Prevalence of risk factors of prion-related disease according to the French circular 138 (DGS/DH/5C/DHOS/E2/2001/138) among patients referred for gastrointestinal endoscopy

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SUMMARY

Aim of the study — To assess the prevalence of risk factors of prion-related disease transmission in a gastrointestinal endoscopy unit.

Methods — Clinical evaluation of the risk of transmission of prion-related diseases using the criteria defined by the French circular 138 in patients referred for digestive endoscopy without anesthesia.

Results — 1017 patients were included in this study. According to circular 138, 7 patients (0.68%) were at high risk of transmitting prion-related disease. According to these criteria, a high index of suspicion of prion-related disease was detected in 26 patients (2.55%). Clinical evaluation of risk was not possible for 56 patients (5.51%), due to coma or sedation (38 patients) or communication impairment (18 patients).

Conclusions — Application of circular 138 led us to consider that 2.55% of patients in this study had a high risk of prion-related disease. The circular criteria cannot be assessed in patients with sedation for mechanical ventilation, coma or communication impairment.

Conclusion

Prévalence en endoscopie digestive des situations à risque d’infection par prion définies par la circulaire DGS/DH/5C/DHOS/E2/2001/138

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Objectif — Déterminer dans une unité d’endoscopie digestive la prévalence des situations à risque de transmission de maladies à prion telles que définies par la circulaire 138.

Méthode — Interrogatoire et examen clinique systématiques orientés vers la recherche de facteurs de risque ou de suspicion de maladie à prion chez les malades adressés pour endoscopie digestive sans anesthésie générale.

Résultats — Ont été inclus au total 1 017 malades. Sept (0,68 %) étaient considérés à risque, 26 (2,55 %) considérés comme suspects ou atteints. Chez 56 malades (5,51 %), le niveau de risque ne pouvait être déterminé, soit en raison d’un coma ou d’une sédation (N = 38), soit en raison de difficultés de communication (N = 18).

Conclusions — Les critères de la circulaire 138 sont peu spécifiques, conduisant à considérer comme suspects ou atteints 2,55 % des malades de cette étude. Ces critères ne sont pas applicables chez les malades avec troubles de conscience, sous sédation ou ceux présentant des difficultés de communication.

Introduction

Variant Creutzfeld-Jacob disease (vCJD) is a transmissible subacute spongiform encephalopathy (TSE) linked to a pathological prion protein PrPsc [1]. The first case was detected in Great Britain in 1995 [2]. Since that time, more than 140 cases have been diagnosed, including six in France [3-5]. The incubation period of this constantly fatal disease is unknown [6]. There is no diagnostic test enabling confirmation of infection in the routine setting. The disease is thought to be transmitted by the oral route via consumption of contaminated bovine meat [6]. Peyer’s patches are the probable sites for the intestinal uptake of prions [7]. Unlike the classical form of CJD (a pathological protein has never been isolated from the digestive tract) several reports demonstrate the presence of PrPsc in tissues which can come in contact with material used for gastrointestinal endoscopy: tonsil, appendix, rectum, ileum and olfactory epithelium [8-12]. Although no documented case of iatrogenic transmission of vCJD [13] has been identified, the risk cannot be excluded. Furthermore, the pathological prion protein is highly stable and resistant, particularly against methods used to disinfect endoscopy equipment [14-18].

Considering the available data, and in application of the principle of precaution, the French health authorities published on March 14, 2001 a regulatory circular (DGS/DH/5C/DHOS/E2/2001/138) [19] which sets out criteria defining an index of patient-related risk. Three levels are described: absence of risk factor, presence of a risk factor for classical CJD, presence of overt or suspected disease. This classification is based on history taking and physical examination. For the first two risk levels, reinforced disinfection measures must be taken after employing the endoscopy material. If the index of suspicion is high (overt or suspected disease), material coming in contact with any tissue with the slightest risk of harboring the pathological protein must be sequestered or destroyed. Any patient presenting a recent progressive intellectual or psychiatric disorder and a neurological sign is considered to have a high risk. Rigorous history taking and a complete neurological examination are required to detect the neurological signs listed in the circular: myoclonia, visual dis-
orders, cerebellar disorders, epilepsy, ataxia, chorea, akinetic mutism, extrapyramidal disorders, dystonia, persistent painful sensorial symptoms, psychomotor impairment, dementia, depression, anxiety, apathy, behaviour changes, delirium. In many situations, it is quite difficult to determine the level of risk, particularly when the neurological examination and history taking are limited due to coma or sedation. Circular 138 does not specify the precautions required in this situation. The frequency of such risk situations in a gastrointestinal endoscopy unit is not known.

