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REVIEW

A Forgotten Episode of Marburg Virus Disease: Belgrade, Yugoslavia, 1967

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SUMMARY In 1967, several workers involved in poliomyelitis vaccine development and production fell ill at three different locations in Europe with a severe and often lethal novel disease associated with grivets (*Chlorocebus aethiops*) imported from Uganda. This disease was named Marburg virus disease (MVD) after the West German town of Marburg an der Lahn, where most human infections and deaths had been recorded. Consequently, the Marburg episode received the most scientific and media attention. Cases that occurred in Frankfurt am Main, West Germany, were also described in commonly accessible scientific literature, although they were less frequently cited than those pertaining to the Marburg infections. However, two infections occurring in a third location, in Belgrade, Yugoslavia, have seemingly been all but forgotten. Due in part to their absence in commonly used databases and in part to the fact that they were written in languages other than English, the important articles describing this part of the outbreak are very rarely cited. Here, we summarize this literature and correct published inaccuracies to remind a younger generation of

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scientists focusing on Marburg virus and its closest filoviral relatives of this important historical context. Importantly, and unfortunately, the three episodes of infection of 1967 still represent the best in-depth clinical look at MVD in general and in the context of "modern" medicine (fully resourced versus less-resourced capacity) in particular. Hence, each individual case of these episodes holds crucial information for health care providers who may be confronted with MVD today.

KEYWORDS Belgrade, *Filoviridae*, filovirus, Marburg hemorrhagic fever, marburgvirus, Marburg virus, Marburg virus disease, MHF, MVD, Torlak, VHF, viral hemorrhagic fever

INTRODUCTION

Marburg Virus Disease

Marburg virus disease (MVD) (WHO International Classification of Diseases version 11 [ICD-11] code 1D60.10 [1, 2]) is a severe, acute, and rarely occurring human disease originating from Africa. A total of 14 MVD outbreaks have been documented, encompassing 480 human infections in which 378 individuals succumbed to the disease (average lethality, 80.6%). These outbreaks occurred in or were exported from eastern Africa (Kenya and Uganda), central Africa (Democratic Republic of the Congo), and southern Africa (Angola and Rhodesia [Zimbabwe]) from 1967 to the present. In addition, at least two laboratory-acquired MVD cases, one of them lethal, have occurred in Soviet laboratories (3, 4).

MVD can be caused by two distinct viruses belonging to the species *Marburg marburgvirus* (genus *Marburgvirus*, mononegaviral family *Filoviridae*): Marburg virus (MARV) and Ravn virus (RAVV) (3, 5, 6). Both viruses appear to be maintained in nature by subclinically infected Egyptian rousettes (i.e., cave-dwelling frugivorous bats of the pteropodine species *Rousettus aegyptiacus* Gray, 1821) roosting in Africa (7–12). The transmission pathway from bats to humans is unclear, but most MVD outbreaks were epidemiologically associated with natural or artificial caves located in arid woodlands, suggesting that infections occur within caves after contact with, for instance, bat excretions or secretions (13, 14).

Knowledge of MVD due to RAVV infection is limited to only two publications (15, 16), and MARV has been responsible for the vast majority of MVD cases (479 cases, resulting in 386 deaths [including both laboratory-acquired infections], compared to 3 cases with 2 deaths due to RAVV) (3). The current, very rudimentary understanding of MVD still is sourced largely from clinical case reports published (often in non-English languages) in the aftermath of MVD outbreaks in developed countries, i.e., in West Germany (Germany) in 1967 (17–29), Rhodesia (Zimbabwe)/South Africa in 1975 (30–34), and Netherlands in 2008 (35), and after the occurrence of a laboratory-acquired MARV infection in the USSR (Russia) in 1990 (36). Only a few publications report at least basic clinical manifestations of MVD in other outbreaks, notably in Kenya in 1980 (37) and the Democratic Republic of the Congo in 1998 to 2000 (38–40). Together, these reports are the basis for the definition of the clinical presentation of MVD in terms of general vital signs, basic serum chemistry, and routine gross pathology and histopathology. Accordingly, MVD might be clinically indistinguishable from the more infamous Ebola virus disease (EVD) (ICD-11 code 1D60.01; average lethality over the recorded 33,639 cases, 44% [case numbers updated from reference 3 using reference 41]).

MVD begins abruptly after an incubation period of 7 to 11 days (range, 2 to 21 days). Phase 1 of MVD resembles a nonspecific influenza-like illness, whereas phase 2 involves abdominal, central nervous system, hemorrhagic, respiratory, and vascular manifestations. Typical clinical signs include abdominal pain, anorexia, diarrhea, fatigue, malaise, nausea, myalgia, maculopapular rash, sore throat, and vomiting. Thrombocytopenia, elevated transaminase activities, and electrolyte abnormalities are typical laboratory findings. Death is assumed to be a direct result of multiorgan dysfunction syndrome (MODS) subsequent to hypovolemic shock due to third spacing or gastrointestinal fluid loss (3, 42, 43). Patients who survive this period often have long, difficult in-hospital

recoveries that may be complicated by secondary infections, orchitis, and neuropsychiatric illness. Though poorly characterized, MVD survivors appear to suffer prolonged clinical sequelae that include arthralgia, neurocognitive dysfunction, and uveitis (17, 33). Disease relapse has been described (33, 36), indicating that MARV may persist in survivors under yet-to-be-described circumstances. Indeed, one case of sexual transmission related to persistent MARV infection after recovery from MVD has been reported (44), and experiments with nonhuman primates (NHPs) suggest that MARV can persist in the testes for prolonged periods of time after recovery from the acute disease (45).

