Introduction

Post-infectious olfactory loss (POL) is defined as a sudden loss of olfactory function following an upper respiratory tract infection (URTI) and was described for the first time more than twenty years ago.\(^1\) The upper respiratory infection subsides over time and leaves the patient with an olfactory dysfunction that persists over a long period. There is a close connection in time between the URTI and the onset of the olfactory disorder.\(^2\) The exact pathogenic agent is rarely determined but is assumed to be viral and so this disease is known as “post-viral” or “post-infectious olfactory loss”. The exact incidence of olfactory dysfunction following URTI is not known as many patients with URTI do not report their symptoms, so the exact incidence of common cold in the population is unknown. However, POL is diagnosed in approximately one quarter of the patients in groups presenting to specialised centres such as smell and taste clinics.\(^3\)\(^4\) When all causes of olfactory loss in the general population are considered, POL appears to be the cause of an olfactory dysfunction in 11%.\(^4\) As no effective medical treatment has yet been found for this entity, prognosis and counselling based on a complete clinical evaluation of the patient is of primary importance.

Clinical characteristics and diagnosis

Patients with POL are usually women and the disease typically occurs between the fourth and the sixth decades of life.\(^5\)\(^6\) Onset of the upper respiratory tract infection (common cold, bronchitis,...) is often sudden and awareness of the olfactory dysfunction is present when major symptoms secondary to the infection subside. Many patients also have endoscopic or radiological evidence of rhinosinusitis. It is therefore mandatory to treat this condition and observe the impact of this treatment on the sensorineural disorder. Patients usually complain of moderate to severe olfactory loss (quantitative). The degree of olfactory loss is usually less severe than in patients with head trauma.\(^7\) Qualitative disorders such as parosmia and phantosmia are frequent and range from 10%\(^8\) to 50%,\(^9\) 65%\(^9\) and even 70%.\(^10\) Seasonal variation in the incidence of POL has been
demonstrated, with the highest incidences being in March and May.\textsuperscript{11} This is probably due to the seasonal variation of viral particles such as parainfluenza virus type 3.\textsuperscript{3,12,13}

Diagnosis should be based on:\textsuperscript{1} history of an olfactory disorder following an infection of the upper respiratory tract and a close temporal relationship between the two,\textsuperscript{2} patency of the olfactory cleft at the endoscopic examination,\textsuperscript{3} absence of any other causes such as toxic exposure (medication taken to treat the URTI and possibly causing an olfactory disorder themselves), an inflammatory process in the nasal fossa (diagnosed with an endoscopic evaluation) or neurological problems such as neurodegenerative diseases.\textsuperscript{14}

**Physiopathology**

The exact mechanism leading to POL is not yet fully understood. Viral particles may damage the olfactory receptor neuron and provoke an immune response that also leads to damage in the olfactory neuro-epithelium and damage to the central olfactory pathways. Viruses are capable of penetrating the brain via the fovea ethmoidalis. This mechanism is even a putative cause of pathogenesis for neurodegenerative disease.\textsuperscript{15,16} Many viruses may cause olfactory impairment, examples being the influenza virus, parainfluenza virus, respiratory syncitial virus, coxsackievirus, adenovirus, poliovirus, enterovirus and herpes virus. The exact determination of the viral agent is not useful in the clinic and viral serology is not mandatory. Experimental intranasal infection with influenza virus A leads to increased apoptosis and increased fibrosis in the olfactory neuro-epithelium.\textsuperscript{17,18} This mechanism is thought of as a protective one that limits the access of viral particles to the brain. On the other hand, virus injection into the olfactory bulb leads to the spread of viral infection, possibly leading to the death of experimentally treated animals.\textsuperscript{17} Histopathological findings relating to the olfactory neuro-epithelium of patients with POL have revealed that severely affected patients have reduced numbers of ciliated olfactory receptor cells.\textsuperscript{14} Moreover, histopathological findings have also demonstrated that, after POL, dendrites on the olfactory receptor neurons usually fail to reach the epithelial surface and therefore have no contact with odorant particles. Attempting to correlate the importance of olfactory neuro-epithelial damage with the extent of the olfactory dysfunction, as well with the chances of recovery, generated conflicting results.\textsuperscript{14,19} Thallium transport from the nasal cavity to the olfactory bulb should be studied in the future.\textsuperscript{20} This could, theoretically, be an objective method for assessing viral migration from the periphery to the brain via the olfactory bulb.

