SKIN

IN-DEPTH REVIEW

A Systematic Review of the Association of Elastosis Perforans Serpiginosa and Congenital Disorders

Elizabeth M. Flatley, MS[1], Rucha Janodia[2], Carolyn J. Heckman, PhD[3]

[1] Rutgers Robert Wood Johnson Medical School, Piscataway, New Jersey, USA
[2] Rutgers New Jersey Medical School, Newark, New Jersey, USA
[3] Rutgers Cancer Institute, New Brunswick, New Jersey, USA

ABSTRACT

Background: Elastosis perforans serpiginosa (EPS) is a skin condition marked by transepidermal elimination of abnormal elastic fibers, with a classical presentation of papules or plaques arranged in serpiginous, annular, or arcuate patterns on the neck, face, arms, or other flexural regions. A previous review of the literature reported that approximately 1/4 of EPS cases are associated with congenital disorders, including Down syndrome, Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum. To the knowledge of these authors, no review examining the association of EPS and congenital disorders has been performed since 1968.
Objective: The primary objective of this paper is to perform an updated review of the literature focused on the associations between EPS and congenital disorders.
Methods: We searched electronic databases (Medline, Web of Science, PubMed) for literature pertaining to EPS and Down syndrome, Ehlers-Danlos syndrome, Marfan syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum.
Results: Evidence for the association of EPS and congenital disorders is 57 cases from 48 published papers.
Conclusions: Our results suggest an association between EPS and congenital disorders. However, current evidence is limited to case reports, underscoring the need for future research investigating the relationship between EPS and congenital disorders.

INTRODUCTION

Elastosis perforans serpiginosa (EPS) is an uncommon perforating skin disease characterized by transepidermal displacement of abnormal elastic fibers. Classically, EPS presents as papules or plaques arranged in serpiginous, annular, or curved patterns on the neck, face, arms, or other flexural regions.[1,2] EPS is categorized into three subtypes: the idiopathic subtype, the drug-induced subtype, frequently arising secondarily to treatment with D-penicillamine, and the reactive subtype, which is associated with connective tissue diseases.[2]

Twenty-six percent of EPS cases are reported to be associated with congenital disorders, including Down syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, and Marfan syndrome.[3] The rarity of EPS may lead to

delays in diagnosis, but establishment of the association between congenital disorders and EPS may limit delays in recognition of EPS.[2] Currently, there is an absence of an up-to-date summary of the literature pertaining to the association of EPS and congenital disorders. Therefore, a review of available literature was conducted to provide a comprehensive summary of the current existing data pertaining to the association between EPS and Down syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, pseudoxanthoma elasticum, or Marfan syndrome. Increased knowledge of the relationship between congenital disorders and EPS can enhance understanding of this disorder and improve clinical identification of EPS in patients with such genetic conditions, allowing for improved patient outcomes.

METHODS

Data Sources and Searches

We searched electronic databases (Medline, Web of Science, PubMed) using search terms specified in **Table 1**.

Table 1. Search Terms Used in Search of Databases

Category	Search Term
Ehlers-Danlos syndrome	Elastosis Perforans Serpiginosa AND Ehlers-Danlos syndrome
Down syndrome	Elastosis Perforans Serpiginosa AND Trisomy 21 Elastosis Perforans Serpiginosa AND Down syndrome Elastosis Perforans Serpiginosa AND Down's syndrome
Marfan syndrome	Elastosis Perforans Serpiginosa AND Marfan syndrome
Osteogenesis imperfecta	Elastosis Perforans Serpiginosa AND Osteogenesis imperfecta
Pseudoxanthoma elasticum	Elastosis Perforans Serpiginosa AND Pseudoxanthoma elasticum

All papers not written in English, animal studies, and papers not addressing the association of EPS and Down syndrome, Ehlers-Danlos syndrome, osteogenesis imperfecta, or Marfan syndrome were excluded. Genetic disorders were selected for inclusion based on associations between these disorders and EPS identified by Mehregan in 1968 informed by on a summation of case reports. References of eligible articles were also searched manually. Ten additional articles indicating an association between EPS and genetic disorders were cited by Mehregan and colleagues but were not included in this review as they were inaccessible or not in English. The study selection and exclusion process are shown in **Figure 1**.

