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ORIGINAL ARTICLE

Cytokine production by leukocytes of Papillon–Lefèvre syndrome patients in whole blood cultures

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Abstract Papillon–Lefèvre syndrome (PLS) is characterised by aggressively progressive periodontitis combined with palmo-plantar hyperkeratosis. It is caused by "loss of function" mutations in the cathepsin C gene. The hypothesis behind this study is that PLS patients' polymorphonuclear leukocytes (PMNs) produce more proinflammatory cytokines to compensate for their reduced capacity to neutralize leukotoxin and to eliminate *Aggregatibacter actinomycetemcomitans*. Production of more interleukin (IL)-8 would result in the attraction of more PMNs. The aim of this study was to evaluate the cytokine profile in PLS patients' blood cultures. Blood was sampled from eight PLS patients (one female) from six families (anti-infective therapy completed: six; edentulous: two) with confirmed cathepsin C mutations and deficient enzyme activity. Nine healthy males served as controls. Whole blood cultures were stimulated with highly pure lipopolysaccharide (LPS) from *Escherichia coli* R515 and IL-1β plus tumor necrosis factor (TNF)-α. Thereafter, release of IL-1β (stimulation: LPS and LPS plus adenosine triphosphate), IL-6, IL-8, interferon-inducible protein (IP)-10, and interferon (IFN)-γ (stimulation: LPS, IL-1β/TNFα) were detected by ELISA. Medians of cytokine release were, with the exception of IP-10, slightly higher for PLS than for controls' cultures. None of these differences reached statistical significance. Increased production of IL-1β, IL-6, IL-8, IP-10, or IFNγ as a significant means to compensate for diminished activity and stability of polymorphonuclear leukocyte-derived proteases could not be confirmed in this study. Cytokine profiles in blood cultures may not be used to identify PLS patients.

Keywords Papillon–Lefèvre syndrome · Blood culture · Interleukin-1β · Interleukin-6 · Interleukin-8 · Interferon-inducible protein-10 · Interferon-γ

Introduction

Papillon–Lefèvre syndrome (PLS) is a rare autosomal recessive disorder (one to four cases per million), described for the first time in France in 1924 [1]. It is characterised by severe aggressively progressing periodontitis of the deciduous and permanent dentition combined with palmo-plantar hyperkeratosis (PPK). PPK is often transgredient, affecting also the dorsa of the fingers and toes. Additionally, elbows, knees, or the trunk can exhibit hyperkeratosis. Further sporadic findings include calcification of falx cerebri, mental or somatic retardation, arachnodactyly, and hyperhidrosis [2, 3]. Approximately 20–25% of PLS cases suffer from an increased susceptibility to infections other than periodontitis, most of them show a predisposition to mild skin infections such as furunculosis or pyodermas. Occasionally, severe infections such as liver abscesses or pneumonia occur [4, 5].

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Table 1 Characteristics of analyzed individuals

Individual #	Family #	Year of birth	Origin	Consanguinity	Phenotype	Nucleotide	Exon	Effect
1 (Eickholz et al. 2001)	2	1987	Germany	No	PLS (typical findings[b])	c.947 T>G	7	L316R[d]
						c.1268 G>C	7	W423S[d]
2[a] (Noack et al. 2008)	3	1979	Morocco	Yes	PLS (typical findings[c])	c.854 C>T	6	P285L[d]
3[a] (Noack et al. 2008)	3	1995	Morocco	Yes	PLS (mild skin findings)	c.854 C>T	6	P285L[d]
4[a] (Schacher et al. 2006)	5	1999	Eritrea	No	PLS (typical findings)	c.755 A>T	5	Q252L
5[a] (Schacher et al. 2006)	5	2002	Eritrea	No	PLS (typical findings)	c.755 A>T	5	Q252L
6 (Noack et al. 2008)	6	2000	Russia	Adopted	PLS (typical findings)	c.566-572Del	4	T189FS199X
						c.628 C>T	4	R210X
7 (Rüdiger et al. 1999)	9	1988	Germany	Yes	PLS (typical findings[c])	c.566-572Del	4	T189FS199X
8 (Noack et al. 2008)	10	2001	Germany	No	PLS (typical findings)	c.901 G>A	7	G 301 S

