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Oral inflammation and systemic health: is the association only an artefact?

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I was asked to talk about the association between oral inflammation and systemic health as well, and to make it somewhat different to the previous speaker, my topic is more directed to the epidemiological data. Furthermore, I will try to show the problems we have taking example studies instead of the whole range of published data to understand the potential relationship between oral inflammation and systemic disease.

We started this symposium with the biofilm 'plaque' and we learnt a lot about this entity. Although biofilms are difficult to define because of their complexity, several characteristics can be seen constantly, some of which are relevant for the specific situation in the oral cavity: we have stable gradients of acidity and oxygen levels, the bacteria organize themselves in compartments, and the idea is mentioned that these compartments act as a whole, almost as simple organisms – as Professor Marsh already pointed out – and not as single bacteria. Plaque is, therefore, highly differentiated, has to be regarded as a variable ecosystem and its 'inhabitants' are less susceptible to toxins than planktonic bacteria. Living with this plaque in the mouth, we must keep in mind that the microorganisms can enter the body more deeply through different potential portals. At first, the microorganisms can enter via the upper respiratory tract by aspiration, and consequently there are some ideas that oral plaque is related to pulmonary diseases. Second, there is the potential entrance via the digestive tract by swallowing consequently resulting in the idea that infections and/or re-infections of the upper digestive tract, for example with *Helicobacter pylori*, might be related to the accumulation of plaque, as this biofilm gives protection to *H. pylori* throughout its eradication from stomach and duodenum during the antibiotic therapy. And third there is an active or passive invasion of soft tissues by the bacteria leading to acute and recurring bacteraemia, and that's probably the

point, which is of the highest interest in dealing with the possible association between periodontitis and systemic disease.

In reviewing the association between gingivitis and plaque, I recently looked at the data of a case–control study with 694 participants, we performed a couple of years ago. On the graph is shown, which simply relates gingivitis to plaque (Fig. 1). What you can see is that there is a clear correlation between plaque and gingivitis, but there is also a huge interindividual variation in this correlation, probably indicating that the reaction of the body to plaque is different on an individual base. Although, this type of data acquisition and analysis is a very rough instrument, these individual inflammatory responses are seen and reported, frequently. Therefore, the pathogenetic model of periodontitis grew during the last few years, and we moved away from the very simple monocausal model indicating that there are periodontal pathogens leading to periodontal disease. The actual published model takes into account that the process from microbiological exposition to periodontitis is modulated by genetic risk factors as well as by environmental and acquired risk factors (1). Smoking is regarded as one of the important risk factors in the latter group, but it is also one of the major risk factors associated with ischaemic stroke, cardiovascular disease, adverse pregnancy outcomes and other diseases (2).

As we see, nothing is as simple as it used to be. Things become more and more complex and we move away from linear causalities. We have to deal with risks, and more and more statistical or better stochastical risk models. Two expressions have to be distinguished in the correct use: the expression 'risk factor' is defined as a parameter with a proven causal relationship, whereas the expression 'risk indicator' or 'risk marker' means that there exists an association but there is no proof of a causal relationship. Although, this has to be regarded as completely different it is often mixed up in the literature, most likely because we have not enough knowledge to clearly distinguish between both.

Risk factors can now be included into risk models, where they have to be weighted to refer to their impact on the disease. Therefore, risk models are difficult to understand. Furthermore, it is even more difficult to transform this understanding into concrete action in medical therapy. The only possible approach is to use statistical measures. The most frequently used are the 'relative risk' and the 'odds ratio'. Which one you take, depends on the study design, as in the case of a representative population sample, out of which you identify a diseased subgroup, you will have to use the relative risk, and in the case of comparing a disease group from consecutive patients, e.g. of one clinic with a representative population control you will have to take the odds ratio. This background leads to the fact that in most cases relative risk is used in 'longitudinal studies' while odds ratio is mostly used in 'cross-sectional studies'.

