review article

Wien Klin Wochenschr (2008) 120 [Suppl 4]: 24–29
DOI 10.1007/s00508-008-1072-8
Printed in Austria

Wiener klinische Wochenschrift
The Middle European Journal of Medicine

Sandflies and sandfly-borne infections of humans in Central Europe in the light of climate change

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Sandmücken und durch Sandmücken übertragene Erreger von Infektionen des Menschen in Mitteleuropa aus der Sicht von Klimaveränderungen

Zusammenfassung. Sandmücken (Diptera: Psychodidae: Phlebotominae) sind in Europa typische mediterrane Faunenelemente von geringer Expansivität, die in über 20 Spezies im Mittelmeerraum weit verbreitet sind. Einzelne Arten dringen nordwärts in extramediterrane Gebiete (Westeuropa, Osteuropa) vor, in Mitteleuropa nördlich der Alpen wurde das Vorkommen von Sandmücken jedoch bis vor kurzer Zeit ausgeschlossen. Seit 1999 allerdings wurden Phlebotominae u.a. in einigen Teilen Deutschlands und Belgiens gefunden; diese Nachweise wurden ursprünglich mit Klimawandel und globaler Erwärmung in kausalen Zusammenhang gebracht. Inzwischen muss man aber annehmen, dass Sandmücken lange Zeit, vermutlich seit den holozänen Optima (ca. 4500 und 2500 v. Chr.) als Ein-(Rück-)Wanderer aus mediterranen Refugien in Mitteleuropa sporadisch vorkommen und bisher einfach übersehen worden sind. Dass aber eine Klimaerwärmung zur weiteren Ausbreitung in Mitteleuropa führen wird, steht außer Zweifel. Klimatologische Analysen der bisher bekannten Fundorte haben ergeben, dass die Temperatur den Schlüsselfaktor darstellt. Vergleiche mit den Klimaverhältnissen in Österreich (von wo bisher keine sicheren Funde von Phlebotominae vorliegen) haben ergeben, dass bereits eine Temperaturerhöhung um 1°C im Vergleich zum Zeitraum 1971–2000 in vielen Gebieten zu Bedingungen führen würde, die für ein Vorkommen von Sandmücken geeignet sind. (Die Szenarien für eine Klimaerwärmung schwanken zwischen 1,5°C bis 4,5°C zum Ende des Jahrhunderts; 3°C erscheint auch kritischen Autoren als realistische Größe.) Eine Erhöhung der Winter-(Januar-Durchschnitts-)Temperaturen könnte im Westen Österreichs zur Etablierung von *Ph. mascittii* führen, eine Erhöhung der Sommertemperatur würde besonders im Osten und Südosten zu für *Ph. neglectus* geeigneten Bedingungen führen.

Leishmanien kommen ursprünglich in Mitteleuropa sicher nicht vor, doch sind in den letzten Jahren zunehmend autochthone Infektionen bei Menschen und Tieren festgestellt worden. Mit großer Wahrscheinlichkeit sind diese Infektionen auf autochthon vorkommende Sandmücken zurückzuführen, die sich an Hunden infiziert haben. Mit Leishmanien infizierte Hunde werden von mitleidvollen Mitteleuropäern immer wieder – meist illegal – von Südeuropa mitgebracht, und es hat sich sogar ein florierender Markt entwickelt, in dem solche erkrankten Hunde aus dem Mittelmeerraum per Internet von geschäftstüchtigen Personen angeboten werden. Angesichts der Gefährlichkeit der viszeralen Leishmaniose (besonders für Kleinkinder und Immunsupprimierte) muss dieser Situation große Beachtung geschenkt werden.

Phleboviren sind bisher in Mitteleuropa nicht festgestellt worden, könnten sich aber bei Klimaerwärmung und bei Einschleppung möglicherweise etablieren, insbesondere, wenn es sich um Stämme handelt, bei denen außer dem Menschen andere Vertebraten als Reservoir fungieren können.