Although case reports exist indicating the inducement of both EPS and PXE in patients due to D-penicillamine treatment, this article focuses on the concurrence of PXE and the reactive subtype of EPS. Additionally, reports

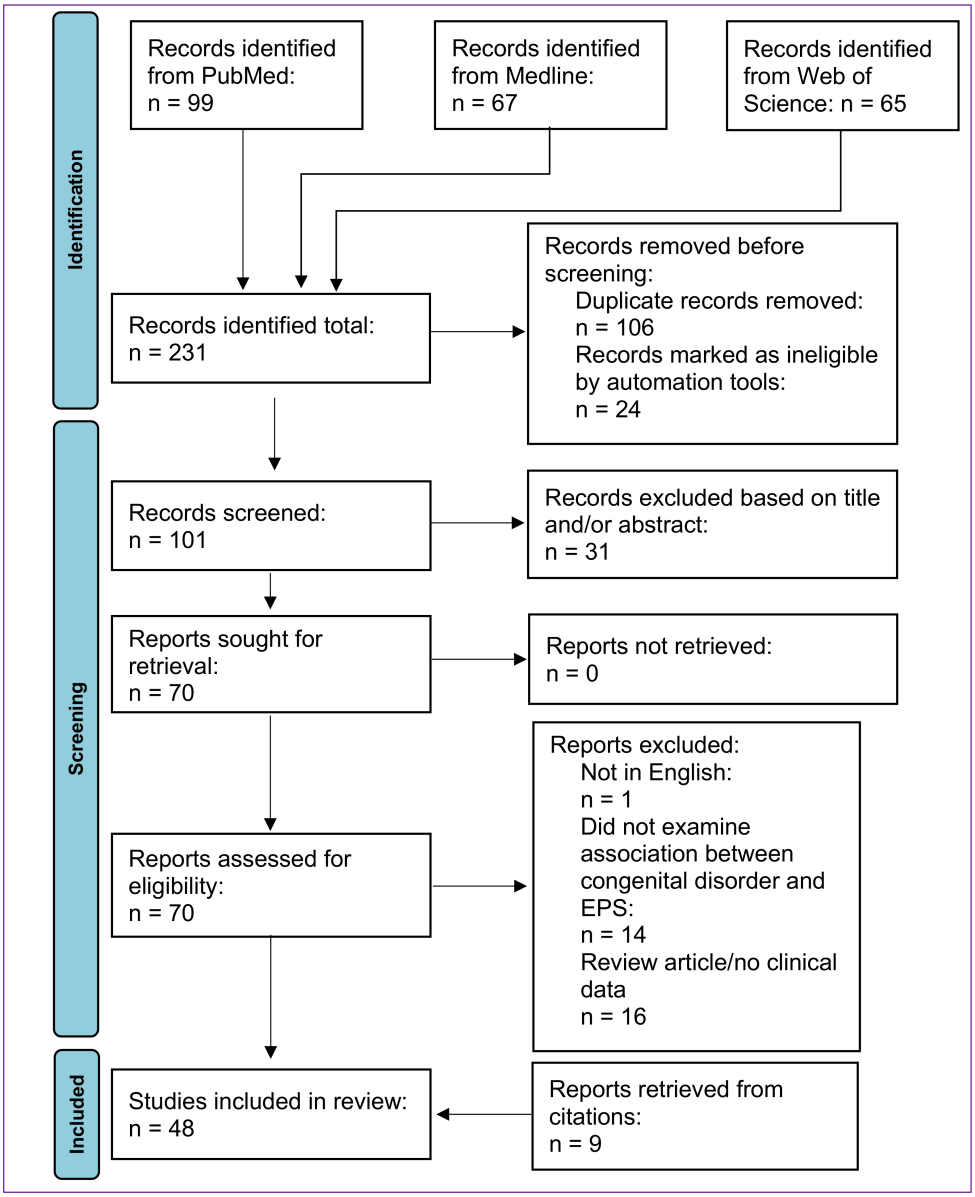

Figure 1. PRISMA flow diagram illustrating screening and selection of studies

of PXE with "EPS-like" changes were excluded, with studies limited to diagnosed cases of EPS concomitant with PXE.

RESULTS

Ehlers-Danlos Syndrome

Ehlers-Danlos syndrome (EDS) is a hereditary disorder of connective tissue characterized by joint hypermobility potentially leading to dislocations, skin hyperextensibility, and tissue fragility.[4] Evidence for the association of EPS and EDS includes 6 case reports. Meara reported EPS localized to the left popliteal fossa and bilateral forearms in a patient with EDS while Mehregan described a single lesion on the midline of the chin in a patient with EDS.[3,5] The subtype of EDS was not available from the reports provided by Meara and Mehregan. Notably, four case reports (Mehta et al., Asherson et al., Ahmadi and Choi, and

Uldall Pallesen et al.) describe EPS occurring in association with vascular-type (type IV) EDS.[6-9] Case reports are summarized in **Table 2**.

