



Papillon-Lefèvre Syndrome

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Papillon-Lefèvre Syndrome (PLS)

- ❑ Sjukdomen PLS – hur ser symptomen ut?
- ❑ Är PLS resultatet av en immunologisk avvikelse?
- ❑ Patientfall
- ❑ 1924 och 1999

Papillon-Lefèvre Syndrome kardinal symptom

- ❑ Palmoplantar hyperkeratos
- ❑ Aggressiv parodontit

Papillon-Lefèvre Syndrome andra stigmata

- ❑ Palmoplantar hyperkeratos
- ❑ Aggressiv parodontit
- ❑ Ökad infektionskänslighet
 - abscesser i huden
 - inflammatoriska pseudotumörer eller pyogena abscesser i levern
- ❑ (Intrakraniella kalkificationer, mental retardation)

Papillon-Lefèvre Syndrome

342 PLS articles, 204 with PLS and periodontal inflammation (PubMed 2007)

KFSH&RC patient pool (2003):
54 patients, aged 2 – 24 years
2 – 9 years, n:o 22 patients
10 – 15 years, n:o 20 patients
16 – 24 years, n:o 12 patients

Papillon-Lefèvre Syndrome

Palmoplantar hyperkeratos



Aggressiv parodontit

Papillon-Lefèvre Syndrome

"Dermatologic and oral findings in a cohort of 47 patients with Papillon-Lefèvre syndrome"

Are the dermatologic changes correlated to age, severity of periodontal inflammation - or both ?

!

"The two cardinal features were expressed independently of each other. The palmoplantar hyperkeratosis showed no correlation to age"

Papillon-Lefèvre Syndrome

"Dermatologic and oral findings in a cohort of 47 patients with Papillon-Lefèvre syndrome"

Conclusion

The findings support the concept that the two major components of PLS are unrelated to each other.

J Am Acad Dermatol 2003;48:345-51

Papillon-Lefèvre Syndrome

"foreslagna" orsaker till oral infektion

- ❑ Aggressiv periopato-gen flora
- ❑ Dyskeratos av den orala mucosan
- ❑ Anatomisk defekt av den epiteliala barriären

Finns det någon immunologisk förklaring?

Dysfunktion av polymorfkärniga neutrofiler

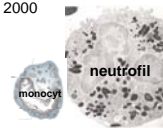
Defective leukocyte adhesion
Stalder et al 1988

Impaired production of superoxide radicals
Bullon et al. 1993

Depressed chemotaxis
Liu et al. 2000

Depressed phagocytic and lytic activity
Ghafler et al. 1999

Impaired monocyte phagocytosis
Preus & Mörländ 1987



Depressed chemotaxis
Firatli et al 1996

Increased release of superoxide radicals
Bimstein et al. 1990

Impaired chemotaxis
Tinanoff et al. 1986

Papillon-Lefèvre Syndrome

- ❑ Autosomal recessiv ärf-tlighetsgång
- ❑ 'Loss-of-function mutations' av kathepsin C – genen (lysosomal cysteine protease, DPPI) Toomes et al. 1999
Hart et al. 1999
- ❑ Mer än 41 olika mutationer av kathepsin C- genen har påvisats
- ❑ "almost no detectable cathepsin C activity in leukocytes in PLS-patients" (Zhang et al. 2002, de Haar et a. 2004)

Papillon-Lefèvre Syndrome

"Phenotypic Variation and Allelic Heterogeneity in Young Patients with Papillon-Lefèvre syndrome"

Results:

- ❑ 39 patienter
- ❑ 3 olika genotyper
- ❑ 2 mutationer identifierade (R272P och G300D)

Papillon-Lefèvre Syndrome

"Phenotypic Variation and Allelic Heterogeneity in Young Patients with Papillon-Lefèvre syndrome"

Results:

- ❑ significant difference between R272P and G300D regarding hyperkeratosis of the feet
- ❑ no significant difference regarding hyperkeratosis of hands or periodontal condition

Papillon-Lefèvre Syndrome

"Phenotypic Variation and Allelic Heterogeneity in Young Patients with Papillon-Lefèvre syndrome"

Conclusion

- the phenotypic expression of the disease characteristics could not be associated with either of the two cardinal mutations
- interaction of environmental factors and/or influence of other genes shape the PLS phenotype

Acta Dermato-Venereologica, 2006 ;86 :3-7

Papillon-Lefèvre Syndrome

Interaction of environmental factors and/or influence of other genes shape the PLS phenotype

PLS is a 'single gene disorder'