Summary. In Europe, sandflies (Diptera: Psychodidae: Phlebotominae) are typical Mediterranean faunal elements of low expansivity, which are widely distributed in more than 20 species in many parts of Southern Europe. A few species have extended their distribution to the northwest invading extramediterranean regions (Western, Eastern Europe); any occurrence in Central Europe north of the Alps was excluded until recently. Since 1999 sandflies have been found in several parts in Germany and in Belgium; originally these records were ascribed to climate change and global warming. Meanwhile, the more likely assumption is that sandflies have always, probably since the Holocene climate optima (ca. 4500 and 2500 B.C.), been in Central Europe sporadically to where they have come as immigrants (or re-immigrants) from Mediterranean refugial areas. It is, however, without question that global warming will lead to an extension of the distributional areas of sandflies. A climatological analysis of the localities where sandflies have been found in Central Europe has revealed that temperature is the key factor. A comparison of climato-

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logical parameters in sandfly-localities with the climatic conditions in Austria (where sandflies have not yet been found) has shown that an increase of temperature by 1°C in January (*Ph. mascittii*) or 1°C in July (*Ph. neglectus*), respectively, would lead to suitable conditions for the occurrence of sandflies in certain parts of Austria. (The scenarios for an increase of temperature until the end of the century vary between 1.5°C to 4.5°C; 3°C seem to be realistic also for critical climatologists.)

Leishmaniae certainly do not occur in Central Europe primarily, but an increasing number of infections in humans, as well as in animals, acquired in Central Europe has been registered. It is highly likely that these infections are due to sandflies which have been infected by sucking blood on infected dogs. Dogs infected with *Leishmania* and presenting a variety of clinical symptoms are frequently brought by compassionate tourists from Mediterranean countries – often illegally – to Central Europe. Meanwhile, a flourishing market for dogs of miserable appearance suffering from leishmaniosis has been developed by profit-oriented opportunists in Mediterranean countries.

With respect to the serious course of visceral leishmaniosis (particularly in infants and in immunocompromised persons) this dangerous condition merits intensive attention.

Phleboviruses have not been found in Central Europe, so far. However, in the course of global warming an establishment of biological cycles after an introduction of the pathogens, particularly if vertebrates other than humans can also act as reservoir hosts, seems possible.

Key words: Sandflies, *Leishmania*, phleboviruses, Central Europe, climate change.

Introduction

Sandflies (Diptera: Psychodidae: Phlebotominae) are very hairy, delicate, small midges (Nematocera) measuring only a few mm. The subfamily comprises about 800 species, most of which occur in tropical and subtropical, some also in warmer temperate zones. Both, males and females feed on secretions of plants, as well as on aphid excretions; in addition, females suck blood, which they need for the maturation of their eggs, from mammals, birds or reptiles. Larvae are terrestrial and develop in detritus of various kind, in decaying organic matter, in rubbish heaps, in caves, in crevices of rocks, in wall cracks of old buildings and ruins and other dark and moist habitats. Adults are active mainly on calm evenings at dusk and during the early night hours. Many species suck blood on humans and can thus transmit a considerable number of pathogens: viruses (particularly several *Phlebovirus* species), bacteria (*Bartonella bacilliformis*) and Protozoa (many species and strains of *Leishmania*).

Sandflies in Central Europe

About 25 species of Phlebotominae belonging to two genera (*Phlebotomus*, *Sergentomyia*) have so far been recorded in Europe. For a long time, sandflies have been regarded as typical Mediterranean faunal elements of low expansivity (which they are, indeed), outside the Mediterranean regions there are several records of sandflies in climatically favoured, warm (particularly southern) regions of Western and Eastern Europe. However, apart from several records in southern, southwestern and southeastern border regions, the occurrence of sandflies in Central Europe was unknown. In particular, Germany, as well as Austria, were thought to be free of Phlebotominae. In 1999, sandflies were found in the southwest of Germany for the first time, and further records in subsequent years confirmed the autochthonous occurrence of sandflies in Germany. Presently, altogether at least four (possibly six) species of Phlebotominae have been recorded in Central Europe and adjacent extramediterranean regions [1–4].

Phlebotomus (*Transphlebotomus) mascittii* Grassi, 1908, has been recently found in various parts of Baden-Württemberg in the southwest of Germany [1, 3, 5] and in Belgium [6]. Prior to these findings the species has been known from Switzerland [7] and France (overview of records: 8). Moreover, the species occurs in Spain, Italy, Greece and Cyprus [2].