PLS Papillon–Lefèvre syndrome

[a] Siblings

[b] Typical findings: palmo-plantar hyperkeratosis, aggressively progressing periodontitis resulting in premature tooth loss in deciduous and permanent dentition (if already erupted)

[c] Juvenile patients that are edentulous or have only very few remaining permanent teeth at present. All have reported premature tooth loss also of deciduous teeth due to aggressively progressing periodontitis

[d] Analysis of enzyme activities showed almost complete loss of CTSC, CTSG, and NE activity compared to wild-type controls

Up to now, most PLS patients suffer from premature tooth loss. However, if started providently in timely manner, mechanical debridement, suitable antibiotic pharmacotherapy, and a consequent maintenance therapy can provide successful periodontal management [6–11].

Since the gene locus for PLS was mapped to chromosome 11q14 in 1999, and the disease-associated gene was identified as the cathepsin C (*CTSC*) gene [12, 13], more than 70 different homozygous or compound heterozygous mutations in typical PLS families as well as in atypical cases have been reported [14].

Biallelic mutations in the *CTSC* gene causing PLS result in an almost total loss of enzyme function. CTSC takes part in processing of serine proteases including neutrophil-derived cathepsin G (CTSG) or neutrophil elastase (NE) [15]. Reduced CTSC activity results in decreased activity and stability of polymorphonuclear leukocyte (PMN) derived proteases [16–18]. These proteases may play a crucial role in the regulation of innate immune responses against invading bacteria [19, 20]. Recent studies have analyzed the pathogenic role of CTSC deficiency in periodontitis, showing that PMN capacity to neutralize leukotoxin and to eliminate *Aggregatibacter actinomycetemcomitans* is reduced in PLS [19]. Further studies have highlighted the importance of CTSC in human NK-cell function in controlling infection, and an impaired NK cell cytotoxicity in PLS-associated periodontitis is being considered [21, 22].

In whole blood, interleukin-1β (IL-1β) is released by monocytes. It is a major proinflammatory cytokine closely related to periodontal breakdown [23]. IL-6 and IL-8 are produced by mononuclear blood cells (lymphocytes and monocytes). Interestingly, IL-1β and IL-6 also have been characteristically associated with inflammatory cell migration and osteoclastogenesis. IL-6 is related to bone resorption [23]. IL-8 is a key neutrophil chemoattractant. Neutrophil migration into the gingival sulcus is associated with transepithelial gradients of IL-8. Human interferon-inducible protein 10 (IP-10), inhibits bone marrow colony formation, has antitumor activity in vivo, is chemoattractant for human monocytes and T cells, and promotes T cell adhesion to endothelial cells [24]. In blood, it is released from monocytes in response to interferon γ (IFN-γ). IFN-γ is being considered the main phagocyte-activating cytokine, and is characteristically associated with the production of inflammatory cytokines, chemokines, and microbicidal

Table 2 Interleukin-1β: median and interquartile range (pg/ml)

Stimulation	PLS *N*=6	Healthy controls *N*=7	*p*
Not stimulated	539.0 (253.2–654.4)	454.2 (336.2–739.4)	0.617
100 ng/ml LPS	1,100.0 (896.2–2,572.1)	896.2 (771.2–2,014.0)	0.520
100 ng/ml LPS+2 mM ATP	9,860.9 (7,495.1–14,875.0)	7,888.7 (6,641.4–21,854.5)	0.943
2 mM ATP	400.8 (196.0–454.2)	347.4 (328.2–523.7)	0.565

PLS Papillon–Lefèvre syndrome, *LPS* lipopolysaccharide, *ATP* adenosine triphosphate

Table 3 Interleukin-6: median and interquartile range (pg/ml)

Stimulation	PLS N=6	Healthy controls N=7	p
Not stimulated	21.4 (0.0–30.8)	31.2 (9.3–64.0)	0.469
100 ng/ml LPS	65,559 (40,365–108,260)	45,734 (34,056–66,365)	0.317
10 ng/ml LPS	42,058 (28,173–57,284)	31,368 (25,022–38,934)	0.253
50 ng/ml IL-1β+50 ng/ml TNF-α	3,445.8 (2,495.7–4,308.3)	2,855.9 (2,247.3–5,454.8)	0.775

PLS Papillon–Lefèvre syndrome, *LPS* lipopolysaccharide, *IL-1β* interleukin-1β, *TNF-α* tumor necrosis factor-α

molecules [25]. Concerning periodontitis, IFN-γ is present at high levels in periodontal lesions, and is associated with progressive lesions.

