Reliable detection of subtypes of nailfold capillary haemorrhages in childhood-onset systemic lupus erythematosus

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Abstract

Objective

In systemic lupus erythematosus (SLE), it is necessary to obtain biomarkers that predict cardiovascular complications due to premature atherosclerosis, which is related to endothelial dysfunction. Nailfold capillary abnormalities might be a biomarker for endothelial dysfunction. In adults and children with SLE, nailfold capillary haemorrhages have shown to be significantly correlated with disease activity. Recently, different subtypes of capillary haemorrhages have been described in childhood-onset SLE (cSLE). The aim of the current study was to assess the inter- and intra-rater reliability of observations of different subtypes of haemorrhages in cSLE patients.

Methods

Five raters blindly evaluated 140 capillaroscopy images from 35 cSLE-patients (diagnosed according to the 2012 SLICC criteria). The images were assessed qualitatively (present or absent) and quantitatively (total number) on four different subtypes of haemorrhages: 1) punctate extravasations, 2) perivascular haemorrhage, 3) large confluent haemorrhage and 4) non-definable. As subgroups 1) and 2) were interpreted as a continuous spectrum, a post-hoc analysis with "merged" (mean) kappa/ICC was additionally calculated as one sub-group.

Results

Qualitative assessment showed a kappa 0.65 (95% CI: 0.60–0.70) for "punctate extravasations and perivascular haemorrhages merged" and a kappa 0.78 (95% CI: 0.72–0.83) for large confluent haemorrhages. For the quantitative assessment, ICC was 0.82 (95% CI: 0.76–0.87) for the "merged groups" and ICC 0.93 (95% CI: 0.91–0.95) for large confluent haemorrhages.

Conclusion

Our study shows that different subtypes of capillary haemorrhages in cSLE-patients could be reliably reproduced by different raters. This confirms our recent observation of perivascular extravasations as a subgroup of capillary haemorrhage in cSLE that might reflect endothelial dysregulation.

Key words

capillaroscopy, childhood-onset, systemic lupus erythematosus, capillary haemorrhage

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Introduction

Systemic lupus erythematosus (SLE) is a severe lifelong systemic autoimmune disease with a waxing-waning course which can influence any organ system. Childhood-onset SLE (cSLE) represents 10–20% of all SLE cases and is a more severe disease than adult-onset SLE with higher cumulative disease activity over time and earlier and more accrual of damage (1-4). Cardiovascular complications, due to premature atherosclerosis, are an important cause for mortality in SLE (5). Case-control studies in SLE have shown that the risk of cardiovascular disease is increased up to 17-fold and even over 50-fold in female patients between 35-44 years (6). The pathophysiology of premature atherosclerosis in cSLE is not yet completely understood but endothelial dysfunction plays an important role (7). To improve outcome in SLE, more biomarkers for endothelial dysfunction are needed and the presence of nailfold capillary abnormalities might be such a biomarker.

Recently, two systematic reviews were published on nailfold capillary findings in respectively adult- and childhood-onset systemic lupus erythematosus (cSLE) (8, 9). Cutolo *et al*. concluded that SLE-patients show more capillary haemorrhages when compared to healthy controls (8). For cSLE, data on capillary haemorrhages from the literature were mostly inconclusive or non-interpretable (9). Subsequently, our group described capillary abnormalities from a cross-sectional cSLE-cohort (n=41) that showed significantly more capillary haemorrhages in cSLE-patients *versus* matched healthy controls and the number of capillary haemorrhages in cSLE was significantly correlated with disease activity and presence of nephritis but not with Raynaud, antiphospholipid syndrome or anti-RNP antibodies (10). A high frequency and total amount of "pericapillary extravasations" was observed in cSLE patients, possibly revealing a new subtype of capillary haemorrhage that might reflect endothelial damage in these paediatric patients. In this cross-sectional study, the two subgroups of capillary haemorrhages were defined: large pathological haemorrhages as 'large deposit of haemosiderin with a capillary-like appearance'(11) and pericapillary extravasations presenting as 'small point-shaped haemorrhages surrounding the capillary loop'. Large pathological haemorrhages as well as pericapillary extravasations were significantly more frequently detected in cSLE-patients compared to healthy controls (respectively in 75.6% (31/41, $p<0.001$) and 87.8% (36/41, $p<0.001$) of the cSLE-patients (10).