Another finding was that olfactory bulb volume as assessed with MRI is reduced in patients with POL.\textsuperscript{21,22} In this particular case, there was no obvious evidence that viral particles were found in the olfactory bulb or that their presence leads to a fibrosis with a subsequent reduction in volume. Another mechanism may be that sensory deprivation at the periphery reduces input to the olfactory bulb, leading to a reduction in volume. However, a strong correlation between olfactory bulb volume and the olfactory dysfunction has now been demonstrated, with the lowest olfactory bulb volume being in patients with severe olfactory dysfunction and with parosmia.\textsuperscript{21,22}

Overall, POL is probably secondary to a viral attack both at the periphery level (olfactory neuro-epithelium) and at the central level (olfactory bulb) and these two sites interact both in the pathological condition and in the recovery phase.\textsuperscript{23}

**Treatment**

At present, there is no medical therapy for POL patients that has been proven effective. Many drugs have been tried in non-randomised and uncontrolled trials: topical or systemic corticosteroids,\textsuperscript{24} zinc sulphate,\textsuperscript{25,26} quinoxaline derivates,\textsuperscript{27} alpha lipoic acid\textsuperscript{28} and pentoxifylline.\textsuperscript{29} Although early promising results with some molecules have been demonstrated, these medications helped patients to achieve partial or full recovery in unpredictable ways.\textsuperscript{30} Olfactory training has been provided, with some interesting results: 28% of the patients achieved olfactory improvement (causes of olfactory loss other than POL were included in this study).\textsuperscript{31} Olfactory training was given for twelve weeks based on four different odours (phenyl ethyl alcohol (rose-like), eucalyptus, lemon and cloves) and is required at least ten minutes twice a day by this protocol.\textsuperscript{31}

For patients with qualitative disorders such as phantosmia, some authors advocate the surgical removal of the olfactory neuro-epithelium, possibly damaging quantitative capacity but resolving the qualitative problem.\textsuperscript{32} This option has been adopted in very few cases.
Although such treatment is based on empirical grounds, patients with second or multiple episodes of olfactory dysfunction during an URTI should receive oral corticoid treatment if the olfactory loss persists after the URTI symptoms in order to reduce the risk of viral injury and permanent olfactory dysfunction.

Prognosis

The spontaneous recovery of olfactory performance is found, due to the plasticity of our olfactory system, in about one-third of POL patients. Olfactory dysfunction may decline (rare), not change, show some improvement, a major improvement, improve into the absolute normal range or into the range adjusted for age. In a study of a large cohort of 208 patients, London et al. demonstrated that improvement into age-adjusted olfactory ranges was more common if there was a moderate decline at the first evaluation rather than a severe one. The prognosis seems to be related to the time between the onset of the problem and initial baseline testing, the degree of olfactory dysfunction (moderately affected patients have a better chance of recovery than severely affected ones) and age at baseline (young patients have a better chance of recovery than older patients).

POL has a major impact on daily life and there is no proven medical therapy, so counselling patients and giving them the best prognosis for recovery seems to be of primary importance. Recovery does not seem to be related to the presence or the absence of qualitative disorders such as parosmia.

Recovery usually starts after six to twelve months after the initial URTI but may be present up to two to four years after. The longer the disease persists, the lower the chance of recovery.

It is not clear whether psychophysical olfactory testing, olfactory bulb volume or chemosensory event-related potentials are effective ways of predicting the probability of recovery. A formula taking into account all the variables should be an interesting way of exploring this field.

The consequences for daily life and the coping strategy should be integrated in clinical management for these patients, focusing on instructional information about fire alarms, domestic gas, hygiene, etc.

Cohort study

Subjects

This study was conducted at the Department of Otorhino- laryngology of the Saint-Luc university hospital in Brussels between June 2005 and June 2009. Patients with POL underwent an otorhinolaryngological investigation including nasal endoscopy, had a detailed interview with an experienced otorhinolaryngologist (PR), underwent psychophysical tests of olfactory performance (orthonasal and retronasal) and electrophysiological recording after chemosensory stimulus. Magnetic resonance imaging of the paranasal sinuses, the olfactory cleft and the anterior cranial base was performed in all patients. A total of 122 patients were included in this study. Olfactory bulb volume was calculated for 50 patients.

Psychophysical testing of olfactory performance

Psychophysical testing of olfactory performance took place with the validated Sniffin’ sticks test. Odours are presented to the patients in felt-tip pens birhinally. This test encompasses 3 different approaches. First, odour thresholds are assessed with n-butanol with stepwise dilutions in a row of 16 felt-tip pens. Secondly, patients are asked to discriminate between odours. For each discrimination task, 3 pens are presented, two containing the same odour and the third containing the target odour. The target odour must be recognised in a series of 16 trials. Thirdly, a row of 16 odours is presented to the patients, together with a list of 4 verbal descriptors. To judge olfactory function, the results from the testing of odour threshold (T), odour discrimination (D), and odour identification (I) are combined to produce a TDI score. In healthy subjects, the TDI score at the 10th percentile is 30.3 for the 16 to 35 year age category, 27.3 for 36 to 55 years, and 19.6 for patients > 55 years. Anosmia is diagnosed if the TDI score is less than 16. Patients with a TDI score between 16 and the normal age-related value are considered to be hyposmic.

Retronasal olfactory testing was performed by using a standardised protocol with 20 odourised powders presented to the patient’s mouth and an identification task. In healthy subjects, retronasal testing gave a median score of 18 for patients aged 36-55 years and 16 for those aged > 55 years.