The hypothesis behind this study is that PLS patients' blood cells produce more proinflammatory cytokines to compensate for their reduced capacity to neutralize leukotoxin and to eliminate *A. actinomycetemcomitans*, e.g., production of more IL-8 would result in the attraction of more PMNs. As a response to ineffective phagocytosis increased IL-1β and IL-6 levels may accelerate bone resorption.

Thus, the aim of this study was to evaluate the capability of PLS leukocytes to produce key inflammatory cytokines under conditions of immunoactivation.

Material and methods

Materials

Lipopolysaccharide (LPS; *Escherichia coli*, serotype R515) was purchased from Alexis (Lausen, Switzerland) and adenosine triphosphate (ATP) from Sigma (Deisenhofen, Germany). Tumor necrosis factor α (TNF-α) was kindly provided by the Knoll AG (Ludwigshafen, Germany). IL-1β was from Invitrogen/Biosource (Karlsruhe, Germany).

Patients and healthy donors

Five patients with established diagnose of PLS are under periodontal treatment at the Department of Periodontology, Center for Dental, Oral, and Maxillofacial Medicine (Carolinum) of the Johann Wolfgang Goethe-University Frankfurt am Main. Antiinfective therapy with adjunctive antibiotics has been rendered to all of them and they are under regular and frequent supportive therapy. The Department of Periodontology has contact to additional five PLS patients that are edentulous or under periodontal therapy elsewhere. All patients underwent complete oral examinations as well as inspection of the skin of the palms and soles. Each adult patient or parents received clinical and genetic counselling, and signed a consent form approved by the ethic committees of the Universities of Dresden and Frankfurt/Main. Clinical data and mutations of all patients have been reported before [7–9, 14, 26, 27]. All these patients were invited to take part in this study. Healthy donors had abstained from taking drugs for 2 weeks prior to the study. Due to widespread use of oral contraceptives, only male probands were chosen. The study complied with the rules of the Declaration of Helsinki and was approved by the institutional review board for human studies of the medical faculty of the Johann Wolfgang Goethe-University Frankfurt/Main (application # 31/05). All participating individuals were informed on risks and benefit as well as the procedures of the study and were given written informed consent.

Whole blood culture

Heparinized blood was mixed with an equal volume of culture medium (RPMI 1640 supplemented with 25 mM HEPES, 100 U/ml penicillin, and 100 μg/ml streptomycin) and 1 ml aliquots were transferred into loosely sealed round-bottom polypropylene tubes (Greiner, Germany). Whole blood cultures were kept at 37°C and 5% CO_2 for the indicated time periods. Thereafter, cell-free plasma/RPMI samples were obtained by centrifugation and stored at −70°C until assessment of cytokine concentrations by enzyme-linked immunosorbent assay (ELISA). Experiments were started within 60 min of blood withdrawal. Thus, the whole blood cultures consisted of the whole range of white blood cells as well as erythrocytes. Except for determination of IL-1β release, cultures were either kept as unstimulated control or stimulated with LPS (10 or 100 ng/ml), or with the combination of IL-1β [28] plus TNF-α [29] (50 ng/ml each) for 24 h. For determination of IL-1β release, cells were kept as unstimulated control or were stimulated with Toll-like receptor 4 ligand LPS [30]

Table 4 Interleukin-8: median and interquartile range (ng/ml)

Stimulation	PLS N=8	Healthy controls N=9	p
Not stimulated	0.2 (0.1–0.2)	0.2 (0.1–0.3)	0.386
100 ng/ml LPS	50.5 (29.3–79.9)	44.4 (24.7–46.6)	0.441
10 ng/ml LPS	36.2 (28.5–49.6)	26.0 (17.76–30.81)	0.178
50 ng/ml IL-1β+50 ng/ml TNF-α	27.9 (14.9–60.5)	23.3 (20.3–49.0)	0.773

PLS Papillon–Lefèvre syndrome, *LPS* lipopolysaccharide, *IL-1β* interleukin-1β, *TNF-α* tumor necrosis factor-α

Table 5 Interferon-inducible protein-10: median and interquartile range (pg/ml)

