disorders involving calcium-phosphorus metabolism have been described.
- Associated with Trisomy 21, MICC typically occurs in children and affects the hands and feet.
- The association of MICC with a benign tumor, Syringoma, is seen almost exclusively in Trisomy 21.
- MICC lesions, which persist on average for 18 months and resolve spontaneously in adulthood, do not require therapeutic intervention.

Transient Abnormal Myelopoiesis (TAM):

- About 5 to 10% of newborns with T21 have Transient Abnormal Myelopoiesis (TAM), characterized by a high level of circulating blasts/megakaryoblasts with clinical and biological features resembling acute myeloid leukemia (AML).
- In 5% of TAM cases, there are typically cutaneous signs appearing within the first few days of life, presenting as a diffuse rash, usually beginning on the face, with vesicles, vesiculo-pustular lesions, crusted papules, and pustules on an erythematous background.
- In approximately 25% of cases, lesions develop on pressure areas or sites of skin trauma.
- Mosaic T21 is present in 25% of cases, and the sex ratio favors males.
- There is no correlation between cutaneous signs, the age of TAM onset and the level of leukocytosis or circulating blasts in peripheral blood.
- Lesions typically heal without sequelae within 1 to 2 months.
- The diagnosis of TAM should be considered in any child with T21 presenting with a vesiculo-pustular rash during the neonatal period, even if onset is late.
- Similarly, the diagnosis of T21 (especially mosaic T21) should be considered in any newborn presenting a vesiculo-pustular rash and leukocytosis, even without a phenotype suggestive of Trisomy 21.

Syringomas :

- Syringomas are benign skin tumors of the eccrine sweat gland duct. Their prevalence in the general population is about 0.6%, with a higher incidence in females.
- They can be: Localized (typically multiple, rarely solitary); Generalized (eruptive, with several dozen syringomas appearing within a short time frame); Familial; and T21-associated.
- Syringomas typically present as multiple small, firm, smooth papules, white or brown, rounded or flat with angular borders, ranging in size from 1 to 5 mm.
- The most common location is on the lower eyelid and the periorbital region.
- The prevalence of syringomas in T21 is around 30 times higher than in the general population, with a clear female predominance, onset in adolescence, and increasing with age.
- Eyelid involvement, the possibility of generalized eruptive forms, and the strong association with Milia-like Idiopathic Calcinosis Cutis are characteristic of syringomas in Trisomy 21.
- Syringomas are asymptomatic, non-progressive, persist throughout life, and do not require treatment.

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Multiple eruptive dermatofibromas (MEDF):

- A dermatofibroma is a common benign fibrohistiocytic skin tumor in solitary form. More rare are the multiple eruptive forms, typically defined by the presence of 5 to 8 dermatofibromas appearing within a 4-month period.
- The primary MEDF lesion is a small (<0.5 cm), round, hard, smooth, reddish-brown nodule that protrudes from the surrounding skin and is sometimes surrounded by a pigmented halo visible on dermoscopy. On palpation, it feels like a hard, lenticular, painless nodule embedded in the dermis that retracts when the skin is compressed.
- The association of MEDF with Trisomy 21 is robust (8/50 cases described) and is related to immune dysregulation in Trisomy 21.
- The mean age of onset is 39 years, and 75% of cases involve women.
- The course is benign, with nearly 50% of cases showing no progression or regression of lesions.