Currently, no licensed antivirals or vaccines are available to treat or prevent MVD. Consequently, therapy of MVD patients relies entirely on supportive care, and prevention of MVD is based largely on avoidance of direct contact with infected people or contaminated materials (3, 42, 43).

Marburg Virus Disease, West Germany, 1967

MVD was observed for the first time in August of 1967 during an outbreak in Marburg an der Lahn and Frankfurt am Main, West Germany (Germany). Twenty-nine people developed clinical signs, and seven of them eventually succumbed (46–54). Prior to developing disease, all primary cases had either direct contact with grivets (Primates: Cercopithecidae: *Chlorocebus aethiops* Linnaeus, 1758) imported from a single Ugandan primate exporter via London, UK, or direct contact with grivet-derived tissues. Based on epizootiological/epidemiological studies and the current understanding of MARV endemicity in Africa (13, 14), the grivets likely had already been infected with MARV prior to leaving Uganda. Exactly where and how the grivets could have become infected remain obscure (55–62), and natural infections of grivets with MARV have not been described since 1967.

The outbreak in Marburg an der Lahn occurred among laboratory personnel of a manufacturer of poliomyelitis vaccines (Behringwerke AG). Retrospective studies indicated that infection occurred during activities aimed at the establishment of primary grivet cell cultures using tissues from the imported Ugandan grivets. Further, nosocomial infections occurred after sick employees had been admitted to a local medical university hospital. The outbreak in Frankfurt am Main involved laboratory personnel working at a West German government facility responsible for the safety testing of poliomyelitis vaccines (Paul Ehrlich Institute [Paul-Ehrlich-Institut]). Employees became infected during handling of tissues derived from the imported Ugandan grivets. At least two nosocomial infections occurred during treatment/pathological examination of patients (29, 46, 48–54, 63).

In addition to the Marburg an der Lahn and Frankfurt am Main infections, two infections occurred in Belgrade, Yugoslavia (Serbia). Both infections were epidemiologically connected to the West German outbreaks and the same Ugandan primate exporter. Here, we review this almost-forgotten episode of MVD.

METHODS

To locate all publications and still-available primary data on the 1967 MVD episode in Belgrade, Yugoslavia, we first personally searched the historical archives of the Institut za virusologiju, vakcine i serume "Torlak"/Институт за вирусологију, вакцине и серуме "Торлак" in Belgrade, Serbia, followed by in-depth searches of general medical and scientific databases, including PubMed (https://www.ncbi.nlm.nih.gov/pubmed/), Scopus (https://www.scopus.com), and Web of Science (https://login.webofknowledge.com), and specialized Serbian databases such as the Serbian Citation Index (SCIndeks) (https://scindeks.ceon.rs). Search terms included the names of the scientists involved in the 1967 investigations and their correctly spelled Serbo-Croatian Latin and Cyrillic equivalents (see Table S1 in the supplemental material) and the various names used in the 1960s and 1970s for Marburg virus disease (MVD) and Marburg virus (MARV) (e.g., "CBHF," "Cercopithecus borne haemorrhagic fever," "FMS," "Frankfurt-Marburg syndrome," "green monkey disease," "Marburg disease," "Marburg

simian disease," "Marburg monkey disease," "Marburg virus disease," "vervet monkey disease," and derivations thereof [2, 4]). Retrieved data files and published reports were screened for relevance and, if necessary, translated into English by native speakers. Discrepancies among published reports were reconciled by accessing the primary historic data files at the Institute of Virology, Vaccines and Sera "Torlak." In this article, such discrepancies and their reconciliations are listed in Table S2 in the supplemental material.

MARBURG VIRUS DISEASE, BELGRADE, 1967

Epidemiology/Epizootiology

From 18 July to 1 August 1967, the Institute of Virology, Vaccines and Sera "Torlak" (see Appendix) received three shipments of nonhuman primates from Uganda via a German dealer. Each of the shipments was slated to contain 100 grivets (*Chlorocebus aethiops* Linnaeus, 1758; females and males weighing from 2 to 5 kg). Two of these shipments, the first and the third, were routed through London, UK (arriving on 18 July and 1 August, respectively), whereas the second one was routed through Munich, West Germany (arriving July 23). Twelve animals in total died during these three shipments. The remaining 288 grivets were quarantined at "Torlak" following the then-current WHO guidelines, with one room assigned per shipment. During quarantine, an unusually high number of animals died in all three rooms: 46/99 (46%) of the first shipment through London, 20/95 (21%) of the shipment through Munich, and 30/94 (32%) of the second shipment through London (third shipment total) (Fig. 1) (64). Due to the high lethality, a 45-year-old experienced veterinarian from the "Torlak" Enterovirus Department (identified as Ж.Ст. [Ž.St.] in references 64 to 66 and a coauthor of references 64 and 67 to 69) was assigned to perform necropsies on two of the deceased grivets from the third (London) shipment on August 25 in the surgical room. He worked using rubber gloves "and other protective garments" (66) (cotton laboratory coats and rubber aprons, rubber boots enclosed in plastic bags, hats or headscarves, doubled surgical masks, protective goggles, and triple [single-use] gloves for sequential doffing after leaving the working area in the preparation room, after leaving the preparation room, and prior to entering a bath/shower room [A.S.G., personal observation]). Internal institute reports reviewed by one of us (A.S.G.) clarify that while placing a piece of grivet liver into a petri dish, Ž.St. did not realize that he had inadvertently contaminated the outside of the dish with grivet blood. After leaving the surgical room, he removed the personal protective equipment, washed and disinfected his hands, showered, and then handled the petri dish without gloves. After noticing blood on his diaphoretic palm, he immediately reported this incident to the appropriate institutional authorities but refused monitoring for the subsequent 6 days (this description of events stands in contrast to that in reference 64: "The infection. . .occurred. . .most probably through some small abrasions on the unprotected forearm or through conjunctivae"—implying that Ž.St. did not wear proper personal protective equipment). On August 30, Ž.St. performed another necropsy together with a colleague, M.P. (64).