Taking in mind that plaque is to some extent physiological and more and more risk factors become more and more important in the understanding of the aetiology of periodontitis, it is only a small step to move on to another model, completely giving up any linear cause–effect relationship, and including all known or suspected causal parameters as risk factors instead. That means in the individual situation, the process from the healthy situation to periodontal breakdown might be – or might not be – initiated and driven by morphological and microbiological risk factors, infectious and inflammatory risk factors as well as psychosocial and habitual risk factors (Fig. 2). Although this model is new, it is the conse-

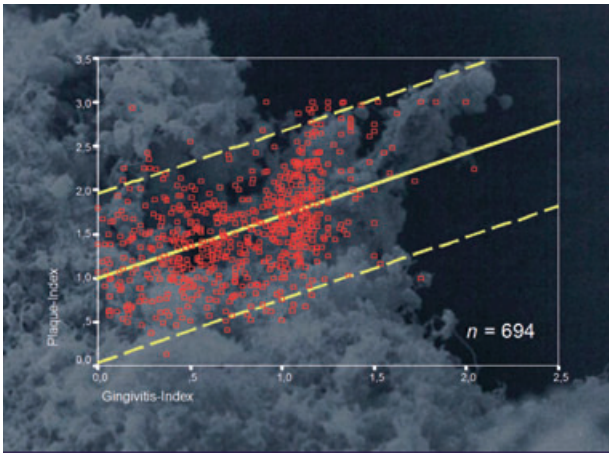

Fig. 1. Correlation between plaque and gingivitis.

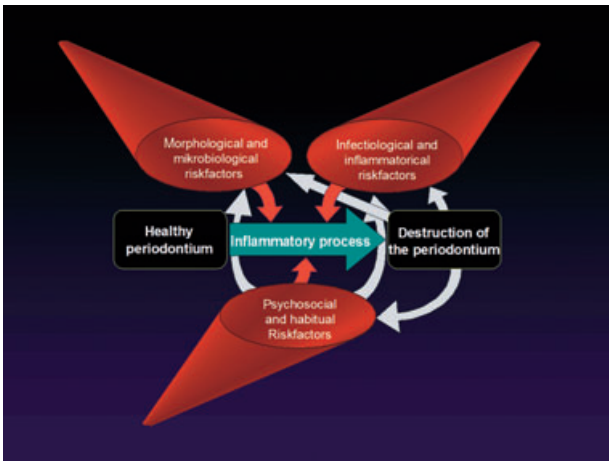

Fig. 2. Stochastical disease model for periodontitis.

quent successor of the model of Page, I referred to previously (1). The development of this model follows several analogies from other subjects, like atomic chemistry or physics, where the increase of knowledge made it also necessary to use stochastical models for the understanding of phenomena or – in our case – chronic diseases and their inter-relationships. As you will see in a few minutes, this model hopefully will help us to understand, why it is so difficult to prove the causal relationship between oral inflammatory diseases and systemic disease.

During the following presentation, I will focus on diabetes mellitus, on adverse pregnancy outcomes, on cardiovascular disease and finally on cerebrovascular disease.

Diabetes mellitus

There is a lot of evidence that diabetes mellitus is a risk factor for periodontal disease, when the blood glucose level is not controlled properly. However, acute inflammatory processes induce metabolic changes, which potentially lead to a distortion of the blood sugar levels in diabetics: inflammation reduces the insulin-mediated uptake of glucose into the skeletal muscles in rats (3), endotoxins and inflammatory mediators reduce the effect of insulin (4), and there is a high association between periodontitis and the blood glucose levels in Pima Indians, who almost all get diabetes due to a genetic defect (5, 6). The idea of the relationship between diabetes and periodontitis, therefore, turned somewhat around going to the direction that probably periodontitis is the risk factor for diabetes instead of diabetes being a risk factor for periodontitis.