In the current available literature, the 'pericapillary extravasation' subtype has seldomly been described. Two articles were found with similar observations, describing this phenomenon as "leakage of capillary content" in central serous chorioretinopathy (12) or as "extravasations of red blood cells, with the impression of punched out windows" or "pearl necklaces of extravasates" seen in adult SLE patients (13, 14). These extravasations were never described in cSLE patients. To assess whether different subtypes of capillary haemorrhages can be observed in cSLE, this observation has to be reliably detectable.

The aim of the current study was to assess the inter- and intra-rater reliability of observation of different subtypes of haemorrhages in cSLE patients, including the newly described perivascular extravasations.

Methods

Capillaroscopy and image selection

The capillaroscopic images were obtained in a longitudinal, prospective cohort study, which was conducted at the outpatient paediatric departments of two Dutch hospitals. Capillaroscopic images were collected using nailfold videocapillaroscopy during a routine visit at the outpatient clinic. Included patients had been diagnosed with cSLE (start of disease before the age of eighteen years old), according to the 2012 SLICC classification criteria (15). The videocapillaroscope was equipped with a x200 magnification lens from Optilia with accompanying 'Optipix' image analysis software. All fingers of both hands excluding the thumbs, were examined. Per finger, four images were stored. From this database, 140 representative capillaroscopic images with

good visibility were selected from 35 cSLE-patients.

Scoring of capillaroscopy images

The capillaroscopic images were anonymised and sent to five (paediatric) rheumatologists (in training). Beforehand, a form was sent to the raters which contained instructions and definitions for evaluating the images. This comprehension of the instruction form was orally evaluated before scoring. Then, the raters evaluated the images on the pre-defined subtypes of capillary haemorrhages. Raters were asked to indicate for each image which subtype of haemorrhage(s) they observed and also quantify these haemorrhages in a non-restricted fashion (*i.e.* between 0 and ∞ haemorrhages of a specific subtype). Three weeks later, the same images, but in a different order, were sent to the same raters and they were asked to repeat the same scoring procedure.

Three authors (SB, DS and VS) defined four subtypes of haemorrhages. Definitions were as follows (see Supplementary Figure S1 for clarification with images): 1) punctate extravasations (Suppl. Fig. S1, part A); characterised by a point-shaped small appearance, localised around the capillary or in the middle of the capillary loop. 2) perivascular haemorrhage (Suppl. Fig. S1, part B); as the punctate extravasation, but in grouped/confluent aspect, mainly apically located, but can also be observed along the loop of the capillary. 3) large confluent haemorrhage (Suppl. Fig. S1, part C); larger bleeding, confluent in nature which migrates in line with the capillary, distal to the cuticle. 4) Non-definable; this category contains haemorrhages that cannot be defined to the other three categories.

After scoring the images, the raters mentioned that a distinction between the subgroups 1) and 2) was often difficult to make. We considered that these two groups are part of a continuous spectrum with the punctate extravasation (subgroup 1) as a 'milder' variant of the perivascular haemorrhage (subgroup 2). Therefore, a *post-hoc* analysis was performed by merging these two subgroups, defining them as "perivascular extravasations".

Table I. Interpretation of kappa and ICC values.