Clinical Presentation, Course, and Treatment

Patient 1 (Ž.St.). On 1 September (day 1 of illness), veterinarian Ž.St. became sick with (unmeasured) fever and chills (65, 66), but he did not consider these symptoms to be connected to a possible laboratory infection. He was placed under home surveillance by medical personnel of the University Clinic of Infectious Diseases (Univerzitetska klinika za infektivne bolesti/Универзитетска клиника за инфективне болести), Belgrade, Yugoslavia (today Clinic for Infectious and Tropical Diseases Prof. Dr. Kosta Todorović [Klinika za infektivne i tropske bolesti „Prof. dr Kosta Todorović"/Клиника за инфективне и тропске болести „Проф. др Коста Тодоровић"]) through 6 September (day 6 of illness). The fever (38.6°C on 2 September, day 2 of illness) (Fig. 2) was unresponsive to acetylsalicylic acid and "bemycin" (a combination of oxytetracycline and an unspecified B vitamin). Conjunctivitis became apparent on 2 September. On the evening of 3 September (day 3 of illness; fever, 39.6°C), he developed severe headache,

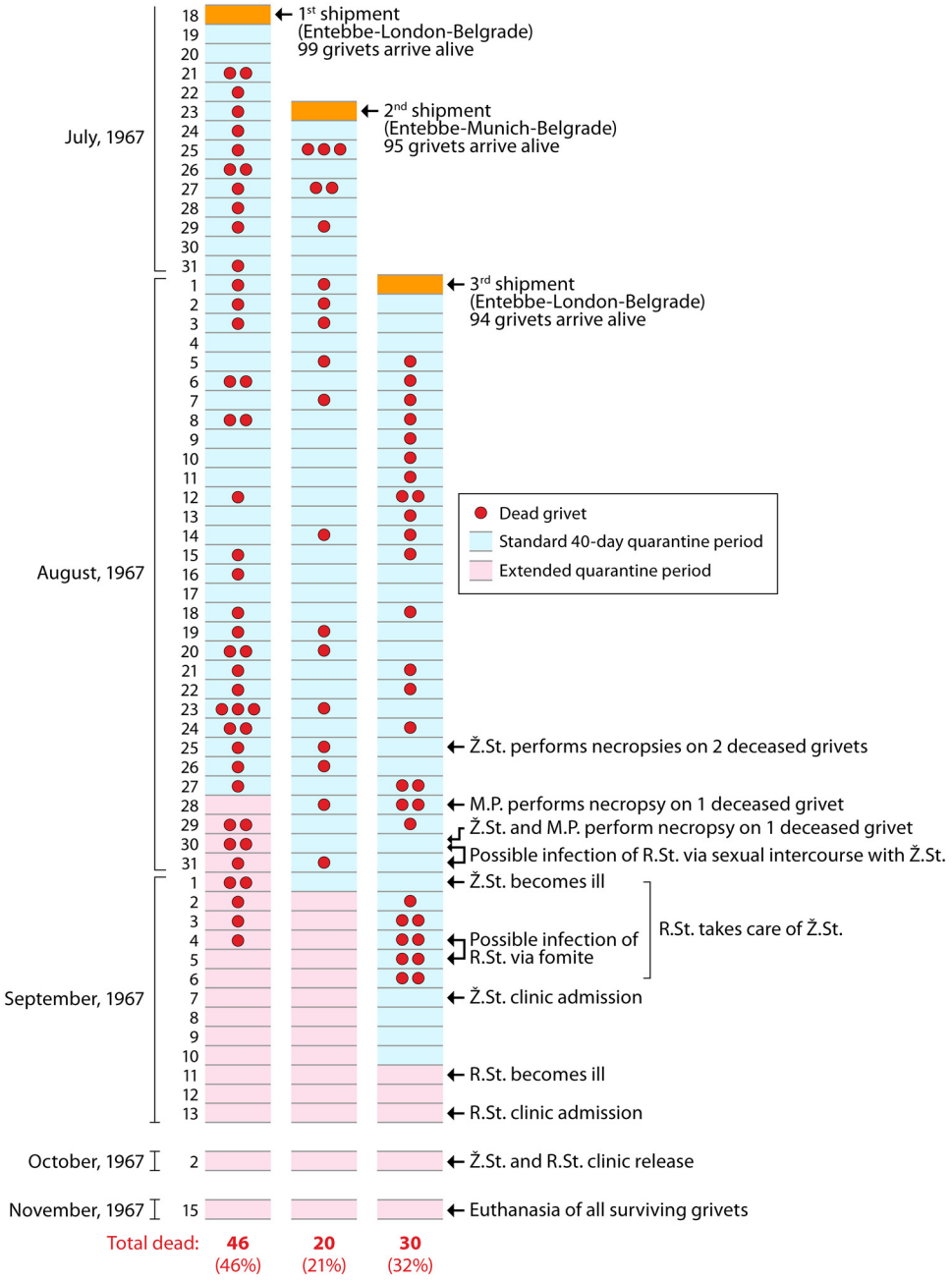

FIG 1 Timeline of grivet epizootics associated with three shipments imported from Uganda to the "Torlak" Institute and time association of epizootics with occurrence of Marburg virus disease in a veterinarian (Ž.St.) and secondary contact (R.St.). Red dots indicate grivets that died during the quarantine and peri-quarantine periods. (Based on data from reference 64.)