Stimulation	PLS N=8	Healthy controls N=9	p
Not stimulated	201.4 (81.9–256.2)	181.3 (14.0–328.7)	0.699
100 ng/ml LPS	12,902.5 (8,105.5–15,735.5)	11,563.0 (9,164.0–19,758.0)	0.773
10 ng/ml LPS	10,614.0 (6,751.2–12,514.0)	13,903.0 (9,740.4–17,110.0)	0.248
50 ng/ml IL-1β+50 ng/ml TNF-α	6,318.5 (4,330.3–8,843.8)	5,989.8 (2,936.0–14,318.0)	0.847

PLS Papillon–Lefèvre syndrome, *LPS* lipopolysaccharide, *IL-1β* interleukin-1β, *TNF-α* tumor necrosis factor-α

(100 ng/ml) for 5 h altogether. For efficient release of IL-1β from activated cultures, LPS was combined with ATP (2 mM) which was added during the last 2 h of the 5-h stimulation period in order to achieve activation of the purinoreceptor $P2X_7$ [31].

Analysis of cytokine release by ELISA analysis

Concentrations of IL-8, IL-6, IP-10, IFNγ (Pharmingen/BD Biosciences), and IL-1β, (R & D Systems), in plasma/RPMI samples were determined by ELISA according to the manufacturers' instructions.

Statistics

The individual patient or proband was defined as statistical unit. Data are shown as median with interquartile range and are presented as pg/ml (IL-1β, IL-6, and IP-10) or as ng/ml (IL-8). Medians were compared between PLS patients and healthy volunteers using the non-parametric Mann–Whitney *U* test. Statistical analysis was performed using a computer program (Systat™ for Windows version 10.0, Systat Inc., Evanston, IL, USA).

Results

Eight PLS patients (one female: #7) from six families were recruited. Patient characteristics are summarized in Table 1. For all patients, *A. actinomycetemcomitans* had been detected from subgingival plaque prior to antiinfective therapy and in some cases in later stages of therapy (#7). Most patients were also positive for other periodontal pathogens. All adult patients (#1, 2, and 7) have reported premature tooth loss of deciduous teeth caused by severe periodontitis. Patient #1 was treated successfully and has retained 26 permanent teeth up to now [7, 32]. Patients 2 and 7 were edentulous or had left only very few remaining permanent teeth at the time point of examination. For analysis, cytokine production by whole blood cultures derived from PLS patients was compared to that of whole blood cultures from nine healthy donors (all male).

Medians of cytokine release were, with the exception of IP-10, slightly higher for PLS than for controls' cultures. This may in particular apply to IFNγ at 10 ng/ml. However, none of the differences reached statistical significance: IL-1β (Table 2), IL-6 (Table 3), IL-8 (Table 4), IP-10 (Table 5), and IFN-γ (Table 6).

Discussion

In PLS mutations in the *CTSC* gene cause an almost total loss of enzyme function. Reduced CTSC activity results in decreased activity and stability of PMN-derived proteases [16–18]. These proteases apparently play a crucial role in the regulation of innate immune responses particularly against invading bacteria [18, 19]. Notably, the PMN capacity to neutralize leukotoxin and to eliminate *A. actinomycetemcomitans* is reduced in PLS [19].

The outcomes reported after periodontal treatment of PLS patients are quite variable. Conventional periodontal therapy (oral hygiene instructions, scaling and root planing, periodontal surgery, and systemic antibiotics) often failed [6, 33, 34]. Some case reports described favorable results after early extraction of all erupted teeth, followed by an edentulous period, to prevent subsequent infection of the non-erupted teeth [10, 11, 35–37]. However, successful cases in which *A. actinomycetemcomitans* had either not been detected before treatment or had been eliminated by treatment have also been described that did not include large-scale extractions [7, 9, 32, 38–40]. Success of periodontal therapy in PLS may be related to infection with *A. actinomycetemcomitans* and its elimination, respectively. If this periodontal pathogen is at least suppressed below detection limits, therapy will be suc-

Table 6 Interferon-γ: median and interquartile range (pg/ml)

Stimulation	PLS N=8	Healthy controls N=9	p
Not stimulated	3.1 (0.4–30.3)	29.7 (11.4–61.5)	0.245
100 ng/ml LPS	3,704.5 (2,629.5–4,372.8)	3,317.4 (2,538.5–5,487.8)	0.847
10 ng/ml LPS	2,123.1 (609.6–3,281.5)	754.9 (586.3–1,675.1)	0.501

PLS Papillon–Lefèvre syndrome, *LPS* lipopolysaccharide

cessful. If *A. actinomycetemcomitans* persists, periodontitis will progress [8, 10].