To prove causality, you need intervention studies, and diabetes is an ideal disease to perform those. Why? Because you should see an effect of your treatment within a relatively short time span, which gets you off the ethical problem of not treating a treatable disease in your control group. Within a 6–9 months delay, a medium severe chronic periodontitis most likely will not create problems, but if you postpone the therapy for 5 years, as you would to have to do in the case of performing an intervention study with cardiovascular or cerebrovascular disease, then you would run into an ethical problem. Therefore, there exist a couple of intervention studies in diabetes mellitus, which you can divide into those, treating periodontitis mechanically, only, and those treating periodontitis mechanically with an adjunctive antibiotic component. If you look at the four intervention studies with mechanical treatment, only, no influence of the therapy on the blood glucose level was seen (7–10). So these studies could not show that periodontal treatment will improve the situation of the diabetic people. If you take the other three intervention studies with the adjunctive antibiotic therapy component, they found an effect of the periodontal treatment on blood glucose levels (11–13). As we know, antibiotics not only act against microbiota; although the reports about the effect of antibiotics on the pancreatic islets are controversial – some suggesting their harmless action, some depicting a beneficial role and others indicating deleterious effect – a direct influence on the insulin production cannot be excluded. So the problem is that there is still no proof for periodontitis being a causal factor for diabetes mellitus or periodontal therapy improving the situation for diabetic patients, despite the fact that we have seven published intervention studies.

Preterm birth and low birth weight

What do we know about periodontitis and negative pregnancy outcomes? Let us first have a look on the association level. Several studies report associations between periodontitis and low birth weight, preterm birth or higher complication rates during pregnancy (14–19). However, there are also several studies, which did not find this association (20–26). If you more deeply analyse the data and look at 'never smokers', only, then these associations were not consistently found (27). On the other hand, higher levels of antibodies against the periopathogens *Tannerella forsythensis* and *Campylobacter rectus* were found in preterm birth and low birth weight babies (28–30).

Summarizing these data, we must again state that there are conflicting results and the relationship between periodontitis and adverse pregnancy outcomes is not clear. When we search for intervention studies, we find one published by Lopez and coworkers in 2002 (31). Four hundred women participated, a size which gives enough power, and in the treatment group periodontitis was only treated mechanically. The authors reported an excellent effect of the periodontal therapy as in the periodontal treatment group adverse pregnancy outcomes were significantly reduced. The odds ratio of not treating periodontitis was 4.70 and the 95% confidence interval ranged from 1.29 to 17.13.

The problem with this study is, however, that within the control group, the patients did not have the same amount of social contacts as in the test group. Self-confidence, acceptance of being pregnant and being socially integrated are major protective factors against negative pregnancy outcomes. If you take patients with a low socioeconomic status – as it was done in this study – any kind of affection and sympathy will increase these women's self-confidence, self-consciousness,

acceptance of being pregnant and their status within their social environment. Periodontal treatment sessions as a time-consuming and repeatedly performed procedure gives all that beside the effect of reducing the infection, and this intervention alone most likely will result in a positive effect on the pregnancy outcome. So, we are in the situation that we have nice results on one hand, but on the other hand we have the problem that we cannot be sure that the results are the consequence of the study-induced psychosocial effects rather than the consequence of the periodontal therapy.

The next study of this group was bigger in numbers, but it was not even randomized (32). Other data, published 3–5 years ago, showed good effects of periodontal therapy as well, but these were preliminary data, only – without multivariate analyses and therefore not regarding smoking and socioeconomic status as confounding variables – and the final results have not published up to now (18, 30, 33). Other groups did not find a causal relationship between periodontitis and negative pregnancy outcomes, recently (34). Up to now, therefore, the database on the association between periodontitis and pregnancy in terms of the intervention studies, is still weak and again the causality is not really proven.