dry cough, and insomnia. On 4 September (day 4 of illness; fever, 37.7°C), Ž.St. developed nausea and vomited upon taking "vitamin B" (65, 66). After treatment with "tetrabiocin/тетрабиоцин" (likely a sulfonamide antibiotic) on 5 September (day 5 of illness), the headache improved. He complained of throat irritation (pruritus) (65) and then developed dysphagia, odynophagia, and "pharyngeal cramps." Oropharyngeal erythema, dry blood, and caked mucus were noted on oral examination (64, 66). These signs and symptoms were accompanied by severe watery diarrhea (profuse, odorous, without mucus or blood), impaired liver and kidney function, and anorexia starting on 6 September (66). On that day, he also developed a thin and point-like rash on the

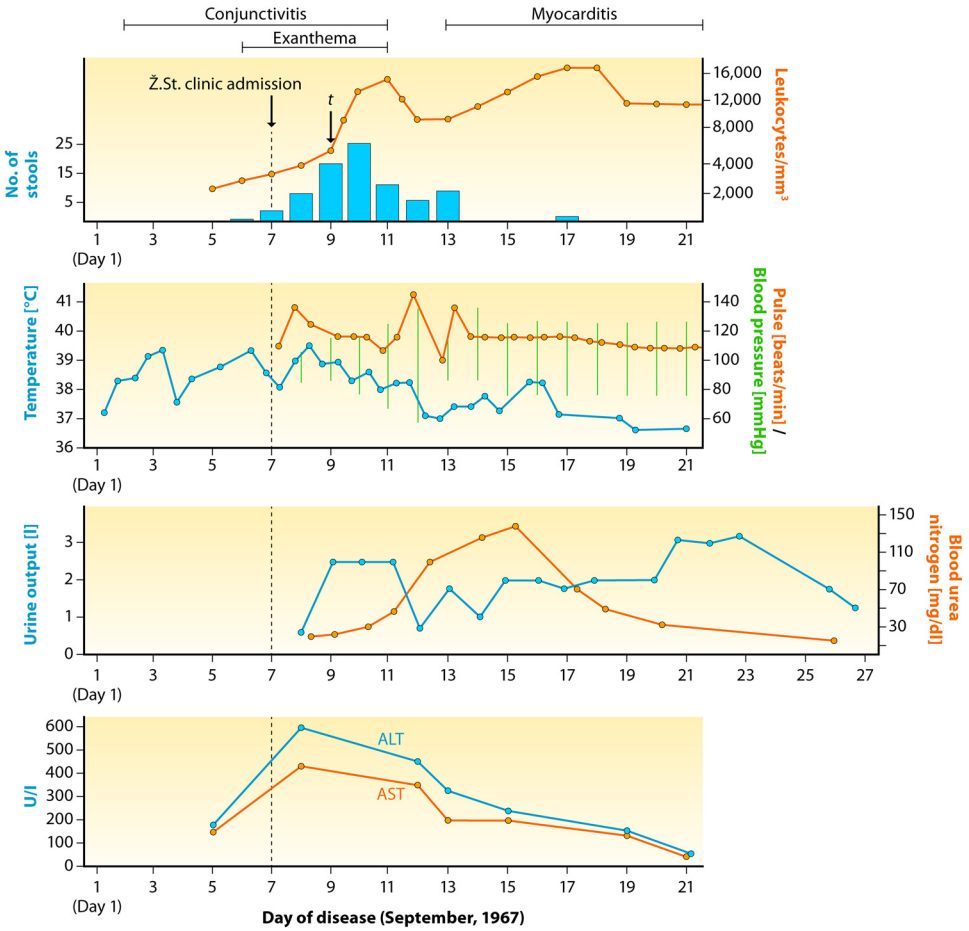

FIG 2 Clinical course of Marburg virus disease in the index patient (Ž.St.) of the Belgrade, Serbia, outbreak. Dots on curves in the bottom three panels likely represent sampling times on a 24-h clock scale. *t*, administration of convalescent-phase plasma from a Marburg virus disease patient from the 1967 Frankfurt am Main outbreak. (Adapted from reference 65 with permission of the publisher.)

upper chest that rapidly spread to the entire body (Fig. 2). The patient developed a dry cough (without sneezing) and erythema of the face (65, 66). Preadmission laboratory investigations (4 to 6 September) revealed leukopenia (4 to 5 September; white blood cell [WBC] count = 2,200/mm^3 with 68% polynuclear cells in the absence of eosinophils), thrombocytopenia, elevated liver transaminase activities, proteinuria and microscopic hematuria, and a normal chest radiograph (64–66).

On 7 September (day 7 of illness), the veterinarian was transferred to the University Clinic of Infectious Diseases. Presenting symptoms and signs on 7 and 8 September (days 7 and 8 of illness) included persistent high fever, asthenia, fatigue, more ample skin rash, frequent diarrhea, increasing WBC counts (Fig. 2), anorexia, and hyperacusis. Vital signs were normal, but he appeared severely ill. The examination was significant for notable anxiety, skin erythema and edema (including the face, eyelids, and lips) including petechiae and sometimes larger hematomas (including injection-site hemorrhages), enanthema, dry mucous membranes, hyperactive bowel sounds, hepatosplenomegaly, nuchal lymphadenopathy, mild jaundice, and scleral icterus. Amplified physiological deep tendon reflexes, Kernig's sign, a light tremor of the tongue, and coarse tremor of the arms were noted on neurological examination (65, 66). On 8 September, Ž.St. received transfusions of 350 cm^3 of blood and 250 cm^3 of albumin. On 9 September (day 9 of illness), Ž.St. developed tremors and severe weakness that left him unable to move without assistance. A consulting team was formed of employees of the University Clinic of Infectious Diseases, members from the Serbian Academy of

Sciences and Arts (Srpska akademija nauka i umetnosti/Српска академија наука и уметности), and doctors from Behringwerke AG and Paul Ehrlich Institute in West Germany. After consultation, the veterinarian received 250 cm^3 of convalescent-phase plasma from a West German (likely Frankfurt am Main) MVD survivor brought to Belgrade, another blood transfusion, and gamma globulin (47, 65, 66) (Fig. 2).