Kappa	Interpretation	ICC	Interpretation
<0	Poor agreement		
0.01–0.20	Slight agreement		
0.21–0.40	Fair agreement	<0.50	Poor agreement
0.41–0.60	Moderate agreement	0.50–0.75	Moderate agreement
0.61–0.80	Substantial agreement	0.76–0.90	Good
0.81–1.00	Almost perfect agreement	>0.90	Excellent

Table II. Baseline characteristics of cSLE patients subjected to NVC in this study (n=35).

Baseline characteristics	Value
Female, no (%)	31 (88.6)
Ethnicity, no (%)	
Caucasian	11 (31.4)
African/Afro-Caribbean	16 (45.7)
North-Africa/Middle-East	3 (8.6)
Asian	3 (8.6)
Mixed/other	2 (5.7)
Age at onset in years, median (IQR 25-75)	14 (10-15)
Age at capillaroscopy in years, median (IQR 25-75)	17 (14-18)
ANA at diagnosis, no (%)	35 (100)
anti-ds-DNA, no (%)	22 (62.9)
anti-ENA, no (%)	24 (68.6)
anti-RNP, no (%)	13 (37.1)
anti-Sm, no (%)	12 (34.3)
Antiphospholipid antibodies, no (%)	4 (11.4)
Nephritis, no (%)	11 (31.4)
Mucocutaneous involvement, no (%)	24 (68.6)
Neuropsychiatric involvement, no (%)	4 (11.4)
Arthritis, no (%)	21 (60)
Raynaud's phenomenon, no (%)	12 (34.3)
SLEDAI score at diagnosis, median (IQR 25-75)	12 (10-16)
SLEDAI score at capillaroscopy, median (IQR-75)	5 (2-10)

ANA: anti-nuclear antibodies; anti-ds-DNA: anti-double stranded DNA antibodies; anti-RNP: anti-ribonuclear protein; anti-Sm: anti-Smith antibodies; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; IQR: interquartile range.

Statistical analysis

The assessments from the different raters generated both qualitative (*i.e.* categorical) and quantitative data. For the qualitative assessment of the haemorrhages, Fleiss' and Cohen's kappa analyses were calculated. For the quantitative data analysis, the intraclass correlation coefficient (ICC) was calculated. To measure the inter-rater reliability, Fleiss' kappa and the ICC were used (to analyse the qualitative and quantitative data, respectively). To assess the intra-rater reliability of the qualitative datasets, Cohen's kappa was used, whereas for the intra-rater reliability of the quantitative datasets the ICC analysis was used. The interpretation of the Fleiss' kappa and intraclass correlation coefficient measurements was according to Landis *et al*. and Koo *et al*., respectively (Table I) (16, 17).

The calculations described above were performed with the "Two-Way mixed" (ICC(3)) model using the SPSS statistics software v. 26 (IBM).

Ethical consideration

The capillaroscopy images used in this study are part of a prospective longitudinal cSLE-cohort study, approved by the Medical Ethical Committee from Amsterdam UMC (with number NL60885.018.17 from Dutch trial register). Permission from cSLE-patients to use the capillaroscopy images for research purposes was given by a signed informed consent (child from 12 years of age and/or both parents for children under the age of 16).

Results

Characteristics of raters and patients

Five independent raters (DS, AN, AV,

KM, MB) from three different hospitals (in two countries) participated in this study. The raters had a mean experience of three years (range 1.5–4 years) in interpreting capillaroscopic images.
Demographic variables and specific disease characteristics of the cSLE patients, from which the nailfold capillaroscopic images were obtained in this study, are shown in Table II.

Inter-rater *reliability*
The reliability of the qualitative assessments of the capillaroscopic images for haemorrhages are shown in Table III (first and second assessment), in which the values are categorised per haemorrhage subtype. A substantial agreement was observed for "punctate extravasations and the perivascular haemorrhages merged" with a Fleiss' kappa of 0.65 (95% CI 0.60–0.70). A good agreement was observed for the large confluent haemorrhages subtype with a Fleiss' kappa of 0.78 (95% CI 0.72–0.83). The inter-rater reliability for quantitative data, measured by ICC values, are depicted in Table IV (first and second assessment). The 'merged group', the perivascular extravasations, showed a good agreement in both assessments with an ICC of 0.75 (95% CI 0.68–0.81) and a highest ICC of 0.82 (95% CI 0.76–0.87) The ICC of the large confluent haemorrhages was excellent in both assessments (ICC 0.93 (95% CI 0.91–0.95) and 0.93 (95% CI: 0.91–0.94).