Down Syndrome

Down syndrome, also known as Trisomy 21, is a genetic disorder caused by an extra copy of the 21st chromosome.[10] Evidence for the association of Down syndrome and EPS includes 31 cases. Four patients with Down syndrome, representing 1% of the population with Down syndrome at the Fairview Hospital and Training center, seen by Rasmussen between the years 1968-1971, were reported to have disseminated EPS.[11] All these patients presented initially with several clustered, annular, hyperkeratotic, and erythematous lesions on their necks, arms, and legs. There was variable resolution of the lesions between patients at follow-up, with

Table 2. Summary of case reports of EPS associated with EDS

Authors, Year	Age, Sex	Location	Arrangement	Treatment of EPS	Outcome of EPS
Meara, 1958	41, F	Forearms, Popliteal fossa	Crescent	Not discussed	Not discussed
Mehregan, 1968	11, F	Midline of chin	Annular	Not discussed	Stripping by cellophane (Scotch) tape effective; new small, isolated lesion later appeared
Mehta et al., 2001	22, F	Bilateral neck, upper arms	Serpiginous	Previous treatment of topical steroids under occlusion, 0.25% Retin-A gel, 2% salicylic acid ointment, oral isotretinoin, intralesional corticosteroid, repeated cryotherapy, curettage and cautery of lesions, phenytoin, and narrow band UVB	Previous treatments ineffective
Asherson et al., 2006	19, M	Forearms, elbows, popliteal fossae, shins, (posterior, upper) thighs	Concentric circles	Not discussed	Not discussed
Ahmadi and Choi, 2011	26, M	Extensor forearms, left antecubital fossa	Serpiginous	Not discussed	Not discussed
Pallesen et al., 2019	26, F	Hips, thighs, upper arms	Serpiginous	Potent topical corticosteroids	Poor efficacy of treatment

3 of the 4 patients showing some degree of progression to scarring associated with the papules. In further case reports of single patients, EPS was localized to the right upper extremity and left lateral neck, the right neck, thighs, and lower legs, the upper lip, bilateral

preauricular areas, ears, and right forearm, the upper extremities, the lower extremities, both the upper and lower extremities, the face, or had a diffuse (> 3 body regions) distribution.[2,3,6,10,12-30] Additional case reports with unique or unspecified distribution patterns, as well as all reported cases of EPS in association with Down syndrome, are described in **Table 3**.[31-32]

Table 3. Summary of case reports of EPS associated with Down syndrome.

Authors, Year	Age, Sex	Location	Arrangement	Treatment of EPS	Outcome of EPS
Ritchie et al., 1960	22, F	Posterior, lateral aspect of thighs bilaterally	Arciform or serpiginous borders	Tincture of iodine, ethyl chloride spray, griseofulvin	Tincture of iodine, ethyl chloride spray - "some success"; Griseofulvin – “no apparent beneficial effect”
Walshe, 1963	14, M	Lateral aspect of face bilaterally, posterior neck, outer upper arms	"... most are arranged in arcuate groups."	Not discussed	Not discussed
	14, M	Extensor aspect of elbows, Extensor and lateral aspects of knees	"mainly arranged in arcate groups...a few scattered in no particular pattern"	Not discussed	Not discussed
Tanenbaum and Miller, 1966	7, M	Upper lip, preauricular areas bilaterally, tragus of ears, right forearm	Arciform, circular, grouped	Not discussed	Not discussed
Mehregan, 1968	19, F	Extensor of forearm	Serpiginous	Nitrogen mustard	No new lesions at follow-up
Rasmussen, 1972	13, M (Patient I)	Posterior neck, upper and lower extremities	Annular, grouped, or isolated	No treatment	Spontaneous resolution with scarring and “numerous isolated papules”
	16, M (Patient II)	"Closely resembled… Patient I in relation to…configuration, distribution, and extent of involvement"	"Closely resembled… Patient I in relation to…configuration, distribution, and extent of involvement"	Not discussed	“No observable change in 6 months.”
	12, M (Patient III)	"Closely resembled… Patient I"	"Closely resembled… Patient I"	Not discussed	“Original lesions predominate, but many show progression to short, linear scarring.”