Cardiovascular disease

Let's come to cardiovascular disease and atherosclerosis, now. In this area, there exists the oldest serious study, which was published in 1963, looking after an association between atherosclerosis and periodontitis (35). In one subgroup Mackenzie and Millard (1963) compared 54 subjects with atherosclerosis and a healthy control group. They found that in the atherosclerosis group 62% of the subjects had higher bone loss compared to the control subjects. Although the differences did not reach statistical significance due to the small number of subjects, we would call that a pilot study today and this study was the first serious hint that there might be an association between periodontal infections and systemic health. Twenty-six years later, there was the study from Mattila and coworkers (36, 37) comparing 100 individuals suffering from myocardial infarction with 102 age- and gender-matched control subjects. They used the total dental index as variable, which is a compound parameter from all major pathological changes in the oral cavity. They found after adjusting the model for age, cholesterol, triglycerides, high blood pressure, diabetes mellitus and smoking an association between high total dental index values and cardiovascular disease. The problem with this study is that the total dental index doesn't indicate on what kind of dental disease the association is based on, because it summarizes every pathological process in the oral cavity, including impacted teeth and caries.

In 1996, Beck and coworkers found an increasing incidence of both cardio- and cerebrovascular disease with increasing periodontal bone loss (38). This 'dose–effect' relationship between the alveolar bone loss and the incidence of coronary heart disease could be taken as an indicator for a causal relationship between periodontitis and coronary heart disease. However, it is not, when you take in mind that both diseases have important risk factors in common.

The publication from DeStefano and coworkers, which I already referred to, is at the first glance a very impressive one, because of the huge database (39). This group found, based on the data set of NHANES I, that periodontitis in males increased the risk of cardiovascular disease by 70%, and after adjustment for all common risk factors for cardiovascular disease they reported a relative risk of 1.72. At that time, everybody in the dental profession was very excited, because periodontal treatment seemed to be good for saving lives instead of saving teeth, only. A couple of years later we were drawn back to reality by Hujoel and coworkers, because they took the same data as DeStefano – once again, the identical data – and only optimized the statistical model. While improving the adjustment for smoking, they found that the association reported by DeStefano's group could be explained by an inadequate adjustment of the data for smoking and social economic status (40).

So if we take both publications, the one from DeStefano and coworkers and the one from Hujoel and coworkers, and analyse them, then we can state that they both are based on longitudinal studies, which gives them a high power, but there was a single dental examination at the beginning of the study, only. No dental follow up was performed. These data, therefore, are not appropriate to proof a causal relationship between periodontitis and coronary heart disease. That is the state of knowledge on the association between periodontitis and cardiovascular disease up to now.

Cerebrovascular disease

If we now look at cerebrovascular disease, then we will find a quite similar situation. One side is represented by the study from Wu and coworkers in 2000, who analysed the data from NHANES I in terms of incidence of stroke (41). They found in periodontitis patients that they had a relative risk of 2.1 for stroke, independent from smoking, diabetes mellitus, social economic status and pre-existing vascular disease. The statistical approach and analysis have been appropriate. Even

adjusting the data in different ways would not seriously change the results. It could be, therefore, that there is more evidence on an association between periodontitis and stroke than between periodontitis and cardiovascular disease. However, there is again the opposite opinion published, this time by Joshipura and coworkers (42, 43). She postulated that the interpretation of Wu and coworkers was overdone and based this statement on the data of an ongoing cohort study, where she found only a slightly increased risk for ischaemic stroke in periodontitis patients, just making the level of statistical significance. If you find a wide 95% confidence interval, then the odds ratio is very susceptible to changes in the statistical analysis, meaning that the actual risk value can vary substantially. If the lower border of the 95% confidence interval is only slightly above 1, the hypothesized association easily can lose statistical significance. So don't look at the odds ratio only, but take the range and the lower value of the 95% confidence interval in mind as well when estimating the solidity of the model. Coming back to the article of Joshipura, she concluded that higher associations, which are reported by other groups, are based on inadequate adjustment for smoking and social economic status. Joshipura's study is huge and it is good in that sense as it is a cohort study, however, the problem with this study is that the patients were not clinically examined for periodontitis. They were only asked about their periodontal status. Even trying to validate these data with radiographs in a subsample is not sufficient to increase the quality of the assessment. The conclusions that were drawn, therefore, are not valid, and we have another low power statement which cannot be used as an argument pro or contra the association between periodontitis and ischaemic stroke.