The purpose of this work was to determine the prevalence of patients with a high risk of prion-related disease as defined by circular 138 among patients referred to a hospital gastrointestinal endoscopy unit.

Patients and methods

This prospective study was designed to apply the criteria set out in circular 138 for patients undergoing gastrointestinal endoscopy in a hospital endoscopy unit. A specific chart listing the neurological and psychiatric signs defined in circular 138 was completed for each patient. The chronology of the symptoms and changes over time were noted. Patients were considered to have a high risk of vCJD if they presented at least one neurological sign which had developed recently and progressively without remission in association with intellectual or psychiatric disorders. Patients were considered to have a risk of classical CJD if history taking revealed one of the following elements: 1) past treatment with extracted growth hormone, 2) member of the genetic family with transmissible subacute spongiform encephalopathy linked to a mutation of the gene coding for PrPC, 3) prior surgery with dura mater breach, in particular neurosurgery or extensive cerebral exploration (sterotactic examination), excepting procedures performed in France after January 1, 1995.

All patients who underwent an endoscopic procedure without general anesthesia at the Lille University Hospital between November 1, 2001 and February 1, 2002 were included in this study. The history taking and neurological examination were performed by the operator before the endoscopic procedure. If there was any doubt concerning the evolution of signs detected or the results of earlier complementary examinations, the referring physician (primary care physician for outpatients, head of the hospital endoscopy unit) was contacted by phone for further information.

Results

The series included 1017 consecutive patients: 595 men (58.5%), 422 women (41.5%). Mean age was 55.1 years. The endoscopic procedure was performed for 602 outpatients (59.2%) and 415 inpatients (40.8%).

Among the 1017 patients included in the study, seven (0.68%) presented a risk factor for classical CJD. All seven had undergone a neurosurgical procedure before 1995.

Twenty-six patients (2.55%) were considered to have a high risk of vCJD due to the presence of a neurological sign and recent development of intellectual and/or psychiatric disorders. The age distribution is presented in Table I. The following neurological signs were detected: pyramidal disorders (N = 12), epilepsy (N = 5), extrapyramidal disorders (N = 4), visual disorders (N = 4), dystonia (N = 1), the following intellectual and/or psychiatric disorders were detected: dementia (N = 16), delirium (N = 3), depression (N = 3), anxiety (N = 3), behaviour changes (N = 1). All of these patients attended a subsequent neurological consultation where the diagnosis of TSSE was ruled out. The endoscopic procedure was performed before the neurological consultation in three patients because of an emergency situation; the endoscopic material was sequestered temporarily.

**Table I.** Age distribution of patients with high index of suspicion of prion-related disease.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number of patients</th>
<th>High index of suspicion</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 30 years</td>
<td>77</td>
<td>1 (1.29%)</td>
</tr>
<tr>
<td>30-40 years</td>
<td>146</td>
<td>2 (1.36%)</td>
</tr>
<tr>
<td>40-50 years</td>
<td>166</td>
<td>1 (0.6%)</td>
</tr>
<tr>
<td>50-60 years</td>
<td>204</td>
<td>2 (0.98%)</td>
</tr>
<tr>
<td>60-70 years</td>
<td>132</td>
<td>4 (3.03%)</td>
</tr>
<tr>
<td>&gt; 70 years</td>
<td>292</td>
<td>16 (5.48%)</td>
</tr>
</tbody>
</table>

The level of risk could not be determined in 56 patients (5.51%) because of coma or sedation (N = 38 patients) or difficult communication skills preventing pertinent history taking (N = 18). The endoscopic procedure was performed in an emergency setting in the 38 patients with coma or sedation. Since memorandum 138 does not specify the procedure in this situation, the material was not sequestered after the endoscopic procedure for these patients. For the other 18 patients who required non-urgent endoscopy, the procedure was delayed until adequate information could be collected from family (N = 10 patients), the primary care physician (N = 6 patients), or after a neurological consultation (N = 2 patients). The endoscopic procedure was then performed in these 18 patients.