Phlebotomus (*Larroussius) perniciosus* Newstead, 1911, has recently been found in Rheinland-Pfalz in the west of Germany. The species has been known from various parts of Switzerland [7] and Northern Italy [9]; for details see 8. Moreover, *Ph. perniciosus* has been recorded from Portugal, Spain, and Cyprus [2].

Phlebotomus (Larroussius) neglectus Tonnoir, 1921, has been found in various parts of Italy [9, 10], in Hungary [11] (for details see 8), and Greece [2]. So far, there are, however, no records from Central Europe north of the Alps.

Sergentomyia (S.) minuta (Rondani, 1843) has been found in various parts of Switzerland [7] and in Northern Italy [10] and is widely distributed in Portugal, Spain, and Greece [2]. *S. minuta* sucks blood on reptiles and is thus without importance for humans.

Besides these four, two additional species of *Phlebotomus* – *Phlebotomus (Ph.) papatasi* (Scopoli, 1786) and *Ph. (Larroussius) perfeliewi* Parrot, 1930 – have been recorded from regions bordering Central Europe in the south; according to Naucke (pers. comm.) these records may be due to misidentifications (for details see 8).

Sandfly-borne infections in Central Europe

In Europe, sandflies are vectors of *Leishmania*, on one hand, and of phleboviruses, on the other hand. Both are widely distributed in Mediterranean regions [12–14]. *Phlebovirus* infections (e.g. Pappataci Fever, Toscana *Phlebovirus* infection) are apparently restricted to southern parts of Europe. *Leishmania* infections have, however, often been diagnosed in Central Europe, but until recently it was believed that all these cases had been imported from Mediterranean countries or from other tropical or subtropical regions outside Europe. (*Leishmania* species occur in many species and strains

not only in Europe, but also in many parts of Africa, Asia and America.)

In the past decades, however, hints have increasingly surfaced for the occurrence of *Leishmania* infections acquired in Central Europe [15–17], and nowadays it cannot be questioned that cases of autochthonous visceral leishmaniosis can be found in Central Europe, also north of the Alps, particularly in Germany [18–21]. Recently, an apparently autochthonous case of leishmaniosis was even described from Surrey in England [22].

Provenance of sandflies and of autochthonous leishmaniosis in Central Europe

The fact that sandflies (*Phlebotomus mascittii, Ph. perniciosus*) were not found in Germany before 1999 led primarily to the consideration and assumption of a recent immigration and establishment of *Phlebotomus* in Central Europe north of the Alps. It is understandable that this was also seen in the light of the discussions on climate change and particularly global warming. Moreover, it seemed difficult to believe that a long-time occurrence of phlebotomines in a country with a long tradition of field entomology might have been overlooked. Nevertheless, today we consider that the occurrence of sandflies in climatically favoured parts of Germany represents the remains of an immigration from Mediterranean regions (probably via the Rhône-Rhine-valleys) during a very early warmer postglacial period. The development of the climate in the Holocene during the past 12000 years, after the end of the last glacial period, shows a particularly warm period (the so called Holocene optimum or Atlanticum) about 6500 years ago and another one about 4500 years ago during which an intensive (re-)immigration of animals and plants from Mediterranean refugial centres must have taken place. Many of these organisms conquered large parts of Central (and even Northern) Europe and were widely distributed but died out again some hundred years later when the climate became colder again. Some of them survived, however, in more or less restricted areas, which were and remained climatically favoured throughout the following millennia [23]. There are sundry convincing examples, particularly among insects, and certainly sandflies are also representatives of this biogeographical phenomenon. A serious and important argument against a recent immigration of *Phlebotomus mascittii* into Central Europe is the fact that the species was recorded from Strasbourg (in the southeast of France) already in 1950 [24]. The distance from Strasbourg to the recent records of *Ph. mascittii* in the southwest of Germany is so short that it may reasonably be assumed that the occurrence of sandflies in both regions is to be traced back to the same wave of immigration from southwestern Mediterranean regions.

The surprisingly late detection of sandflies in Germany may simply be due to the fact that these delicate insects are active only in calm and warm nights, that they are restricted to small areas, that they are extremely stenotopic and that they are attracted only by certain faint lights, in short, they are not easily collected.

In contrast to the reasonable assumption that sandflies have occurred in Central Europe for thousands of years, we lack any convincing hint suggesting an extended occurrence of *Leishmania* in this part of Europe.