	14, F (Patient IV)	“Same” initial manifestations as patients I, II, III	“Same” initial manifestations as patients I, II, III; Grouped for 3 years, previously annular lesions.	Not discussed	“Numerous linear scars containing a single hyper-keratotic papule at one end. Many papules not associated with scars.” Involved lateral aspects of neck, extensors of upper extremities, and anterior aspects of lower limbs
Tschen, 1980	41, F	Not discussed	Not discussed	Topical treatments: iodine, ethyl chloride, liquid nitrogen, tretinoin, steroids, tar, methotrexate, salicylic acid, sulfur Systemic treatments: vitamins A and E, griseofulvin, zinc sulfate, systemic steroids	All previous treatments unsuccessful. Development of new lesions with healing of older lesions resulting in hyperpigmented scars
Crotty et al., 1983	19, M	Anterior thighs, medial calves, neck, and extensor and lateral forearms	Arcuate, serpiginous, linear	Not discussed	Not discussed
Scherbenske, 1990	24, F	Upper and lower limbs	Serpiginous	Not discussed	Not discussed
O’Donnell et al., 1992	28, F	Extensor region of upper and lower limbs	Scattered	Topical moisturizing agents	“Somewhat” improved following treatment
Iwatsuki et al., 1996	15, F	Cheeks, neck	Arciform, annular, "Both discrete and grouped papules were observed..."	Previous unsuccessful treatment with topical steroid. Current treatment with tape stripping with adhesive tape and	Slight improvement with 2 months of treatment

				topical 5% salicylate ointment	
Siragusa et al., 1997	16, M	Left mandibular angle	Annular	Not discussed	By 6 months, primary lesion developed into linear, hypotrophic scar. By 12 mos., no new lesions found
Kaufman, 2000	26, M	Extensor region of upper and lower limbs	Arcuate	Previous unsuccessful treatment with tretinoin and glycolic acid. Current treatment with flashlamp pulsed dye laser	Resolution of lesions with no recurrence occurring at 14 months following treatment with laser
Mehta et al., 2001	21, F	"…predominantly over her face but also trunk and limbs."	Annular, serpiginous	Topical corticosteroids, curettage	Topical corticosteroids ineffective. Improvement of select lesions with curettage
De Pasquale, 2002	20, F	Extensor region of right and left distal thighs	Arciform	Not discussed	Not discussed
Newman et al., 2006	12, F	Right outer upper arm, left lateral neck	Arcuate	Not discussed	Not discussed
Suneja et al., 2007	41, M	Flexural surfaces of right and left forearms	Annular	Not discussed	Not discussed
Espinosa et al., 2008	16, F	Upper and lower limbs	Not discussed	Not discussed	Not discussed
Gregersen et al., 2010	45, M	Right and left forearms and thighs	Annular	Topical corticosteroids and systemic antifungals unsuccessful previously. Current treatment with topical imiquimod 5% cream	Imiquimod 5% cream reduced inflammation, infiltration, and lesion dissemination

Abdullah and Abbas, 2010	16, M	Primarily localized to upper limbs	“Some” annular	Previous ineffective treatment with topical steroids. Current treatment with 0.1% tazarotene gel	Complete resolution across two months of treatment
Pereira et al., 2010	19, F	Medial surface of right forearm, extensor surface of right knee	Arciform or annular	Cryotherapy with liquid nitrogen	“Partial remission has been achieved”
Boccaletti et al., 2011	12, F	Right and left knees, elbows	“Several serpiginous lines”	No treatment	Spontaneous resolution without recurrence at 3 years
Nikam et al., 2015	16, M	Flexor aspect of right and left forearms, extensor region of right arm	“Linearly and in circles or rings…segments of circles showed a coalescing pattern to attain serpiginous and arciform configurations"	Not discussed	Not discussed
Hernández-Ruiz, 2015	16, M	Anterior aspect of right and left thighs	Annular	Topical betamethasone and calcipotriol	Poor response to treatment
Polańska et al., 2016	16, F	Left cheek, upper and lower limbs	Annular, linear	10% urea ointment	Increase in number of lesions upon follow-up
Souza et al., 2019	14, F; (siblings)	Upper and lower limbs	Not discussed	Not treated	Not discussed
	11, M (siblings)	Upper and lower limbs	Not discussed	Not treated	Not discussed
Enos et al., 2021	23, M	Right neck, thighs, and lower limbs	Serpiginous	Triamcinolone 0.1% ointment and oral antibiotics unsuccessful previously. Current treatment with acitretin	Acitretin effective in resolving majority of lesions and reducing appearance of remaining lesions by 3-month follow-up, with residual hyperpigmentation. Following 6-month follow-up “lesions remain quiescent”.

Osteogenesis Imperfecta

Osteogenesis Imperfecta (OI) is a congenital disorder of bone characterized by recurrent fractures, deformation of bones, limb shortening, early-onset osteoporosis, blue sclerae, hearing loss, fragility of teeth, and joint laxity.[33] Evidence for the association between EPS and OI includes 5 case reports.[6,34-37] Of note, 3 of the 5 cases described EPS with involvement of the neck. Case reports are summarized in **Table 4**.

Table 4. Summary of case reports of EPS associated with OI.

