

## Hemorrhagic Hereditary Telangiectasia (Rendu-Osler Disease) and Infectious Diseases: An Underestimated Association

Sophie Dupuis-Girod,<sup>1</sup> Sophie Giraud,<sup>2</sup> Evelyne Decullier,<sup>4</sup> Gaetan Lesca,<sup>2</sup> Vincent Cottin,<sup>5</sup> Frédéric Faure,<sup>3</sup> Olivier Merrot,<sup>6</sup> Jean-Christophe Saurin,<sup>7</sup> Jean-François Cordier,<sup>5</sup> and Henri Plauchu<sup>1</sup>

<sup>1</sup>Service de Génétique et Centre de Référence sur la Maladie de Rendu-Osler, Hôpital de l'Hôtel Dieu, <sup>2</sup>Laboratoire de Génétique Moléculaire and <sup>3</sup>Service d'Oto-Rhino-Laryngologie, Hôpital Edouard Herriot, <sup>4</sup>Département d'Information Médicale and <sup>5</sup>Service de pneumologie et centre de référence des maladies orphelines pulmonaires, Hôpital Louis Pradel, <sup>6</sup>Service d'Oto-Rhino-Laryngologie, Hôpital de la Croix Rousse, and <sup>7</sup>Service d'Hépatogastroentérologie, Hôpital Lyon Sud, Hospices Civils de Lyon, Université Lyon I, Lyon, France

**Among 353 patients with hereditary hemorrhagic telangiectasia retrospectively analyzed during the period 1985–2005, we identified 67 cases of severe infection that affected 48 patients (13.6%). Extracerebral infections accounted for 67% of all infections, and most involved *Staphylococcus aureus* and were associated with prolonged epistaxis. Cerebral infections accounted for 33% of all infections, were mainly due to multiple and anaerobic bacteria, and were associated with the presence of pulmonary arteriovenous malformations and a short duration of epistaxis.**

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by recurrent epistaxis, cutaneous telangiectasia, and visceral arteriovenous malformations (AVMs) that affect many organs, including the lungs, gastrointestinal tract, liver, and brain. Diagnosis is based on the Curaçao criteria [1] and is considered to be definite if at least 3 of the following criteria are met: the presence of spontaneous and recurrent epistaxis, the presence of telangiectasia, familial history of the condition, and the presence of visceral lesions.

Two genes are in different families associated with HHT. HHT type 1 results from mutations in *ENG* on chromosome

9 (coding for endoglin), and HHT type 2 results from mutations in *ACRLV1* on chromosome 12 (coding for activin receptor–like kinase [ALK]–1). Mutations of either of these 2 genes account for most (but not all) clinical cases. In addition, mutations in *MADH4* (encoding SMAD4), which cause a juvenile polyposis/HHT overlap syndrome, have been described elsewhere [2], and recently, a HHT3 locus on chromosome 5 (5q31.3–5q32) has been published [3].

All 3 identified HHT genes encode endothelial cell transmembrane proteins that appear to be components of the receptor complexes for growth factors of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily [4, 5]. Through binding to the TGF- $\beta$  type II receptor, the TGF- $\beta$  can activate 2 different type I receptors (ALK-1 and ALK-5 in endothelial cells), each one having opposite effects on endothelium cell migration and proliferation [6].

Numerous case reports indicate that patients with HHT and pulmonary AVM are more susceptible to cerebral abscesses [7]. However, only 4 cases of life-threatening extracerebral severe infection, including osteoarthritis, septicemia, and spondylodiskitis typically due to *Staphylococcus aureus* infection, have been reported in the literature [8, 9]. Immune functions have been poorly studied, and recently, Cirulli et al. [10] reported abnormally low polymorphonuclear cells and monocyte functions, suggesting that patients with HHT have a higher susceptibility to infectious complications.

To study infectious diseases and HHT, we retrospectively studied a cohort of patients with HHT who attended a single health center to assess the incidence of extracerebral and cerebral infection and to describe the types of infection, the bacteriological features, and risk factors for infection. Furthermore, greater knowledge about the factors that contribute to the development of life-threatening infectious diseases in patients with HHT would improve patient information and management.