Regarding *Leishmania*, the situation is quite different. These protozoa (Euglenozoa: Kinetoplastida: Trypanosomatidae) are – in several species and strains – widely distributed in large parts of tropical, subtropical and warm temperate zones of Africa, Asia, Europe, and South and Central America. In the Mediterranean countries, in particular also in all south European peninsulas, the cutaneous and visceral forms of leishmaniosis have been known for a long time and have already been mentioned in scripts of antiquity.

Until recently, leishmanioses were known in Central Europe only as "tropical diseases" (although many cases came from Mediterranean countries), and all infectiologists and parasitologists were convinced that these parasites do not occur in Central Europe.

Initial speculations on a possible autochthonous occurrence of *Leishmania* in Central Europe resulted from cases in which the infection in a tropical or subtropical region or a Mediterranean country could not be verified. The assumption of an autochthonous occurrence of leishmanioses in Central Europe was, however, thought to be so unlikely that other possibilities (e.g. introduction of infected sandflies by wind or by transportation: cars, trains, airplanes…) were discussed. Nevertheless, the possible sporadic autochthonous occurrence of this parasitic disease was not excluded, as it was known that these parasites occur also in northern parts of Mediterranean countries. After all, cases were described in which an infection in Central Europe could not be excluded, and the increasing number of such cases led finally to the assumption that autochthonous cases of leishmaniosis must occur in Central Europe. This was accompanied by the growing number of records of sandflies in Central Europe so that all findings could be composed to a convincing mosaic. Today, it is unquestionable that a *Leishmania* infection can be acquired – at least in certain parts – in Central Europe.

What we do not know with certainty is the provenance of these strains and the mode of infection. *Ph. mascittii* is suspected to be able to transmit *Leishmania*, but the experimental confirmation has not yet been successful. As in the case of sandflies it was primarily assumed that *Leishmania* strains had reached Central Europe naturally as a consequence of global warming, but finally a much more plausible explanation could be offered.

Leishmania species (strains) are widely distributed in Mediterranean regions. They can infect many mammals, but dogs play a particularly important role as reservoir hosts. In some regions more than 50%, locally up to 90% of stray dogs are infected [25, 26], and even in Northern Italy there is a stable reservoir of *Leishmania* in infected dogs [27, 28]. *Leishmania* infections cause diseases of various clinical pictures in dogs, and the parasites persist in the dog usually throughout the

whole life. Some clinical symptoms are very conspicuous and lead to a miserable appearance. Many of these dogs were brought to Central Europe, particularly to Germany, by compassionate tourists, leading finally to the development of a lucrative market in various Mediterranean countries. In fact, dogs suffering from leishmaniosis are offered for sale via the internet, and there is a surprisingly high number of people, particularly in Germany, who buy such dogs and bring them – often illegally – home. According to conservative estimates about 20000 (!) dogs infected with *Leishmania* are presently living in Germany so that the probability that an infected dog is bitten by a sandfly is high enough to give rise to a *Leishmania* focus [29, 30]. But also horses, cats and other domestic animals are transported throughout Europe and also imported into Europe, and also these animals may play a role as reservoir hosts [31, 32]. Moreover, a focus of *Leishmania* can be maintained by a circulation of the parasites between sandflies and rodents. Thus, the emergence of *Leishmania* infections in Central Europe is a result of globalisation rather than of climate change.

Almost all *Leishmania* strains found in the Mediterranean countries belong to the *L. donovani/infantum* complex, they are characterised by comparatively low virulence and have been known predominantly to cause diseases in children (hence: *L. infantum*!); immunocompetent adults are frequently carriers of the parasite, however, they show often no clinical signs [33]. Until the 1980's infections with *Leishmania* were frequent, but at the same time the disease was rare in Mediterranean countries. This has dramatically changed since the emergence of AIDS. The immunosuppression induced by the HIV leads in many cases to an unlimited replication of the parasites with severe clinical symptoms. An HIV infection increases the risk of a clinical manifestation by the factor 100 to 1000.