Ž.St.'s subsequent hospital course was notable for a progressive, complicated multisystem disease, described here by systems. In addition to anorexia and occasional vomiting, profuse diarrhea (peak of 26 stools per 24-h period on 10 September [day 10 of illness]) led to severe dehydration and electrolyte imbalance. Hepatic transaminase activities were markedly elevated at admission (aspartate transaminase [AST] $>$ 300 U/liter, alanine transaminase [ALT] $>$ 400 U/liter) and improved but remained elevated until normalizing on 21 September (day 21 of illness) (Fig. 2). Hepatomegaly and subicteric jaundice persisted through most of the hospital course (65, 66).

He developed worsening coagulopathy that included bleeding from the skin (a scratched ear and skin ecchymoses), oropharynx (palatal petechiae, gingival bleeding, and blood clots in the nostrils), gastrointestinal tract (hematemesis, numerous bloody stools with sloughed mucous membranes, and one melenic stool), and injection sites (superficial and deep hematomas, uncontrolled bleeding). Coagulation times were notably prolonged and were associated with a platelet count nadir of 90,000/mm^3. He received several blood transfusions (65).

In the context of volume depletion related to ongoing diarrhea, third spacing, and blood loss, the patient maintained normal blood pressure but became tachycardic and oliguric (urine output = 250 cm^3/24 h) with a coincident elevation of blood urea consistent with prerenal azotemia (Fig. 2). Serum creatinine was not measured. He developed hyperchloremia, metabolic acidosis, and electrolyte abnormalities. Urinalysis showed granular casts and proteinuria (65). Over his hospital course, efforts to restore euvolemia included multiple albumin infusions, intravenous fluid replacement (including normal saline, bicarbonate- and lactate-containing solutions, and glucose), and correction of electrolyte abnormalities (potassium chloride, 10% calcium, and insulin with 25 to 47% glucose) (65).

In addition to profound generalized weakness and his abnormal admission neurological exam, evolving neurological symptoms and signs included clouded consciousness, persistent hyperreflexia, tremors (eyelids and extremities) nystagmus, and a Babinski sign (extensor plantar reflex), suggesting upper motor neuron or corticospinal tract involvement (65). He did not have persistent headache or documented neck stiffness, and cerebrospinal fluid examination was not performed. While most neurological manifestations improved late in the second week, hyperreflexia and coarse tremor persisted into the second week of illness (65).

Around day 11 of illness, the patient defervesced, and he generally improved clinically over the next week (Fig. 2). This improvement included decreasing stool frequency (although still positive for occult blood) (65), ceasing of rash progression followed by subsequent clearing and sloughing of damaged skin, and increasing appetite, strength, and mobility. Around the same time, myocarditis and pericardial effusion were suspected due to persistent sinus tachycardia, muffled heart sounds, and evidence of diffuse myocardial impairment on (unpublished and no longer available) electrocardiogram (ECG) readings. He was treated with k-strophantoside (a cardiac glycoside). On 15 September (day 15 of illness), the patient had improved appetite and was able to sit up in bed. Urine output had normalized. Leukocytosis persisted (Fig. 2). Over the next weeks and up to hospital discharge on 2 October 1967 (after 32 days of sickness and 25 days in the hospital), tremors gradually diminished, and blood laboratory values normalized. However, symptoms and signs of myocarditis and a slight bilateral hand tremor persisted for an unspecified number of weeks after hospital discharge (65, 66). As far as is known, Ž.St. did not suffer long-term sequelae, as none were noted on evaluation 2 years later (66).

In addition to the convalescent-phase plasma and other supportive treatments detailed above, antibiotics (penicillin, nystatin, and oxytetracycline) were initiated in the

early phase of illness. These antibiotics did not appear to improve the clinical manifestations but may have reduced the potential for secondary bacterial infections. Other supportive care included nutritional support (tocopherol and vitamin K) and treatment of pain and anxiety (acetaminophen, opium tincture, procaine, and nandrolone phenylpropionate) (65).

Patient 2 (R.St.). The veterinarian's 44-year-old wife, P.Ct. [R.St.], cared for him during the initial phase of his illness at the couple's home. On day 4 or 5 of her husband's disease (4 or 5 September), she had contact with a disposed "soiled" linen and a blood-soaked cotton gauze pad used during blood sample collection from the veterinarian by a laboratory technician (65, 66) ("might have had contact with his blood" [70]). In repeated direct interviews performed by one of us (A.S.G.), neither the veterinarian nor his wife recalled any existing skin lesions at the time, and both denied having had any recent sexual contact. However, the veterinarian reported having had sexual intercourse with his wife on 30 or 31 August in a medical article he coauthored (67).