Now, I will show you the results of a study, we conducted in Heidelberg, and which to my knowledge is the largest case–control study on ischaemic stroke and periodontitis worldwide (44). We performed a case–control study with 303 patients with ischaemic stroke or transient ischaemic attack, who were examined on average 2 days after ischaemia, 300 population controls and 168 hospital controls with non-vascular and non-inflammatory neurological diseases. Patients and controls received a complete clinical and radiographic dental examination. The individual mean clinical attachment loss measured at two sites per tooth was used as main indicator for periodontitis. If you look at the descriptive data then there is not much difference between the stroke group and the population control group, you see the values are quite close together. But in these complex topics the descriptive data do not mean too much, so we evaluated all known or suspected risk factors for both, ischaemic stroke and periodontitis either by examination or through validated questionnaires. In a stepwise procedure, those variables were put into the final model that proved to be statistically significant associated with stroke in a simple multivariate model containing age, gender and number of remaining teeth only.

When looking at the different variables (Fig. 3) one can see that the most important risk is expressed by a history of ischaemic stroke with an odds ratio of 10.4 (95%-CI 4.4–24.5) which is really high. We were often asked why we had this compound parameter in the model, because by summarizing all the other risk factors it also reduces the effect of the more specific factors in the model. But the problem with stroke is that in many cases there is no known reason even when fully diagnosed. So we wanted to cover these 'unknown' risk components and decided to keep the variable in the model.

Precessing cardiovascular disease – as you can see in Fig. 3 – had an odds ratio of 2.4, hypertension of 1.9, diabetes mellitus 3.5, the values being in line with other publications. Alcohol in this model is not statistically significant because at low dose alcohol seems to be protective. As a consequence of this U-shaped risk distribution, you never will get a statistical association between alcohol and stroke when you just have the pure litres in the model. If you make a cut off at 1000 l, then you will see an increased risk, but we were not interested in alcohol as its effect is well documented. The effect of smoking is also well documented.

School education had no influence, academic degree had no influence, but the frequency of dental visits was statistically significant. Did people, who visited the dentist less than once a year, had an increased risk for ischaemic stroke? Does that mean that visiting the dentist actively will reduce your risk of

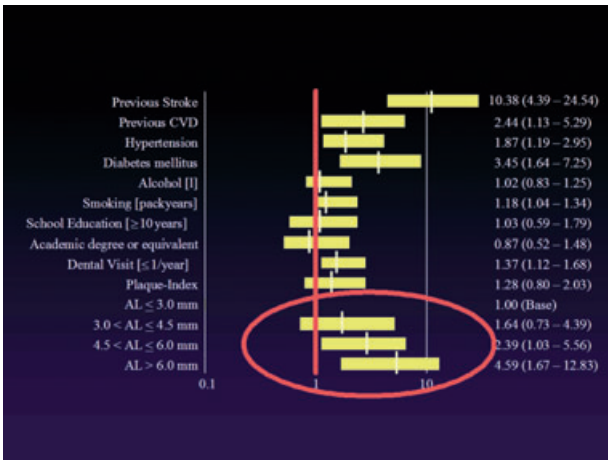

Fig. 3. Associations between loss of attachment (AL) and cerebral ischaemia in a multivariate model with other major risk factors. Odds ratios and 95% confidence intervals are listed.

stroke? No! This is a typical example of a risk indicator, because patients, who go to the dentist on a regular basis have a higher health awareness compared to those that visit the dentist less frequently. And if they have a high health awareness in terms of their teeth they most likely have a high health awareness for their whole body as well, most likely having a diet, exercise more frequently, and do not smoke, resulting in a lower risk for stroke. Therefore the frequency of visiting a dentist might be a good parameter for assessing a person's health awareness but is certainly not a risk factor for stroke. When we analysed the effect of plaque, we found no influence.