**Methods.** All patients with definite HHT (confirmed by genetic analysis after 2000) who had been referred to the French HHT reference center (Hôpital de l'Hôtel Dieu, Lyon) during the period of 1985–2005 were included in the study. Standard definitions are summarized in table 1. Severe infection was defined as any infection that required hospitalization of the patient. We defined 3 groups to compare data: patients who had never experienced severe infection; patients with cerebral infection, including those who had experienced cerebral abscess or meningitis; and patients who experienced any other severe infection (the “extracerebral infection group”). Patients who

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Reprints or correspondence: Dr. Sophie Dupuis-Girod, Service de Génétique, Hospices Civils de Lyon, Hôpital de l'Hôtel Dieu, 1, place de l'Hôpital 69288 Lyon Cedex 02, France (sophie.dupuis-girod@chu-lyon.fr).

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**Table 1. Definitions used in a study of hemorrhagic hereditary telangiectasia (Rendu-Osler disease) and infectious diseases.**

Term	Definition
Septicemia	Clinical symptoms due to infection with the pathogenic microorganism or its toxin in blood and $\geq 2$ cultures of blood samples obtained from different sites and at different times that yield a microorganism
Osteomyelitis	Bacterial infection of bone and bone marrow in which the resulting inflammation can lead to a reduction of blood supply to the bone
Septic arthritis	Bacterial infection in the joint cavity
Spondylodiskitis	Infection of the intervertebral disk and the adjacent vertebral bodies
Erysipelas	Clinically defined as a superficial bacterial skin infection
Abscess	Accumulation of pus; diagnoses of cutaneous, muscular, and hepatic abscesses confirmed by ultrasound for deep abscesses and surgical drainage; cerebral abscesses diagnosed and their locations determined by CT or MRI; a needle biopsy specimen was usually examined to identify the micro-organisms
Meningitis	Inflammation of the meninges confirmed by CSF analysis

could be classified into 2 groups were excluded from the comparison analysis.

The mean duration of epistaxis was calculated using the patients' medical records for the prior 3 months. All patients who had been referred to our health care center were asked to complete a chart with information about the daily total number of episodes and the duration of epistaxis. Because infectious episodes may be affected by recurrent nasal events, we compared the duration of epistaxis in patients who developed serious infection with the duration in those who did not develop serious infection.

Pulmonary AVMs were investigated using a previously described screening algorithm [11]. Liver involvement was assessed by Doppler sonography [12]. Digestive vascular malformations were assessed by endoscopy; cerebral and spinal AVMs were diagnosed by CT or MRI. Mutation analysis was performed as previously reported [13].

SAS software packages (SAS Institute) were used for statistical analysis. Results are expressed as percentages for qualitative data and mean or median values for numeric data. Risk factors for infection and for cerebral abscess were evaluated using Fisher's exact test (for qualitative data). Durations of epistaxis, according to infection status, were compared using a Mann-Whitney test.

**Results.** Three hundred fifty-three patient files (for 204 women and 149 men) were retrieved from the database. One hundred three (45.9%) of 224 investigated patients had pulmonary AVM, 75 (49.0%) of 153 investigated patients had hepatic AVM, 23 (20.0%) of 115 investigated patients had cerebral or spinal AVM, and 51 (50.0%) of 100 investigated patients had digestive AVM. The diagnosis was confirmed by genetic analysis for 213 (94.2%) of 226 DNA samples that were tested. Sixty patients (26.5%) had the *ENG* mutation, and 153 (67.7%) had the *ACRLV-1* mutation. No mutation was identified in the other 13 patients (5.8%) tested.

Forty-seven patients (13.6%) experienced 67 severe infectious episodes; 33 patients experienced 1 episode of severe infection, 10 experienced 2 episodes, 2 experienced 3 episodes, and 2 experienced 4 episodes. Five patients experienced cerebral and extracerebral infections. The mean age at the time of the first severe infection was 44.3 years (range, 12–80 years). No patient in our cohort died from infection.