On 11 September (day 1 of illness), R.St. developed light chills, pain in her calves, and mild fever (37.4°C) (55, 65, 66). Her menses had started 2 days prior (9 September) and ended abruptly with the onset of disease signs (67). On 12 September (day 2 of illness), fever remained constant (37.6°C) but disease worsened: symptoms and clinical signs included asthenia, headaches, myalgia, and persistent cough (65). On 13 September (day 3 of illness), she was admitted to the University Clinic of Infectious Diseases, where she was treated by the same clinical team that treated her husband. She presented with fever (39°C), asthenia, pharyngitis, persistent cough, loin pain, urinary frequency, and diarrhea (65, 66). Over the next few days, she developed facial edema, skin (maculopapular rash and generalized erythema, eyelid hyperemia, and violaceous labial erythema), mucous membrane (conjunctivitis and palatal enanthema), and other gastrointestinal (vomiting and hepatomegaly) manifestations, with evidence of dehydration on physical exam (66, 67). On day 10 of her illness (20 September), she developed mild uterine hemorrhage of uncertain cause that lasted 2 days (67). Laboratory abnormalities included prominent leukopenia (WBC = 1,200/mm^3 on 13 September) (Fig. 3), hemoconcentration, metabolic acidosis, hypocalcemia, "hypovitaminosis" (unclear meaning in the original reports), and elevated transaminase activities (65, 66). Like her husband, she received 250 cm^3 of convalescent-phase plasma from the same West German MVD survivor. Overall, the duration and severity of R.St.'s disease course were less dramatic than those of her husband's illness. She was discharged on 2 October 1967 (day 22 after onset of illness), together with her husband, without significant sequelae (65) except for transient secondary amenorrhea followed by secondary hypomenorrhea (3 days only) for one cycle and subsequent resumption of normal menses 9 weeks after discharge (67).

Virological and Immunological Investigations

Based on Ž.St.'s dramatic clinical course, epidemiological considerations that all but excluded bacterial and parasitic infections, and Ž.St.'s reported contact with likely contaminated blood of a necropsied nonhuman primate, the Belgrade clinicians suspected a viral etiology. Clinical samples taken from Ž.St. were sent to "Torlak" on the day of his hospital admission (7 September, disease day 7) and again on disease days 11, 20, 30, 45, and 218. Twenty male or female domesticated guinea pigs (*Cavia porcellus* Linnaeus, 1758; stock or strain unspecified) were chosen for virus isolation attempts. Serum and coagulum (source unspecified) specimens collected on 7 September from the veterinarian and on 13 September from his wife were inoculated intraperitoneally (i.p.) into 5 guinea pigs per specimen per patient ($n = 20$) (64, 65), and the rectal temperatures of the guinea pigs were checked every morning (64). All guinea pigs developed high fever ($n = 20$; 40.0 to 40.4°C) and severe illness (19 guinea pigs succumbed and 1 guinea pig survived) within 5 to 6 days. During the near-moribund phase, first-passage blood was taken from highly febrile guinea pigs and injected i.p. into 5 new guinea pigs per patient to confirm transfer of a live infectious agent. These

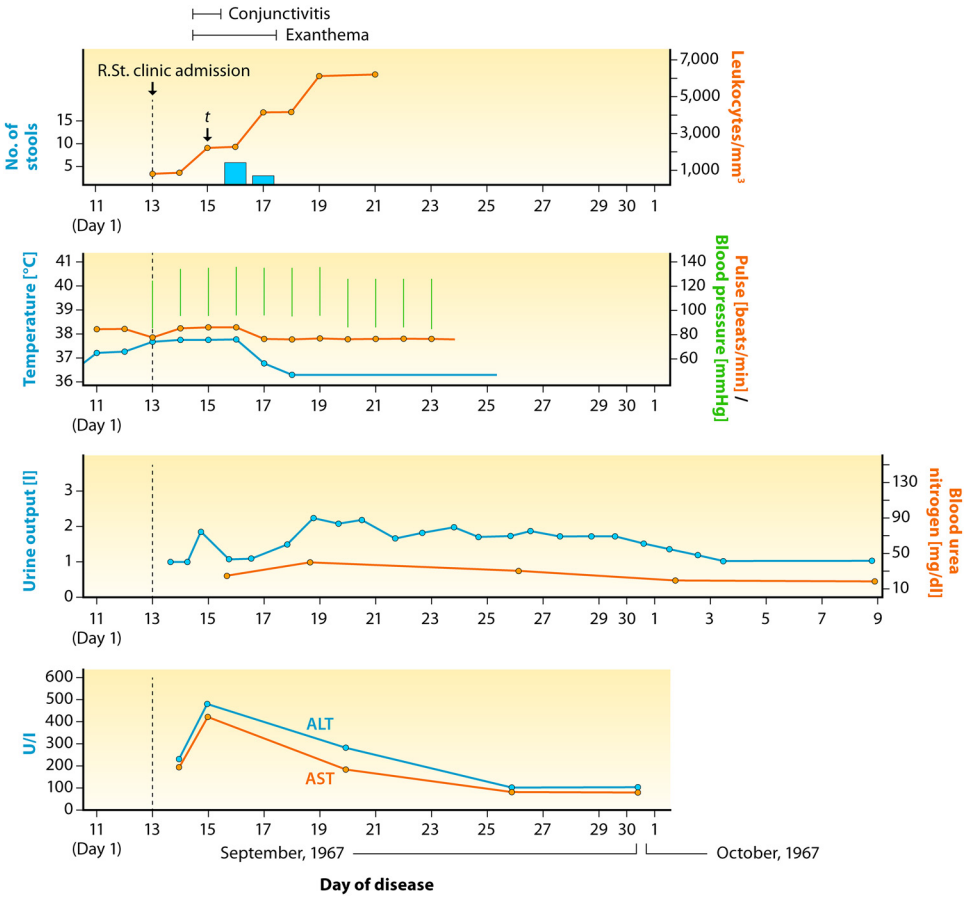

FIG 3 Clinical course of Marburg virus disease in the secondarily infected patient (R.St.) of the Belgrade, Serbia, outbreak. Dots on curves in the bottom three panels likely represent sampling times on a 24-h clock scale. *t*, administration of convalescent-phase plasma from a Marburg virus disease patient from the 1967 Frankfurt am Main outbreak. (Adapted from reference 65 with permission of the publisher.)

second-passage animals developed severe illness in an accelerated fashion (9 guinea pigs succumbed within 2 to 4 days, and 1 guinea pig survived; orchitis was noted in 3 animals). Another passage resulted in uniform mortality. Another two passages (5 passages total) were performed; moribund guinea pigs from the second and subsequent passages were euthanized, and internal organs (kidneys, livers, lungs, and spleens) were collected for electron microscopy studies and antigen preparation (64, 65).