Possible influence of climate change on sandfly-borne infections in Central Europe

Since it is likely that sandflies have always been in certain parts of Central Europe from the time of the Holocene optimum onward (ca. 6500 and 4500 years ago) and have not only recently immigrated due to a climate change, and since it was human activity which probably introduced *Leishmania* parasites via domestic dogs (thus being an effect of one of the many forms of globalisation and not in connection with the global warming), there is no doubt that the distribution of sandflies, and thus also that of pathogens which may be transmitted by them, depends on climatic factors and can be altered by climate change.

There is general agreement even among highly critical climatologists that a further increase of temperature in this century is inevitable [34–35]. The question is not whether the temperature will increase (it will!), but to which degree it will increase by the end of the century. The scenarios vary between less than 2°C and 3.5°C (with a variation between 2.5°C and 4.5°C) [36]. An increase of almost 3°C must be regarded as a realistic scenario [35]. Presently the occurrence of sandflies in Central Europe and in adjacent extramediterranean regions is restricted to certain climatically favoured parts. So far, there are no confirmed records of sandflies in Austria, thus the question was raised, whether the climatic conditions in Austria differ so considerably from those in known "sandfly localities" that they really do not occur presently and whether climate change might lead to suitable conditions in Austria. In a joint project [8] we have tried to analyse the climatological parameters of localities in Central Europe and adjacent extramediterranean regions where sandflies had been found and to compare them with the climatological data of Austria. Our analysis showed that temperature represents the key factor. However, in Austria the critical temperatures necessary for the species' development are presently not being fulfilled in either summer or winter. Nonetheless, an increase of the temperature by only 1°C would lead to conditions that would allow the occurrence of several *Phlebotomus* species in large parts of Austria. Those regions which would become particularly suitable for the occurrence of sandflies in Austria are the Rhine valley, the Danube valley, the eastern parts of the province of Burgenland and the border region to Slovenia. The species which are likely to be expected are *Ph. mascittii* in western parts of Austria (for which the January temperatures are not high enough presently) and *Ph. neglectus* (for which the summer temperatures are not yet high enough) in the east. A precondition would then be either the natural immigration or the (unintentional) introduction of sandflies into those parts of Austria, but once a population has become established, pathogens could be transmitted by the sandflies. Again, this depends on the introduction of the pathogen. In the case of *Leishmania* species/strains this would probably be a matter of a few weeks to months (as infected dogs are also living in Austria). Most probably, phleboviruses could become established, once they have been introduced, and could be transmitted to humans.

Outlook

Since 1999 it has been known that sandflies (which are widely distributed in the Mediterranean countries) occur also in certain climatically favoured parts of Central Europe north of the Alps. Most probably they are remainders of a much larger distribution during the Holocene optimum about 7000 to 4500 years ago. An analysis of the climatological parameters of localities in Central Europe and adjacent extramediterranean regions has shown that temperature is the most important key factor. An increase of temperature by only 1°C would considerably enlarge the potential area of distribution of sandflies in Central Europe. There is now a consensus opinion among climatologists that global warming is a fact and that the temperature will reach values of at least 1.5°C , most probably 2°C, possibly 3°C or more, above the present temperature at the end of the century. As a result, a considerable amplification of the distribution of sandflies in Central Europe may be ex-

pected. This will lead to a significant extension of areas where the preconditions exist for the occurrence of sandfly-borne pathogens, i.e. *Leishmania*, on one hand, and phleboviruses, on the other hand.

The introduction of *Leishmania* from Mediterranean countries to Central Europe by infected dogs in recent years has continuously increased. When sandflies suck blood on infected dogs they may take up leishmaniae leading potentially to an establishment of the parasite in certain regions. It is assumed that cases of autochthonous (actually: pseudo-autochthonous) leishmaniosis in Central Europe will become more frequent in the future. With respect to the high risk, particularly for newborns and young children, on one hand, and for immunosuppressed patients, on the other hand, it will become increasingly important to be aware that this parasitosis exists also in Central Europe so that diagnosis and treatment can be achieved early.

An establishment of biological cycles of phleboviruses in Central Europe is less likely, but cannot be excluded in the future. The precondition for its establishment would be an introduction of the pathogens, particularly by infected humans. A persistence of possibly introduced phleboviruses would, however, probably depend on the integration of other mammals into the biological cycles. At present, our knowledge is still very poor on the vertebrate reservoir of the various phleboviruses.

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