Thirty-two patients experienced 45 extracerebral severe infections. Extracerebral infections accounted for 45 (67%) of all 67 severe infections. They included septicemia (9 infections [13.4%]), arthritis and osteomyelitis (6 [8.9%]), skin infection (abscesses and erysipelas; 6 [8.9%]), muscular abscesses (5 [7.4%]), spondylodiskitis (4 [6.3%]), hepatic abscesses (5 [7.4%]), and other severe infections (endocarditis, pneumoniae, pyelonephritis, tuberculosis, rickettsiose, and acute appendicitis with peritonitis; 10 [15%]). *S. aureus* was identified in 14 cases, 1 case of septicemia was due to *Enterococcus faecalis* and *Pseudomonas aeruginosa* (after a urinary infection), and 2 cases of muscular abscesses were due to *Streptococcus* species and *Pseudomonas aeruginosa* (in one case) and to *Streptococcus viridans* and anaerobes (in the other).

Seventeen patients experienced 19 cerebral abscesses (2 patients had 2 separate episodes of cerebral abscess), and 3 patients had meningitis. Cerebral infections accounted for 22 (33%) of all 67 severe infections. Bacteria were identified in 7 cases, and the microorganisms isolated from cerebral abscesses were in most cases multiple and anaerobic species (*Streptococcus* species, 3 cases; *Haemophilus aphrophilus*, 3 cases; *Actinomyces meyeri*, 2 cases; *Fusobacterium* species, 2 cases; *Eikenella corrodens*, 1 case; *Micromonas micros*, 1 case; *Peptostreptococcus micros*, 1 case; and Gram-positive cocci, 1 case). Three cases of meningitis were observed but bacterial cultures were negative after CSF analysis. The entry route of bacterial infection was not identified.

Risk factors for severe infection are presented in table 2. The

**Table 2. Risk factors for severe infection in patients with hemorrhagic hereditary telangiectasia.**

Factor or characteristic	Patients with severe infection		Patients without severe infection	P <sup>a</sup>
	Extracerebral infection	Cerebral infection		
Female sex	15/27 (55.6)	8/15 (53.3)	178/306 (58.2)	.9
Visceral AVM <sup>b</sup>				
Pulmonary	7/20 (35.0)	13/13 (100.0)	80/187 (42.8)	.0002
Hepatic	8/17 (47.1)	0/5 (0.0)	67/130 (51.5)	.08
Neurological	2/11 (18.2)	1/10 (15.0)	19/91 (20.9)	.71
Digestive	6/11 (54.6)	2/4 (50)	42/84 (50.0)	.96
Gene mutation				
<i>ALK1</i>	15/22 (68.1)	1/11 (9.0)	136/189 (72.0)	<.001
<i>ENG</i>	3/22 (13.6)	10/11 (90.9)	44/189 (23.2)	<.001
<i>HHT3</i>	4/22 (18.1)	0/11 (0.0)	9/189 (4.8)	.03
Not available, no. of patients	6	5	117	
Duration of epistaxis, min/months (range)	55.0 (1–360)	5.0 (0–150)	30.5 (0–4500)	.0045

**NOTE.** Data are no. of patients with characteristic/no. who were evaluated (%), unless otherwise indicated. AVM, arteriovenous malformation.

<sup>a</sup> The  $\chi^2$  test was used for qualitative variables, and a Mann-Whitney test was used for quantitative variables.

<sup>b</sup> AVM was detected by screening. Not all patients were explored for the presence of AVM.

occurrence of cerebral abscess was significantly associated with the presence of pulmonary AVM ( $P < .001$ ) and *ENG* mutations ( $P < .001$ ). The incidence of hepatic, neurological, and digestive AVM did not differ significantly between patients without severe infection and patients with cerebral or extracerebral infection. Extracerebral infections were observed independently of the mutated gene. The *ALK-1* gene was found to be mutated in the group of patients with extracerebral infection with the same frequency as in the group without infection.

In the extracerebral infection group, the median duration of epistaxis was significantly longer than in the group without infection (60.0 vs. 30.5 min/month). Furthermore, in the cerebral infection group, the duration was significantly shorter (5.0 vs. 30.5 min/month).