Finally, let's look at the attachment level. To enter the loss of attachment into the model the continuous variable of the mean approximal attachment loss was stratified in a baseline category with a mean approximal attachment loss of less than 3 mm, followed by strata from 3 to 4.5, 4.5 to 6 and more than 6 mm mean approximal attachment loss. If you look at the incidence of stroke in the different strata, then again you have this 'dose-dependent' curve as Beck already showed in his data set. In the group of 3–4.5 mm attachment loss, the risk is not significantly increased. In the group of 4.5–6 mm attachment loss the odds ratio is 2.39.

Interestingly, if you divide the group into those who are older than 60 and those who are younger than 60 (Fig. 4), the model is still stable with the odds ratios of the established risk factors being still in line with the published values.

However, looking at the periodontal parameters in the older group, the association between attachment loss and ischaemic stroke cannot be detected any more (Fig. 4). There could be several reasons for this phenomenon. One reason, of course, might be that older individuals have less teeth and so it's harder to detect the effect. Another potential reason could be that if you are getting older you are collecting more and more risk factors, and the sum of the risk factors might mask the role of a single one. It seems, therefore, to be plausible that you get a high association in younger patients and a low association in older patients. That is exactly what we found in our population with an odds ratio of 11.8, for a mean attachment loss of more than 5 mm compared to those with a mean attachment loss of less than 3 mm (Fig. 4), indicating that stroke studies should probably be performed with younger stroke patients rather than in an older population.

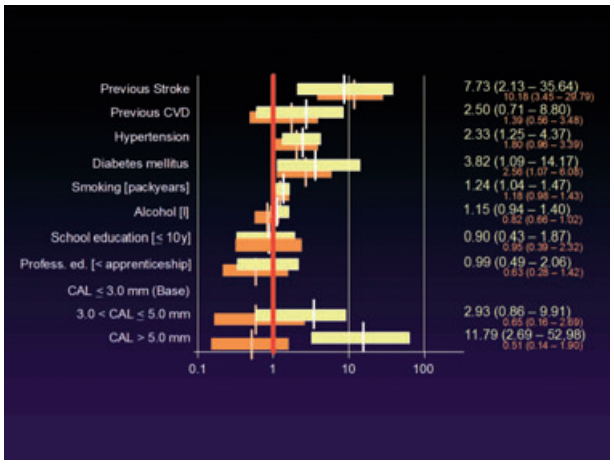

Fig. 4. Multivariate logistic regression model for the association between attachment loss and stroke in subjects older than 60 (orange bars) or up to 60 years (yellow bars) of age. Odds ratios and 95% confidence intervals are listed.

However, there is still the discrepancy in the amount of the odds ratio between the study of Dr Joshipura and coworkers and ours, and, therefore, we also asked the participants, whether they had periodontitis or periodontal therapy before the dental examination, and we found that asking our participants did not result in the detection of an association between periodontitis and stroke but examining them resulted in such an association as I already showed to you. Asking patients is, therefore, definitively not a valid way to detect periodontitis.

I now will come back to what I mentioned previously. In many cases you don't know what the cause of the stroke was. Ischaemic stroke is not a homogeneous disease. It can result from many different pathomechanisms. In the literature, more than 12 different aetiologies of cerebral ischaemia are reported. For epidemiological studies they can be grouped into five categories:

1 atherosclerotic stroke;
2 cardioembolic stroke;
3 microangiopathic stroke;
4 embolic stroke with unknown cause;
5 cause not clear, which means the whole diagnostic procedure was performed, but no cause was found.