Another source of variance may be the different mutations of the *CTSC* gene itself. Atypical PLS cases have been described exhibiting *CTSC* gene mutations [14, 33, 41–45]. These cases included mild or missing skin findings as well as later onset of periodontitis or mild periodontal destruction. The latter form could be a coincidental presence of hyperkeratosis with periodontitis due to the high prevalence of chronic periodontitis in the population. However, the observed phenotypic heterogeneity could not be associated with specific genotypes. For example, specific *CTSC* mutations such as the p.Y347C mutation have been identified in PLS as well as in isolated prepubertal periodontitis [13, 26]. Additionally, identical mutations have been found in PLS and in the closely related Haim–Munk syndrome [46–48]. The p.G301S and the p.R272P mutation, which was discovered in typical PLS families [12–14, 17, 26, 44, 49, 50], have been also associated with atypical cases, late onset of periodontitis [45] and mild skin lesions [16]. A seven base-pair deletion (p.T189FS199X) in one prepubertal periodontitis family [27] was also found in two of the analyzed typical PLS families and has been reported previously in PLS [26]. These results are confirmed by a recent study that failed to associate the severity of hyperkeratosis and periodontitis with different *CTSC* genotypes in 39 PLS patients [51]. In summary, the phenotypic variability of *CTSC* mutations suggests a modulating influence of other genetic or environmental factors that are still unknown. However, eventually different *CTSC* gene mutations respond different to therapy.

Finally, there may exist compensatory mechanisms of the host response that may support the effects of therapy in some PLS cases. In gingival crevicular fluid samples from gingivitis sites of 28 PLS patients, significantly higher levels of IL-1β and matrix metalloproteinase (MMP)-8 were disclosed compared with age- and sex-matched controls. The opposite was found for IL-8 and MMP-1 [11]. In the present study, cytokine levels in whole blood cultures after stimulation with either LPS (+ATP) or IL-1β/TNFα was investigated. With the exception of IP-10, medians of cytokines (IL-1β, IL-6, IL-8, and IFNγ) tended to be higher for PLS whole blood cultures compared to whole blood cultures obtained from healthy volunteers. Modestly increased cytokine production may relate to inflammatory priming of leukocytes due to subclinical infectious conditions seen in PLS patients. However, none of the differences reached statistical significance. One reason for this is the small sample reported in this study. However, PLS is a very rare disease. Thus, we cannot report on more cases. Another issue is the high heterogeneity of the PLS group from an age and ethnic point of view (Table 1). The control group could not be matched perfectly to this heterogeneous PLS group. There were no Eritrean or Moroccan age-matched controls available who were also siblings. One PLS patient was already edentulous at the time of investigation. Again, an age-matched edentulous control was not available. Finally, one PLS patient was female. To avoid the influence of oral contraceptives, the control group consisted only of males. Furthermore, all PLS patients included had either been treated successfully before or were edentulous at the time of blood sampling. Thus, the level of subgingival infection may have been too low to cause systemic compensatory mechanisms that could be analysed in venous blood. All this may have contributed to the fact that higher medians for cytokine levels in the PLS group do not reach statistical significance in comparison to the control group.

E. coli LPS may not be the most significant bacterial stimulus in the clinical context of periodontitis in PLS patients. However, the purpose of the current study was to possibly identify gross abnormalities in cytokine production by PLS leukocytes. In that context, we choose to use highly pure LPS (*E. coli*, R515) as major stimulus because this agent is a prototypic standard toll like receptor ligand that is well characterized concerning its effects on human leukocytes.

Due to reduced cathepsin C activity in PLS and resulting diminished activity and stability of PMN-derived proteases, PLS patients' leukocytes (PMNs and mononuclear blood cells) may produce more proinflammatory cytokines to compensate for their reduced capacity to neutralize leukotoxin and to eliminate *A. actinomycetemcomitans*. However, a statistically significant increase in IL-1, IL-6, IL-8, IP-10, and IFNγ production to compensate for this could not be confirmed in this study.

Conflicts of interest The authors declare that they have no conflicts of interest. This study was funded by the authors and their institutions.

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