Abstract: Intractable hiccups in transplanted patients may be caused by various medical conditions including infections. We report a case of a 44-year-old man who suffered from intractable hiccups after cadaveric kidney transplantation. We identified 3 different hiccup periods with different causes: 1) steroid and anesthetics use, 2) severe ulcerose herpetic and mycotic esophagitis, and 3) pleuropneumonia caused by nosocomial methicillin-resistant *Staphylococcus epidermidis* and pulmonary abscess requiring thoracic surgery.

Hiccups, or singultus, are involuntary spasms of the diaphragm and intercostal muscles causing sudden inspiration and a characteristic sound. They are usually benign and self-resolving. However, in some cases chronic or recurrent hiccups are troublesome for the patient as well as for the clinician (1). Persisting or recurrent hiccups that do not respond to different therapeutic approaches are often a symptom of severe disorder (1–5). Table 1 shows the most important and most common clinical conditions leading to persistent or repeated hiccups (1, 2, 4–6).

Case report

A cadaveric kidney was transplanted into a 44-year-old man. His immunosuppressive regimen included a standardized protocol with steroids, cyclosporine, and mycophenolate mofetil. The postoperative course was characterized by primary graft function without any complications except for recurring hiccup episodes that began immediately after the patient woke up from anesthesia. These hiccups responded to treatment with p.o. metoclopramide, and they were not severe. Presentation and course suggested a medication-induced etiology related to steroid induction and/or anesthesia.

The patient was discharged from the hospital on the 10th day, but 1 day later he was re-admitted because of dyspnea associated with very severe attacks of hiccups. A chest and abdominal x-ray scan was negative, as was abdominal ultrasonography, despite the dramatic course. When the...
Causes of persistent or recurrent hiccups

Non-infectious etiology (references)
Mediastinal or pulmonary tumors (5)
Diaphragmatic herniation, liver tumor (4, 5)
Esophageal tumor or reflux; gastric distention, ulcer, tumor, or bleeding (2, 5)
Neurological disorders affecting brain or phrenic nerves (tumors, injury) (4, 5)
Electrolyte and metabolic disturbances
(↓ Na⁺, ↓ Mg²⁺, ↓ Ca²⁺, ↓ CO₂, uremia) (5)
Pharmacological agents (corticosteroids, anesthetics, ethanol, barbiturates, midazolam, methyl dopa, morphine) (1, 5)

Infectious etiology
Mediastinal abscess (5)
Pleural and pulmonary infections (abscess, tuberculosis, pneumonia, pleuritis) (5)
Liver abscess (4, 5)
Esophagitis (Candida sp., Herpes simplex) (2, 5)
Encephalitis, brain abscess (HIV, toxoplasmosis) (4, 5)

Table 1

patient reported retrosternal pain and odynophagia that were previously not present, he underwent esophagogastroscopy, which revealed severe ulcerative herpetic and candidal esophagitis. After treatment with acyclovir, fluconazole, and omeprazole, the hiccups faded away during the next few days.

During the second hospitalization, the patient was affected by severe acute antibody-mediated rejection Grade IIA of the Banff 97 working classification of kidney transplant pathology (7). Because of corticosteroid resistance, we decided to treat the patient with a course of high-volume plasmapheresis and the replacement of cyclosporine with tacrolimus. During the period of the anti-rejection treatment, the patient acquired nosocomial pleuropneumonia with no other agent identified but coagulase-negative methicillin-resistant Staphylococcus epidermidis (MRSE). Despite combined antibiotic treatment (initially meropenem + clindamycin, but after finding MRSE in the bronchoalveolar lavage fluid, then vancomycin 500 mg/48 h), the patient’s status deteriorated. A computed tomography scan revealed an abscess in the right lower pulmonary lobe. At this time, the patient again reported new episodes of hiccups that became more and more severe. The abscess was successfully removed by a thoracotomy, after which the patient’s status improved rapidly and the hiccups finally disappeared.