Intra-rater *reliability*
In Tables V and VI, the intra-rater reliabilities are shown for each individual rater, indicated per haemorrhage subtype. For qualitative assessments, a substantial agreement (mean kappa 0.70) was observed for the 'merged group' and, an almost perfect agreement (mean kappa 0.86) for the large confluent haemorrhages. Looking at quantitative measurements, a good agreement (mean ICC 0.84) was observed for the 'merged group' and an excellent agreement, (mean ICC 0.96) for the large confluent haemorrhages.

Table III. Inter-rater reliability of qualitative NVC assessment in cSLE patients.

	Fleiss' kappa 1 (95%CI)	Fleiss' kappa 2 (95%CI)
Punctate extravasations	0.56 (0.51–0.61)	0.45 (0.39–0.50)
Perivascular haemorrhages	0.45 (0.40–0.51)	0.52 (0.47–0.57)
Punctate & perivascular "merged"	**0.65** (0.60–0.70)	**0.62** (0.57–0.67)
Large confluent haemorrhages	**0.76** (0.71–0.82)	**0.78** (0.72–0.83)
Non definable	0.04 (-0.03–0.11)	0.11 (0.05–0.16)

CI: confidence interval Fleiss' kappa 1 & 2: first and second assessment.

Table IV. Inter-rater reliability of quantitative NVC assessment in cSLE patients.

	ICC 1 (95% CI)	ICC 2 (95% CI)
Punctate extravasations	0.61 (0.53–0.68)	0.45 (0.36–0.54)
Perivascular haemorrhages	0.55 (0.46–0.63)	0.52 (0.43–0.60)
Punctate & perivascular "merged"	**0.82** (0.76–0.87)	**0.75** (0.68–0.81)
Large confluent haemorrhages	**0.93** (0.91–0.95)	**0.93** (0.91–0.94)
Non definable	0.04 (-0.03–0.11)	0.11 (0.05–0.18)

CI: confidence interval ICC 1 & 2: first and second assessment.

Table V. Intra-rater reliability of qualitative NVC assessment in cSLE patients.

	Mean kappa	Rater 1	Rater 2	Rater 3	Rater 4	Rater 5
Punctate extravasations	0.59	0.65	0.29	0.79	0.64	0.69
Perivascular haemorrhages	**0.70**	0.74	0.55	0.86	0.63	0.81
Punctate & perivascular "merged"	**0.70**	0.70	0.57	0.85	0.64	0.80
Large confluent haemorrhages	**0.86**	0.92	0.75	0.95	0.83	0.96
Non definable	0.26	0.23	0.00	0.65	0.16	-0.13

Table VI. Intra-rater reliability of quantitative NVC assessment in cSLE patients.

	Mean ICC	Rater 1	Rater 2	Rater 3	Rater 4	Rater 5
Punctate extravasations	0.65	0.67	0.26	0.81	0.71	0.82
Perivascular haemorrhages	0.74	0.74	0.57	0.93	0.67	0.79
Punctate & perivascular "merged"	**0.84**	0.84	0.81	0.92	0.71	0.92
Large confluent haemorrhages	**0.96**	0.95	0.95	1.00	0.94	0.96
Non definable	0.17	0.23	0.00	0.35	0.16	-0.01

ICC: intraclass correlation coefficient.