Authors, Year	Age, Sex	Location	Arrangement	Treatment of EPS	Outcome of EPS
Reed and Pidgeon, 1964	11, F	Left antecubital region	Serpiginous	Not discussed	Additional "area of hyperkeratoses several centimeters below the original lesion developed beneath the" adhesive tape applied following excisional biopsy
Kingsley, 1964	19, M	"The lesions were extensive and symmetrical"; location otherwise not discussed	Not discussed	Not discussed	Not discussed
Carey, 1977	17, M	Left lateral neck, anterolateral aspect of elbows	Not discussed	Liquid nitrogen, intralesional triamcinolone acetonide	Lesions partially flattened following treatment
Mehta et al., 2001	16, M	Left posterior neck	"Discrete lesions…mainly in an annular distribution"	Haelan tape, Retin-A, cryotherapy, curettage, Dovonex ointment	Treatment ineffective
Pérez-Pérez et al., 2009	17, M	Right lateral neck	Serpiginous	Previous ineffective treatment with topical retinoids. Current treatment with cryotherapy	Results of cryotherapy treatment pending at time of publication

Pseudoxanthoma Elasticum

Pseudoxanthoma elasticum (PXE) is a congenital disorder with disease manifestation resulting from calcification of elastic fibers composing the connective tissue of the skin, blood vessels, and eyes.[38] Evidence for the association of EPS and PXE is 15 cases. Katagiri et al. reports 3 cases of EPS identified in patients with PXE, 2 of

whom had papules and plaques consistent with EPS arising within cutis laxa-like lesions of the neck, axillae, and/or the lateral aspect of the chest.[39] Caro et al. described 2 cases of EPS occurring on the abdomen and neck, respectively, of patients with PXE.[40] Sen, Pavithran et al., and Venkatachalam and Chennamsetty provided case reports of EPS presenting on the necks of individuals with PXE.[41-43] Lee et al. provided a report of EPS occurring on the left upper arm of an individual with EPS, while case reports from Omarjee et al. and Pai and Zak noted EPS localized to the abdomen of patients with PXE.[38,44,45] Smith et al. described EPS arising in the left axilla and superior to the umbilicus in a 33 year old male with PXE.[46] Case reports of diffuse EPS presenting in individuals with PXE come from Schutt et al., and Funabashi and Tsuyuki.[47,48] Case reports and series are summarized in **Table 5**.

Table 5. Summary of case reports of EPS associated with PXE

Authors, Year	Age, Sex	Location	Arrangement	Treatment of EPS	Outcome of EPS
Smith, 1962	33, M	Left axilla, superior to umbilicus	Grouped	Not discussed	Not discussed
Schutt, 1965	34, M	Neck, scapulae, upper chest, axillae, lower abdomen, and inguinal areas	Serpiginous line	Chymotrypsin (Chymar) ointment	Following treatment with chymotrypsin ointment, “prompt disappearance” of “keratinous-appearing plugs” overlying papules, papule flattening, decreased inflammation, without complete lesion clearance
Funabashi and Tsuyuki, 1966	33, F	Neck, axillae, upper chest, abdomen, inguinal areas	Serpiginous line	Not discussed	Not discussed
Pai and Zak, 1970	52, F	Abdomen	Not discussed	Not discussed	Not discussed
Caro et al., 1975	33, F	Abdomen, just above umbilicus	“Tendency to grouping”	Not discussed	Not discussed
	16, M	Lateral aspects of neck	Serpiginous	Not discussed	Not discussed

Sen, 1976	27, M	Lateral and posterior neck	Not discussed	Vitamin E (Tocopherol)	Treatment not effective
Pavithran et al., 1983	48, M	Right lateral neck	Annular	Not discussed	Not discussed
	21, M	Anterior Neck	Annular	Not discussed	Not discussed
Katagiri et al., 1991	45, M	Neck, axilla, and/or the lateral side of the chest	Circinate	Not discussed	Not discussed
	48, M	Neck, axilla, and/or the lateral side of the chest	Circinate	Not discussed	Not discussed
	47, M	Not discussed	Not discussed	Not discussed	Not discussed
Lee et al., 2009	26, F	Left upper arm	Annular lesions forming serpiginous streaks	Not discussed	Not discussed
Venkatachalam and Chennamsetty, 2016	22, F	Lateral neck, bilaterally	Serpiginous	Not discussed	Not discussed
Omarjee et al., 2020	11, M	Abdomen	Not discussed	Intravenous sodium thiosulfate for treatment of EPS and PXE	Improvement of lesions following treatment

Marfan Syndrome

Although cited as one of the connective tissue disorders associated with EPS, our review did not reveal any confirmed cases of Marfan syndrome associated with EPS.[8]