Pathological examinations of these organs confirmed the suspected viral etiology. Macroscopic examinations revealed white necrotic foci on livers, lungs, and spleens. Spleens were darkly colored, and the spleens and scrotal purses were enlarged. Liver, lung, kidney, and spleen tissues and supernatants of centrifuged plasma collected from highly febrile guinea pigs infected with second- or third-passage blood were collected for impression smears and fixed with methanol. Giemsa, Gram, and Macchiavello staining of the samples revealed cellular inclusion bodies in various organs (records that specify cell types no longer exist). Specimens collected for electron microscopy were fixed with 4% formalin. On 20 November, negatively (phosphotungstic acid) stained electron micrographs (no longer available) revealed virus particles of unusual filamentous shape and size (500 to 800 nm by 80 nm) in samples of all three passages (64, 65). However, the virus could not be isolated in newborn (24-h-old) or adult albino mice (stocks/strains were not reported) after i.p. or intracerebral injection of serum or blood cell suspensions (up to passage 3) from these two patients (64).

Virus antigen for serological investigation was prepared from spleens and livers of virus-infected (fourth-passage) guinea pigs. By complement fixation (CF) test, antibody

titers were first detected on day 11 after symptom onset (1:4 and 1:8) and peaked at days 20 to 21 after symptom onset (1:32 and 1:32) in patients 1 (Ž.St.) and 2 (R.St.), respectively (64). In patient 1, antibody was still detectable at day 45 (1:16) and day 218 (1:8) following symptom onset. Antibodies against the new virus were also detected in sera from 36 of 48 grivets of all three Ugandan shipments that had completed quarantine (118 days), with titers ranging from 1:2 to "1:16 or more" (64) (1:64 was obtained by one of us, A.S.G., in unpublished later experiments), but no antibodies were detected in 5 grivets (and tests of 7 grivets had to be discarded due to nonspecific reactions) (64). These findings suggested that the novel virus indeed arrived with the grivets to Belgrade and that Ž.St. indeed acquired the infection directly or indirectly from a grivet.

Late-convalescent-phase blood samples collected from patient 1 (Ž.St.) at ≈7 months (218 days after disease onset) and then inoculated i.p. into five additional guinea pigs did not cause detectable disease (64). In addition, virus isolation in guinea pigs using blood and kidney tissue from one febrile grivet shipped from Uganda and six pools of kidney tissue from 34 grivets completing the 118 days in quarantine also failed (64, 70).

Informally, the new virus was first named "Marburg/Belgrade virus (MABGV)" among West German and Yugoslav scientists (Serbian, Марбург/Београд вирус). In Belgrade, the disease was first referred to as "Cercopithecus-associated hemorrhagic fever" (cerkopitekusna hemoragijska groznica/церкопитекусна хеморагијска грозница) (69) and "Cercopithecus-monkeys-associated haemorrhagic fever" (cerkopitekusna majmunska hemoragijska groznica/церкопитекусна мајмунска хеморагијска грозница) (at the time, grivets were assigned to the species *Cercopithecus aethiops*) (64), similar to Russian names for the disease ["Cercopithecus borne haemorrhagic fever (CBHF)" (71); "Церкопитековая геморрагическая лихорадка (ЦГЛ)/Cercopithecus hemorrhagic fever (CHF)]" (71, 72). Ultimately the virus became known as Marburg virus (MARV) (5) and the disease as Marburg virus disease (MVD) (2).

Containment

Investigators quickly understood that grivets from the Ugandan shipments were the likely source of the veterinarian's infection and clinical illness. Shortly after Ž.St.'s hospital admission on 7 September, 135 of 192 surviving grivets from the three shipments that were sick or were suspected to be infected were euthanized to diminish any risk of further infection. All ongoing vaccine production was halted. The remaining 57 grivets ("17 or 20 from each shipment"), which were considered healthy, were placed under strict observation (64), and their quarantine period was extended until 15 November (marking 118 days from arrival of the first Ugandan shipment). Because nine more grivets died during this period, it was decided to euthanize all remaining animals. Blood and kidney tissues were collected from some euthanized animals for serological and virological investigations. These investigations also included two control grivet sera from earlier shipments of healthy grivets, some virus-negative human sera, sera from guinea pigs that survived exposure to MVD patient serum or coagulum, and plasma samples from convalescent-phase West German MVD patients. In addition, sera taken from Ž.St. on disease days 11, 20, 30, 45, and 218 and sera from his wife taken on disease days 11, 21, and 36 were tested for the presence of anti-MARV antibodies (64).