Discussion

This is the first study on the reliability of observing different capillary haemorrhage subtypes in nailfolds. This study shows that "pericapillary haemorrhages", as well as "large confluent haemorrhages" can be reliably observed in nailfold capillaroscopic images. A substantial inter-rater agreement and good intra-rater agreement for respectively the qualitative and quantitative assessments of the two subtypes of capillary haemorrhages in cSLE-patients was disclosed. A cohort of cSLE patients was chosen, as it was previously observed that nailfold capillary haemorrhages are common in this patient group and the presence of haemorrhages might be related with disease activity in SLE (8). It confirms our previous observation of a new subtype of capillary haemorrhages, namely 'pericapillary extravasations', in cSLE. These pericapillary extravasations were observed in the majority (8) of cSLE-patients in our cohort (10). Further studies are needed to determine if these pericapillary extravasations are specific for cSLE patients. If so, they could potentially be used as a biomarker for disease activity/-damage and have diagnostic value in cSLE.
Nailfold capillaroscopy has proven to be an important diagnostic as well as a prognostic tool in Raynaud's phenomenon (RP) and systemic sclerosis (SSc) (18). For cSLE however, disease-specific capillary abnormalities have not yet been described before. Besides a scleroderma pattern, other capillary ab-

normalities have been observed in adult SLE-patients, but these have mainly been described as non-specific abnormalities (or non-specific micro-angiopathy) (19-23). Besides, as a recent study shows, for Raynaud patients it is also important to know more about the meaning of non-specific changes. They were found in up to 50% of patients with Raynaud in nailfold capillary investigation by dermatoscopy (24). Recently, Meroni *et al*. investigated if selected capillaroscopic abnormalities could assess the evolution from undifferentiated connective tissue disease (UCTD) to the onset of SLE. They found that not only 'elongated capillaries' but also 'haemosiderin deposits' are significantly linked to SLE onset (25). Capillary haemorrhages might reflect endothelial dysregulation. Endothelial dysfunction and inflammation both play important roles in the process of foam cells-formation, which will form the typical fatty streak in early atherosclerotic lesions. Additionally, defective endothelial regeneration in SLE is caused by decreased number of circulating endothelial progenitor cells (EPCs) which contributes to accelerated atherosclerosis. Intraplaque inflammatory processes further contribute to plaque development (7). Thus, endothelial cells play a central role in the development of early atherosclerosis in SLE. If capillary haemorrhages reflect endothelial dysregulation, they could also be a prognostic biomarker for early atherosclerosis and risk for cardiovascular complications.

Merging the punctate extravasations and perivascular haemorrhages subgroups in our *post-hoc* analysis resulted in a shift from 'moderate' to 'good' agreement. We considered that these two groups are both part of a continuous spectrum and therefore could be analysed as one "merged" subgroup: the punctate extravasation (subtype 1) seems to be a milder variant of the perivascular haemorrhage (subtype 2). The low incidence of SLE, 0.3–0.9 per 100. 000 per year hampers the inclusion of a larger number of patients, especially in a study conducted in a paediatric population (26). Nevertheless, the narrow confidence intervals of the qualitative and quantitative parameters indicate that the statistical power of our study has not suffered from this relatively small sample size.

Conclusion

In conclusion, our findings show that two different subtypes of nailfold capillary haemorrhages in cSLE could be reliably reproduced by five different raters. This confirms the value of our previous observation of two different capillary haemorrhages, which were found in high frequency in a case-control study. Future studies should elucidate whether different subtypes of capillary haemorrhages in SLE are also observed in adults and if they are disease specific when compared to other systemic autoimmune diseases, such as SSc and dermatomyositis. Our longitudinal study in cSLE will show whether these capillary abnormalities change over time and if they are associated with disease activity/damage and endothelial serum markers.

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Key messages

- Recently, different subtypes of capillary haemorrhages have been described in childhood-onset SLE
- These different subtypes of capillary haemorrhages could be reliably reproduced by different raters
- Future studies should elucidate whether different subtypes are disease specific when compared to other systemic autoimmune diseases

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