In our data, we found no association between periodontitis and the subset of atherosclerotic stroke but a very high odds ratio with cardio embolic stroke. There was again no association with microangiopathic stroke, but a very high odds ratio in embolic strokes with unknown cause. The highest odds ratio was found in the subgroup of strokes without known cause (Fig. 5). However, due to the relatively small numbers in this subset, the lower limit of the 95% confidence interval is still close to 1, indicating that the model is not very stable yet (45). As we unexpectedly did not find an association between periodontitis and atherosclerotic stroke, we probably have to get rid of these simple ideas that the bacteria are going into the vessels and directly cause atherosclerosis. The relationship

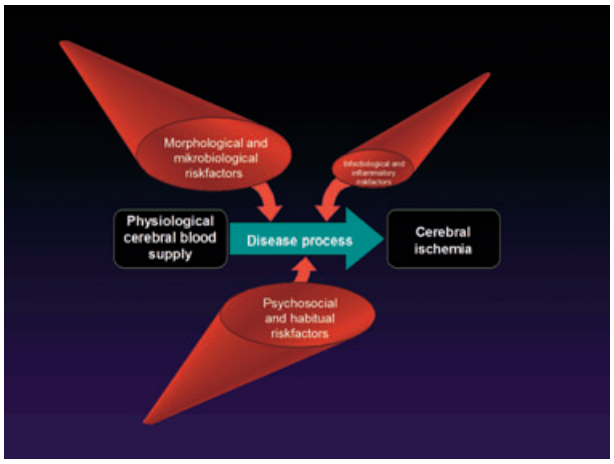

Fig. 5. Stochastical disease model for cerebral ischaemia.

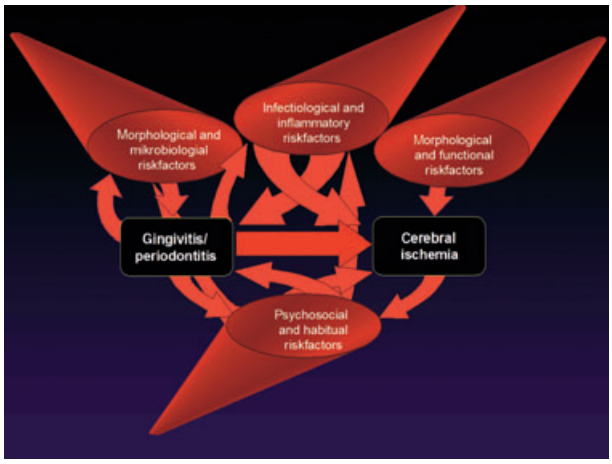

Fig. 6. Potential interactions between periodontitis and cerebral ischaemia.

between periodontitis and stroke seems to be more complex than that.

If we summarize the results of our study, periodontitis was associated with an increased risk of stroke the association only being visible in younger patients. The association was not found in atherosclerotic and microangiopathic strokes, which was unexpected. The association was found in embolic strokes and strokes without known cause.

To make it clear again at this point: the study does not prove causality. It is a case–control study, which is cross-sectional in nature. It is not longitudinal, so causality cannot be proven in that way. However, I showed you that even in disease entities, where published data of intervention studies exist, there is still no final and strong proof of periodontitis being a causal risk factor for systemic disease. Why do we have so many problems with proving the causality? It becomes clear, when we move back to the model I showed you at the beginning of my presentation: the stochastical model for periodontitis. Now we use that type of model to describe the aetiology of ischaemic stroke (Fig. 5). As you see, ischaemic stroke has quite a small infectious and inflammatory component as risk factor. Within this component periodontitis could be one of the potential factors. There are morphological and microbiological risk factors and psychosocial and habitual risk factors in ischaemic stroke, as well as in periodontal disease. As you see, the two diseases have many risks in common, and if we try to combine these two diseases models, you easily can recognize the complexity of potential interactions, and why it is so difficult to prove a direct relationship between periodontitis and cerebral ischaemia (Fig. 6).

The final statement, therefore, is that chronic inflammatory processes in the oral cavity might modify the risk for systemic diseases, which are related to inflammation. However, up to now the cause–effect relationship is not as evident in population-based studies as it should be to state that periodontitis has a meaningful impact on systemic disease. The final proof for such a linkage is still missing.

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