Discussion

Our patient suffered from recurring episodes of hiccups, which could be divided into 3 different periods. The first period was represented by infrequent hiccups and good therapeutic response to metoclopramide. The start of hiccups immediately after transplantation leads us to suspect the anesthetic and/or methylprednisolone as the causative agents (1, 8, 9). The latter drug was given during the 4 days following transplant, and then it was replaced with prednisone. We failed to identify any other possible causes.

Symptoms associated with singultus depending on etiology, and recommended diagnostic approach

<table>
<thead>
<tr>
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<th>Etiology</th>
<th>Diagnosis</th>
<th>References</th>
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<tr>
<td>Dyspnea</td>
<td>Pneumonia, pulmonary abscess</td>
<td>Chest x-ray and CT scan</td>
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<td>Fever</td>
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<td>Cough</td>
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<td>Odynophagia</td>
<td>Esophagitis</td>
<td>Endoscopy</td>
<td>(2, 5, 10–12)</td>
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<td>Retrosternal pain</td>
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<tr>
<td>Pyrosis</td>
<td>Nonspecific</td>
<td>Adverse effects of medication</td>
<td>(6, 8, 9)</td>
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<td>Nausea</td>
<td>Liver tumor</td>
<td>Abdominal ultrasound and CT scan</td>
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<td>Vomiting</td>
<td>Focal neurologic symptoms</td>
<td>Brain abscess, encephalitis</td>
<td>(16, 17)</td>
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<td>Cachexia</td>
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<td>Elevated markers of liver damage</td>
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<td>Cachexia</td>
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Table 2

CT, computed tomography; MRI, magnetic resonance imaging.
The second time hiccups appeared was during a bout of esophagitis. The immunocompromised patient is predisposed to infectious esophagitis involving herpes simplex and Candida sp., which is often accompanied by odynophagia, retrosternal pain, hiccups, and pyrosis (2, 10–12). After treatment of the cause, the endoscopic changes disappeared and all symptoms (including hiccups) ceased as well.

After a hiccup-free period, singultus appeared again and its intensity increased with the severity of pulmonary changes. In this period, the hiccups were definitely of pulmonary origin (1, 13), and their response to different drugs (metoclopramide, chlorpromazine, haloperidol, lidocaine, nifedipine, omeprazole) was weak and short termed. After discovery and removal of a supradiaphragmatic abscess, the hiccups immediately discontinued and they did not appear again.

Few studies have been published about hiccups in transplant patients. We were able to identify 8 articles using a systematic review with the key words ‘hiccups’ and ‘transplantation.’ Five of these articles included patients with chronic renal failure in the dialysis program, but no patients after transplantation. The 3 remaining articles are case reports (11, 14, 15). This lack of evidence-based information makes it impossible to follow any guidelines and allows only approximations based on experience from other fields of medicine, especially oncology. Based on all known data, we may conclude that infections (esophagitis, pleuropneumonia, pulmonary, and liver abscess) and adverse effects of various drugs (steroids, anesthetics) are the most probable causes of hiccups in transplant patients in the early post-transplant period. In later periods, infections and tumors (gastrointestinal lymphomas) are the most likely causes. Neurological causes known from oncology are unlikely to be responsible for hiccups in transplanted patients, as are metabolic and electrolyte disturbances, because patients become accustomed to them. However, brain abscesses as encountered in immunocompromised human immunodeficiency virus-infected patients with AIDS can be a rare cause of intractable hiccups (16, 17). Table 2 refers to the most common clinical symptoms associated with the causes of hiccups and suggests a diagnostic approach.

Conclusions

Usually benign and self-resolving, hiccups can sometimes indicate severe underlying problems, and should be taken into consideration in the clinician’s differential diagnosis and therapeutic approach. Especially in transplant patients, who receive multiple drugs and tend to be very susceptible to various pulmonary, abdominal, and esophageal infections, the presence of hiccups needs careful examination. The recommended diagnostic algorithm should include careful analysis of medication and other symptoms, physical examination, abdominal ultrasound, chest x-ray scan, and esophago-gastro-duodenoscopic examination.

References