DISCUSSION

While the results of our review suggest an association between EPS and congenital disorders, the precise mechanism underlying this potential association has not been established.[2] However, preliminary explanations can be proposed. Ehlers-Danlos syndrome, osteogenesis imperfecta, and pseudoxanthoma elasticum all have disease processes characterized by direct mutations to connective tissue matrix proteins such as collagen and fibrillin. Mehta and colleagues suggest that the underlying connective tissue abnormalities of these disorders may induce the derangements in elastic fiber formation observed in EPS.[8] Similarly, Madan and colleagues proposed that connective tissue dysfunction in patients with Down syndrome, as evidenced by the premature aging, joint hyperlaxity, and acrocyanosis observed in this population, may play a role in the pathogenesis of EPS as it manifests in these individuals.[49] Further hypotheses for the association of EPS and Down syndrome suggest that the

transepithelial elimination of elastic fibers characteristic of EPS may occur secondarily to phagocytic dysfunction present in patients with Down syndrome.[18,28] Future studies investigating the association of EPS and genetic disorders are needed to elucidate the potential involvement of underlying connective tissue protein and phagocytic dysfunction in the pathogenesis of EPS.

Finally, although Marfan syndrome is commonly cited amongst diseases associated with EPS, our review of the literature revealed no case reports of EPS identified in patients with diagnosed Marfan syndrome. A case report from Anning, secondarily cited in the literature as an example of EPS occurring in a patient with Marfan syndrome, describes a biopsy proven case of EPS, but provides no overt reference to Marfan syndrome.[50] Anning's report describes an 18-year-old male patient with acute onset dissecting aortic aneurysm resulting in death, characterized by multiple tears in a thin-walled aorta, with histology of the aorta demonstrating degenerative elastic tissue. Together, this description may suggest a diagnosis of Marfan syndrome, but in the absence of a confirmed diagnosis, we did not count this case amongst our overall number of reports. Further studies and case reports are required to establish an association between Marfan syndrome and EPS.

CONCLUSION

Establishment of the association between EPS and connective tissue disorders provides preliminary insight into possible underlying causes of EPS. Enhanced knowledge of this association has the potential to increase recognition and diagnosis of EPS in those with congenital disorders, avoiding unnecessary treatments due to misdiagnosis and limiting delays in initiation of potentially beneficial treatments. This literature review provides an up-to-date summary of the evidence for potential associations of EPS and genetic disorders. The evidence for the association of EPS and genetic disorders is 48 cases including 57 patients. The current evidence suggests there may be an association of EPS and genetic disorders. Knowledge of this potential association can increase understanding of EPS and allow healthcare providers to consider EPS as a potential diagnosis in patients with genetic disorders, helping improve diagnostic accuracy and avoid unnecessary treatment. Evidence of the association was limited to case reports. Therefore, future observational studies are needed.

Conflict of Interest Disclosures: None

Funding: None

Corresponding Author:
Carolyn J. Heckman, PhD
120 Albany St. New Brunswick, NJ 08901
Phone: 732-235-8830
E-mail: ch842@cinj.rutgers.edu

References:

1. Lewis KG, Bercovitch L, Dill SW, Robinson-Bostom L. Acquired disorders of elastic tissue: part I. Increased elastic tissue and solar elastotic syndromes. J Am Acad Dermatol. 2004 Jul;51(1):1-21; quiz 22-4. doi: 10.1016/j.jaad.2004.03.013. PMID: 15243519.
2. Polańska A, Bowszyc-Dmochowska M, Żaba RW, et al. Elastosis perforans serpiginosa: a review of the literature and our own experience. *Postepy Dermatol Alergol*. 2016;33(5):392-5. [PMID: 27881947].
3. Mehregan AH. Elastosis perforans serpiginosa: a review of the literature and report of 11 cases. *Arch Dermatol*. 1968;97(4):381-93. [PMID: 4230639].
4. De Paepe A, Malfait F. The Ehlers-Danlos syndrome, a disorder with many faces. Clin Genet. 2012 Jul;82(1):1-11. doi:

10.1111/j.1399-0004.2012.01858.x. Epub 2012 Mar 15. PMID: 22353005.
5. Meara RH. Ehlers-Danlos Syndrome and Elastoma Verruciforme Perforans (Miescher). *Trans St John Hosp Derm Soc*. 1958;40(72).
6. Mehta RK, Burrows NP, Payne CM, et al. Elastosis perforans serpiginosa and associated disorders. *Clin Exp Dermatol*. 2001;26(6):521-4. [PMID: 11678881].
7. Asherson RA, Bosman C, Tikly M, et al. Ehlers-Danlos syndrome type IV in a young man. *J Rheumatol*. 2006;33(10):2091-6. [PMID: 17014025].
8. Ahmadi J, Choi JN. Newly diagnosed Ehlers-Danlos syndrome in an adult with elastosis perforans serpiginosa. *J Am Acad Dermatol*. 2011;65(1):226-7. [PMID: 21679829].
9. Uldall Pallesen KA, Lindahl KH, Bygum A. Elastosis perforans serpiginosa related to vascular Ehlers-Danlos syndrome. *Dermatol Online J*. 2019;25(3). [PMID: 30982307].
10. Scherbenske JM, Benson PM, Rotchford JP, James WD. Cutaneous and ocular manifestations of Down syndrome. *J Am Acad Dermatol*. 1990;22(5 Pt 2):933-8. [PMID: 2159488].
11. Rasmussen JE. Disseminated elastosis perforans serpiginosa in four mongoloids. Recognition of residual changes. *Br J Dermatol*. 1972;86(1):9-13. [PMID: 4258486].
12. Newman JS, Fung MA. Elastosis perforans serpiginosa in a patient with trisomy 21. *Dermatol Online J*. 2006;12(5):5. [PMID: 16962020].
13. Enos T, Vasquez R, Vandergriff T, et al. Treatment of extensive elastosis perforans serpiginosa with acitretin in a man with Down syndrome. *Int J Dermatol*. 2021;60(5):611-2. [PMID: 33226122].
14. Tanenbaum MH, Miller RB. Elastosis Perforans Serpiginosa. *Am J Dis Child*. 1966;111(6):620-2.
15. Suneja T, Zelonis B, Hurley MY, Youker SR. Elastosis perforans serpiginosa. *Skinmed*. 2007;6(5):255-6. [PMID: 17786109].
16. Abdullah L, Abbas O. Keratotic papules and plaques in an adolescent with Down syndrome. *Clin Exp Dermatol*. 2010;35(8):935-6. [PMID: 21054489].
17. Nikam B, Kaur H, Kale M, Jamale V. Arciform Eruptions of Trisomy 21. *Indian J Dermatol*. 2015;60(6):638. [PMID: 26677312].
18. De Pasquale R, Nasca MR, Musumeci ML, Micali G. Elastosis perforans serpiginosa in an adult with Down's syndrome: report of a case with symmetrical localized involvement. *J Eur Acad Dermatol Venereol*. 2002;16(4):387-9. [PMID: 12224699].
19. Hernandez-Ruiz E, Garcia-Herrera A, Ferrando J. Scaly Erythematous Patches in a Patient With Down Syndrome. *Actas Dermosifiliogr*. 2015;106(9):753-4. [PMID: 26121907].
20. Boccaletti VP, Ricci R, De Panfilis G. Unknown: Papules on the knees. Elastosis perforans serpiginosa (EPS). *Dermatol Online J*. 2011;17(5):12. [PMID: 21635834].
21. O'Donnell B, Kelly P, Dervan P, Powell FC. Generalized elastosis perforans serpiginosa in Down's syndrome. *Clin Exp Dermatol*. 1992;17(1):31-3. [PMID: 1424255].
22. Kaufman AJ. Treatment of elastosis perforans serpiginosa with the flashlamp pulsed dye laser. *Dermatol Surg*. 2000;26(11):1060-2. [PMID: 11096396].
23. Espinosa PS, Baumann RJ, Vaishnav AG. Elastosis perforans serpiginosa, Down syndrome, and moyamoya disease. *Pediatr Neurol*. 2008;38(4):287-8. [PMID: 18358411].
24. Gregersen PA, Stausbol-Gron B, Ramsing M, Sommerlund M. Elastosis Perforans Serpiginosa in a patient with Down syndrome treated with imiquimod 5% cream. *Dermatol Reports*. 2010;2(2):15. [PMID: 25386246].
25. Souza CDL, Nascimento GG, Dias IR, et al., editors. Elastosis perforans serpiginosa in two sibling patients with Down syndrome: Case report. *J Am Acad Dermatol*; 2019. MOSBY-ELSEVIER 360 Park Avenue S, New York, NY 10010-1710 USA.
26. Pereira AC, Baeta IG, Costa Júnior SR, et al. Elastosis perforans serpiginosa in a patient with Down's syndrome. *An Bras Dermatol*. 2010;85(5):691-4. [PMID: 21152796].
27. Ritchie EB, McCuistion CH. Elastosis Perforans Serpiginosa: Report of a Case. *Arch Dermatol*. 1960;82(6):976-9.
28. Siragusa M, Romano C, Cavallari V, Schepis C. Localized elastosis perforans serpiginosa in a boy with Down syndrome. *Pediatr Dermatol*. 1997;14(3):244-6. [PMID: 9192425].
29. Iwatsuki K, Orikasa R, Kaneko F. Elastosis perforans serpiginosa associated with Down's syndrome. *Eur J Dermatol*. 1996;6(2):147-8. [PMID: WOS:A1996UA83100017].
30. Crotty G, Jr., Bell M, Estes SA, Kitzmiller KW. Cytologic features of elastosis perforans serpiginosa (EPS) associated with Down's