Discussion

During this study, application of the risk criteria enumerated in circular 138 led us to consider that 2.5% of patients had a high index of suspicion of prion-related disease. The level of risk could not be determined for 5.5% of patients.

The conditions of the neurological examination performed in the endoscopy unit before the procedure were probably not optimal. Certain conditions with minimal expression or which are difficult to detect may have been missed: cerebellar syndrome, pyramidal or extrapyramidal signs, depression, anxiety or cognitive impairment. Inversely, suspected disease may have been overestimated since the conditions of the examination did not enable fine assessment of symptom onset and course. Nevertheless, the operator contacted the referring physician by phone for complementary information in case of doubt.

The incidence of prion-related disease is slightly higher in the Nord-Pas-de-Calais region than the national average for France [20]. Mortality attributed to non-conventional transmissible agents remains low in France, between 1.38 and 1.56 deaths per million inhabitants per year. The number of cases of prion-related disease reported to the health watch institute has remained stable over the last years: 104 in 2000, 131 in 2001, 128 in 2002, and 114 in 2003 [5]. There were no reported cases of vCJD in France in 2003 [5]. In Great Britain where the disease reached epidemic proportions, mortality related to vCJD appears to be declining since 2000: 28 deaths in 2000, 20 in 2001, 17 in 2002 [4]. It is also estimated that only 205 subjects would be susceptible of developing the disease in the next few years [21]. Prion-related TSSE is thus an exceptional disease in France [22]. In comparison, the number of patients in this study with a high index of suspicion appears to be overestimated, demonstrating the non-specific nature of the circular 138 criteria.

**ABBREVIATIONS:**

vCJD : variant Creutzfeld-Jacob disease

TSSE : Transmissible subacute spongiform encephalopathy
Unlike TSSE, dementia is a frequent condition in France, particularly in elderly subjects. In a recent report on 1,461 subjects aged over 75 years, Ramaroson et al. [23] found that the prevalence of dementia was 17.8%. Since according to the circular 138 criteria the index of suspicion is high for any patient presenting dementia associated with one neurological sign, it was not surprising to find a high rate of suspected disease among the older patients.

Careful collection of information from the patient or family was necessary to search for the clinical criteria listed in the circular. This was found to be rather difficult in certain situations - perturbed consciousness (coma or sedation), communication problems (language, hearing-speech impairment, aphasia, cognitive disorders) – which explains the high rate of undetermined risk level.

Our results appear to indicate that the circular 138 criteria for screening for prion-related disease are weakened by their lack of specificity and their limited applicability in a large number of clinical situations. This lack of specificity could increase the cost of endoscopy and lead to an excessive number of cases of material sequestration/destruction when the endoscopic procedure has to be performed.

Conclusion

The criteria adopted in circular 138 for selecting patients with a high index of suspicion of prion-related disease lack specificity. This led us to suspect prion-related disease in 2.5% of our patients. Furthermore, the sensitivity of these criteria is greatly limited by the fact that patients are not detected during the incubation period. The fact that the risk level could not be determined for 5.5% of patients also limits the sensitivity of these criteria.

The lack of sensitivity limits interest in applying the circular 138 criteria for gastrointestinal endoscopy patients in order to protect the population against any potential iatrogenic transmission of vCJD. Since the endoscopic procedure cannot be refused for high-risk patients, sequestration and/or destruction procedures would have to be implemented after endoscopy. Due to the lack of specificity of the selection criteria, circular 138 thus has a detrimental effect, i.e. increased cost, on endoscopy practice in France. These findings should be considered in light of the recent data on endoscopic practice in France: more than two million procedures per year, including 300,000 therapeutic procedures, contributing to the diagnosis and treatment of 65,000 malignant tumors [24].

REFERENCES