**Discussion.** The incidence of severe extracerebral infection in our cohort of patients with HHT was high: 9.0% of patients with HHT had at least 1 severe extracerebral infection, and that type of infection accounted for 67% of all severe infections among the patients with HHT in our study. Furthermore, this retrospective analysis probably underestimates the true incidence of infections. In the literature, the incidence of such infections in the general population is not clearly described. However, a study from the United States estimated that the incidence of sepsis in the general population was 240 cases per 100,000 persons per year (for a rate of 0.24%) [14]. In Europe, data from the European Antimicrobial Resistance Surveillance System provided valuable information on the incidence of *S.*

*aureus* bacteremia: they concluded that the incidence was 1–32 cases per 100,000 persons (for a rate of 0.03%) [15].

Brain abscesses are frequent among patients with HHT, as has been reported elsewhere [16], and are thought to be the consequence of pulmonary arteriovenous malformations (PAVMs). Brain abscesses affected 4% of all patients with HHT and 13% of patients with HHT and PAVMs, and they accounted for 28.3% of all severe infections in our cohort. The incidence of cerebral abscess in the general population has not been reported in the literature. However, we studied the incidence of cerebral abscess treated at a single neurosurgery unit at Pierre Wertheimer Hospital (Lyon, France), which has a catchment area that includes 1.7 million people. We identified 150 cases of cerebral abscess during the period 1998–2005. Clearly, the incidence of cerebral abscess in our HHT population is higher than that in the general population.

Interestingly, the pathogen identified in most cases of extracerebral infection was *S. aureus*, as was previously reported for 1 patient with spondylodiskitis [8] and 3 other patients with HHT [9]. In contrast, cultures of cerebral abscess specimens were positive for multiple anaerobic organisms. These 2 different types of infection could reflect different entry routes and mechanisms. It has been suggested that brain abscesses may be a consequence of PAVM and of the direct communication between pulmonary and systemic circulation, with the capillary bed bypassed [17]. Our findings were entirely consistent with this suggestion: all patients with cerebral abscesses had PAVMs,

and none of the patients without PAVMs had cerebral abscess. This association has also been described in the literature for other causes of right-to-left shunting associated with the presence of a patent foramen ovale or congenital cyanotic cardiopathy [18]. Surprisingly, the median duration of epistaxis was significantly lower in the cerebral abscess group than in the group of patients without severe infection. We have no clear explanation for this, but patients with PAVMs may require antibiotic treatment frequently, thereby also leading to treatment of chronic nasal infection (which, in turn, plays a role in recurrent epistaxis).

The mechanism of extracerebral infection is still unclear. To identify the mechanisms of infection, we studied risk factors for severe infection in patients with HHT. First, we hypothesized that the nasal mucosa could be an entry route for infection in patients with HHT. Indeed, epistaxis requires cotton packing, and as noted by Duval et al. [9], such manipulations could lead to traumatized nasal mucosa. The presence of a foreign body may favor nasal *S. aureus* proliferation, as observed in cases of staphylococcal toxic shock syndrome associated with use of tampons during every menstrual period [19] or after nasal packing [20]. Indeed, we found that the median duration of epistaxis is significantly longer in patients with extracerebral infection than in patients with cerebral infection or in those without infection.

Interestingly, extracerebral infections were associated with both *ENG* and *ALK1* gene mutations. This was not surprising, because both genes encode endothelial cell transmembrane proteins interacting with the TGF- $\beta$  signaling pathway; moderate abnormalities of the immune system would be expected to favor infectious diseases. Indeed, TGF- $\beta$  was reported to have the ability to inhibit macrophage activation and to regulate immune responses to a variety of pathogens [21]. There are few data currently available concerning immune functions in HHT, but a recent report showed a reduction in the killing capacity of neutrophils and monocytes in patients with HHT [10]. In contrast, lymphocyte subsets were analyzed by Blanco et al. [22] in a series of 39 patients with HHT, and the authors did not observe any significant difference in that regard between patients and healthy subjects.

In conclusion, we show that HHT is associated with a high frequency of infectious diseases. Mechanical factors associated with moderate abnormalities of the immune system may explain this high rate of infection. Prospective clinical studies are needed to analyze epistaxis and the role of local infection and to assess even mild infections that affect patients with HHT. Furthermore, immunological investigations are needed to highlight the possible role of abnormalities of the immune system. Indeed, an awareness of infectious risks in HHT will facilitate the diagnosis and improve patient care.

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