Chemosensory event-related potentials

Chemosensory function may be assessed with chemosensory
event-related potentials. Olfactory and trigeminal stimuli result in olfactory and trigeminal event-related potentials respectively. In the clinic, electrophysiological responses are usually dichotomous. They are present if a negative-positive complex that is reproducible and obtained after sample averaging is observed. They are absent if averaging fails to produce a complex of this kind. A negative wave called N1 and a positive wave called P2 are described, with latency expressed in milliseconds and amplitude expressed in microvolts.

Detailed information about the clinical applications of chemosensory event-related potentials have been published by our team and pioneers in this field.34,39

Olfactory bulb volume
In the clinic, patients are examined on a 1.5 Tesla magnetic resonance imaging system (Signa Echospeed, GEMS, Milwaukee, WI, USA) using a standardised protocol for OB analysis. The protocol included: (i) 5 mm-thick standard T2-weighted fast spin-echo images covering the whole brain without interslice gap to rule out any organic brain disorder; (ii) 5 mm-thick T2-weighted gradient-echo images using the Echo-Planar imaging technique (EPI-GRE-T2*) covering the whole brain to rule out the presence of any parenchymal or meningeal post-traumatic haemosiderin deposit; and (iii) 2 mm-thick T1- and T2-weighted fast spin-echo images without interslice gap in the coronal plane covering the anterior and middle segments of the base of the skull. OB volumes are calculated with planimetric manual contouring (surface in mm²) and all surfaces were added and multiplied by two because of the 2 mm-slice thickness to obtain a volume in mm³.

This method has proven to be reliable and correlated to olfactory function both in healthy subjects and in pathological conditions.40

Statistical method
Statistical calculations were performed with Medcalc software.41 Pearson’s correlations were calculated between orthonasal scores expressed by the TDI score and retronasal scores (n = 122) and between psychophysical scores and the total olfactory bulb volume (right + left) expressed in mm³ (n = 50).

Results
During the study period, 122 patients were diagnosed as having a post-infectious olfactory loss. There were 86 women and 36 men; the sex ratio was therefore 2.4/1. Mean age was 53.9 years (95% CI for the mean: 51.6-56.1) and the median age was 55.5 years (95% CI for the median: 52.7-58.0). Nineteen patients also presented radiological and/or endoscopic signs of rhinosinusitis at the time of evaluation. This was the second episode of POL for 18 patients. Parosmia (defined as the distorted experience of an odorous stimulation) was present in 58 patients (47.5%) and phantosmia (defined as the experience of odorous sensation in the absence of an odour source) in

### Table 1

<table>
<thead>
<tr>
<th></th>
<th>Lowest value</th>
<th>Highest value</th>
<th>Mean value</th>
<th>95% CI mean value</th>
<th>Median value</th>
<th>95% CI median value</th>
<th>Standard deviation</th>
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<tr>
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<td>3.1</td>
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<td>14.0</td>
<td>7.7</td>
<td>7.1-8.2</td>
<td>8.0</td>
<td>7.0-8.0</td>
<td>3.1</td>
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<td>15.0</td>
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<td>32.0</td>
<td>18.5</td>
<td>17.3-19.7</td>
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<tr>
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<td>10.5</td>
<td>9.8-11.2</td>
<td>10.0</td>
<td>9.0-11.0</td>
<td>4.1</td>
</tr>
<tr>
<td>Olfactory bulb volume in mm³</td>
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<td>95.0</td>
<td>49.2</td>
<td>43.5-54.9</td>
<td>53.0</td>
<td>37.2-59.0</td>
<td>20.1</td>
</tr>
</tbody>
</table>
Post-infectious olfactory loss

22 patients (18%). Table 1 summarises the data for the orthonasal scores (T, D, I and TDI) and retronasal scores. Hyposmic patients were more prevalent than anosmic patients: 79 (64.7%) and 43 (35.3%) respectively.

Olfactory bulb volume was significantly correlated to the TDI score ($r = 0.6584$, $p < 0.001$), the threshold ($r = 0.4667$, $p = 0.006$) and the retronasal score ($r = 0.5728$, $p < 0.001$). Moreover, orthonasal and retronasal scores were significantly correlated for the 122 patients; $r = 0.69$ $p < 0.001$) (Figures 1, 2).

Figures 3 and 4 present MRIs showing reduced olfactory bulb volume.

Due to technical problems, artefacts and poor signal/noise ratio, 7 electrophysiological recordings were not evaluated. On the 115 remaining recordings, 35 showed olfactory event-related potentials (30.4%) and 109 demonstrated reliable and reproducible trigeminal event-related potentials (94.7%).
Conclusions

POL is a major diagnosis when dealing with olfactory dysfunction in the clinic. The diagnosis is mainly based on patient history and upon olfactory evaluation. It is always questionable whether a more detailed clinical evaluation (chemosensory event-related potentials, MRI) will help the clinician to make a more confident prognosis about partial or full recovery. However, the authors are confident that complete clinical evaluation is indeed mandatory for this disease, not only because patients ask for it, but also to elucidate which data have the best predictive value. The cohort study has also demonstrated that the major clinical characteristics already published relating to POL are supported, with middle-aged women being more affected and with qualitative dysfunction being highly prevalent. Medical therapy needs to be further investigated and olfactory training should also be evaluated on a larger scale as its interest seems to be realistic.

References