Phenotype = environment + genotype + biological interactions

Kinane et al. The genetic basis of periodontitis"
Periodontol 2000, 2005;39:91-117

Papillon-Lefèvre Syndrome

Kathepsin C

- ❑ lysosomal cysteine proteas
- ❑ förekommer i många celltyper, framförallt hos celler i immunförsvaret
- ❑ viktig koordinator för
 - o nedbrytning av proteiner
 - o aktivering av serina proteaser

Papillon-Lefèvre Syndrome

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plasmin, granzyme A&B, elastas, kathepsin G, proteinas 3

Papillon-Lefèvre Syndrome

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plasmin, granzyme A&B, elastas, kathepsin G, proteinas 3.

T-lymfocyter

neutrofiler

Kathepsin C defekten

T-lymfocyter

patienter med PLS har ingen generell immunbrist

cytotoxiska lymfocyter behåller en väsentlig granzymeaktivitet

'Natural killer cells' innehåller inaktiv granzyme B

Neutrofiler

cathepsin G, elastase och proteinas 3 är inaktiva

neutrofiler hos patienter med PLS har ingen generell nedsatt bakteriedödande kapacitet

serina proteaser har eventuellt ingen betydelse för denna funktion utan mera med styrning av det medfödda immunförsvaret

Kathepsin C defekten

- de flesta patienter med PLS utvecklar inga allvarliga infektioner – förutom parodontit
- individer med PLS har ingen generell immunbrist
- PLS-parodontit orsakas förmodligen av att mängden aeroba och anaeroba patogener "besegrar" ett försvagat immunförvar

Finns det några "evidens" för att detta stämmer?

Papillon-Lefèvre Syndrome

Treatment protocol (KFSH&RC) deciduous dentition:

- oral hygiene instructions and prophylaxis every 3rd month
- teeth with advanced periodontal disease – extraction
- All deciduous teeth should be extracted at least 6 months prior eruption of the first permanent tooth.

Antibiotics should be given for 2 wk post extraction

Papillon-Lefèvre Syndrome

Treatment protocol (KFSH&RC) permanent dentition:

- oral hygiene instructions and prophylaxis every 3rd month
- mouth rinses with chlorhexidine gluconate 0.2% twice daily
- moderate periodontal disease** (bone loss < 30% of root length, ppd < 5 mm)
 - dental scaling and prophylaxis once a week or once a month
 - systemic antibiotic treatment for 4 wk (Amoxicillin + Metronidazole 20-50 mg/kg/day and 15-35 mg/kg/day resp.)
- advanced periodontal disease** (bone loss > 30% of root length, ppd > 5 mm)
 - extraction

Papillon-Lefèvre Syndrome

"Preventive Periodontal Regimen in Papillon-Lefèvre syndrome"

Gruppindelning

Group 1: Patienter vars behandlingar och kontroller startat redan före den första permanenta tandens eruption

Group 2: Patienter vars behandlingar och kontroller startat först efter den första permanenta tandens eruption

Uppföljningstid \geq 3 år, med permanenta tänder eruperade i minst 2 år .

Papillon-Lefèvre Syndrome

"Preventive Periodontal Regimen in Papillon-Lefèvre syndrome"

Results

	median age	n.o. lost teeth		periodontal disease	
		during FU		no	yes
group 1 (13)	9 (7 – 18)	0.6 (0-6)		12	1
group 2 (22)	15 (9 – 23)	5.0 (0-17)		9	13

Papillon-Lefèvre Syndrome

"Preventive Periodontal Regimen in
Papillon-Lefèvre syndrome"

Results

		periodontitis		pockets		
		no	yes	0	1-5	<5
Adherence/ compliance	yes	21	2	21	2	0
	no	3	9	3	2	7

Papillon-Lefèvre Syndrome

"Preventive Periodontal Regimen in
Papillon-Lefèvre syndrome"

Conclusions

- early diagnosis of the periodontal condition is important
- most patients with periodontal involvement show signs of periodontal disease before age 9
- adherence and compliance to treatment protocol has a strong impact on presence of periodontal disease

Pediatric Dent 2005;27:226-232

Papillon-Lefèvre syndrome alternativa diagnoser

- Haim-Munk syndrom
- Ehlers-Danlos syndrom (vasculär och övrig/klassisk typ)
- Cyklisk neutropeni
- Kronisk familjär neutropeni
- Chediak-Higashi syndrom
- 'Leukocyte Adhesion Defeciency' typ 2
- 'Leukocyte Adhesion Defeciency' typ I
- Prepubertal parodontit