syndrome. *J Am Acad Dermatol*. 1983;8(2):255-6. [PMID: 6219140].
31. Walshe MM. Keratosis Follicularis Serpiginosa. *Trans St Johns Hosp Dermatol Soc*. 1963;49:141-3. [PMID: 14116130].
32. Tschen E, Head E. Elastosis perforans serpiginosa and other complications. *Arch Dermatol*. 1980;116(12):1348. [PMID: 6450568].
33. van Dijk FS, Cobben JM, Kariminejad A, et al. Osteogenesis Imperfecta: A Review with Clinical Examples. *Mol Syndromol*. 2011;2(1):1-20. doi:10.1159/000332228
34. Reed WB, Pidgeon JW. Elastosis Perforans Serpiginosa with Osteogenesis Imperfecta. *Arch Dermatol*. 1964;89:342-4. [PMID: 14096347].
35. Kingsley HJ. Elastosis perforans serpiginosa with osteogenesis imperfecta. *Arch Dermatol*. 1964;90(4):453-.
36. Carey TD. Elastosis perforans serpiginosa. *Arch Dermatol*. 1977;113(10):1444-5. [PMID: 911175].
37. Perez-Perez L, Allegue F, Alfonsin N, et al. An uncommon association: elastosis perforans serpiginosa and osteogenesis imperfecta. *J Eur Acad Dermatol Venereol*. 2009;23(2):172-4. [PMID: 18422533].
38. Omarjee L, Nitschke Y, Verschuere S, et al. Severe early-onset manifestations of pseudoxanthoma elasticum resulting from the cumulative effects of several deleterious mutations in ENPP1, ABCC6 and HBB: transient improvement in ectopic calcification with sodium thiosulfate. *Br J Dermatol*. 2020;183(2):367-72. [PMID: 31646622].
39. Katagiri K, Fujiwara S, Shinkai H, Takayasu S. Heterogeneity of clinical features of pseudoxanthoma elasticum: analysis of thirteen cases in Oita Prefecture from a population of 1,240,000. *J Dermatol*. 1991;18(4):211-217. doi:10.1111/j.1346-8138.1991.tb03070.x
40. Caro I, Sher MA, Rippey JJ. Pseudoxanthoma elasticum and Elastosis perforans serpiginosa. Report of two cases. *Dermatologica*. 1975;150(1):36-42. [PMID: 1149910].
41. Sen S. Pseudoxanthoma elasticum with elastosis perforans serpiginosa. *Indian J Dermatol*. 1976;21(3):51-2. [PMID: 1010610].
42. Pavithran K, Nair RP, Sailakumari B, Mankappan TP. Pseudoxanthoma Elasticum with Elastosis Perforans Serpiginosa. *Indian J Dermatol Venereol Leprol*. 1983;49(6):278-93. [PMID: 28176746].
43. Venkatachalam K, Chennamsetty K. Elastosis perforans serpiginosa in a case of pseudoxanthoma elasticum: A rare association. *Indian Dermatol Online J*. 2016;7(2):103-6. [PMID: 27057491].
44. Lee WJ, Bak H, Chang SE, et al. Autosomal recessive type 2 pseudoxanthoma elasticum presenting with generalized skin laxity. *J Dermatol*. 2009;36(5):288-92. [PMID: 19383000].
45. Pai SH, Zak FG. Concurrence of pseudoxanthoma elasticum, elastosis perforans serpiginosa and systemic sclerosis. *Dermatologica*. 1970;140(1):54-59. doi:10.1159/000252535
46. Smith EW, Malak JA, Goodman RM, McKusick VA. Reactive perforating elastosis: a feature of certain genetic disorders. *Bull Johns Hopkins Hosp*. 1962;111:235-51. [PMID: 13989407].
47. Schutt D. Pseudoxanthoma Elasticum and Elastosis Perforans Serpiginosa. *Arch Dermatol*. 1965;91:151-2. [PMID: 14237598].
48. Funabashi, T., and Tsuyuki, S.: A Case of Elastosis Perforans With Pseudoxanthoma Elasticum , *Jap J Derm* 75:649, 1966.
49. Madan V, Williams J, Lear JT. Dermatological manifestations of Down's syndrome. *Clin Exp Dermatol*. 2006;31(5):623-9. [PMID: 16901300].
50. Anning ST. Elastoma Intrapapillare Perforans Verruciforme (Miescher). Proc Roy Soc Med 1958;51(932).