Source Investigations

Joint epidemiological/epizootiological investigations by the West German and Yugoslav teams quickly established that the MVD outbreaks in Marburg an der Lahn, Frankfurt am Main, and Belgrade had at least one common epidemiological link: all affected grivets at all three locations were provided by the same Ugandan exporter of nonhuman primates. However, variable shipping times, routes, and *en route* stays of the animals (in London or Munich, housed together with other animals from places other than Uganda in London) made definitive confirmation of the source impossible. All grivets associated with the 1967 MVD outbreaks had been moved through an animal holding station in Entebbe, Uganda. To substantiate the hypothesis that MARV came

from Uganda, an epidemiological investigation was initiated in September 1967 to determine anti-MARV antibody prevalence in nonhuman primates (NHPs) and humans at or near this station. Acute-phase sera from ill grivets from Entebbe, Kidera, and Namasale holding stations were shipped to the U.S. Centers for Disease Control (today the Centers for Disease Control and Prevention) in Atlanta, GA. In September 1967, only one NHP of 49 that had just arrived from the Kyoga area to the Entebbe holding station had CF antibodies to MARV antigen. In sera taken at the same time from the nearby Kidera and Namasale holding stations, 0% (0/11) and 20% (10/49) of NHP sera contained CF antibodies (titer of $\geq$1:16), respectively. In October 1967, 33% (1/33), 36% (12/33), and 9% (1/11) of NHP sera from the Entebbe, Kidera, and Namasale holding stations contained CF antibodies, respectively. Nine of 38 paired sera from September and October 1967 had a 4-fold or greater rise in CF antibodies in October 1967 (64, 73). During August and September, seemingly healthy hunters or animal caretakers at the holding stations at Lake Kyoga were interviewed and bled. CF anti-MARV antibodies were detected in 3 of 79 individuals tested; this result was confirmed with MARV neutralization tests. In 55 healthy monkeys imported from neighboring Kenya in 1968 and 1969, sera from 49 monkeys were clearly negative for MARV antibodies, one monkey had a titer of 1:4, and sera from 5 monkeys reacted with antigen and normal control antigen (nonspecific reactivity, 1:8 to 1:32) (64). Together, these results indicate that MARV circulated in NHP populations in Uganda in 1967 and was exported to Europe when NHPs were shipped to European research institutions.

CONCLUSIONS

In an era of modern medicine that prides itself on evidence-based decision-making, knowledge of the availability of information and then access to information are increasingly a priority. This knowledge and access are particularly important regarding high-consequence infectious diseases that are historically shrouded in mystery and about which reliable information from challenging outbreak environments in remote African settings can be difficult to obtain, document, and archive. As part of the first recognized emergence of MVD in humans, the two Belgrade cases of 1967 were important and remain so over 5 decades later. That significance can be considered through several lenses that illuminate historic, sociopolitical, epizootiological/epidemiological, clinical, therapeutic, and virological implications.

Historic Considerations

The two cases of MVD described here occurred over 50 years ago shortly after two epidemiologically connected MVD episodes in West Germany that involved 29 people and included 7 deaths (46–54). Although a total of 14 MVD outbreaks have by now been documented (3, 4), thorough clinical and pathological descriptions of MVD cases are still frustratingly rare in the literature and are almost always limited to basic observations (15–40). Serial patient sampling over the course of disease with subsequent virological, molecular, and biochemical analyses (including, e.g., virus population sequencing over time), state-of-the-art intensive care unit monitoring and treatment, biopsies, autopsies, and long-term monitoring of survivors have rarely or not been performed. Due to this dearth of knowledge, any piece of information on any individual MVD case is of utmost importance for the current generation of health care providers. Unfortunately, as is frequently the case with unusual or rare diseases, these pieces of information are not easily to locate and retrieve, and in addition they are often presented in languages other than English. Here, we summarize the information on 2 MVD cases that occurred in Belgrade, Yugoslavia. These cases were first internationally presented in 1968 at the Eighth International Congress on Tropical Medicine and Hygiene in Tehran, Iran (69), and were discussed again in 1969 during the First Congress of Yugoslav Microbiologists in Belgrade, Yugoslavia (68). The primary publication on the outbreak (65) was written in Serbo-Croatian. Although indexed in PubMed, this publication cannot easily be found, as the entry is not associated with search terms that would be used in a literature search related to MVD. Unsurprisingly, this publication is

also very rarely cited in the MVD literature. Part of this publication is repeated in two book chapters written in English (64, 66), but these chapters are not indexed in PubMed. Further information on the outbreak can be found in other book chapters (70), a Serbo-Croatian conference abstract (68), a medical article written in German (67), and a dissertation written in German (47). Our work provides a detailed summary of all information provided in these publications in a single, citable, and PubMed-indexed review written in English. To build a bridge to the historical literature, we provide all citations in their original languages and throughout the text also provide original spellings of institutes, names, and designations. Most importantly, we reassessed and corrected the historical record by resolving discrepancies that unfortunately exist between the various pieces of the historical literature (see Table S2 in the supplemental material). We did so by accessing internal archives at the Institute of Virology, Vaccines and Sera "Torlak" together with the last surviving member of the core virological and clinical team that handled the 1967 Belgrade MVD outbreak (A.S.G.) (see Table S3 in the supplemental material). Unfortunately, Ž.St. died in 1996 and could not be involved in this work. Likewise, R.St. is deceased.

Sociopolitical Considerations

In contrast to the rather hyperbolic public and media response to the MVD outbreaks in West Germany (47), no public outcry or panic in Belgrade was noted. The Yugoslavian population was informed without government restriction about the events at the Institute of Immunology and Virology "Torlak," including the discovery of a novel virus, via official communication conducted by the Institute for Health Protection of the Republic of Serbia and via rather objective newspaper reports in leading Yugoslav newspapers (e.g., in Borba/Борба, the official gazette of the Yugoslav Communist Party [74]). Yugoslavian and West German authorities collaborated early on to ensure swift containment of the MVD outbreak. This collaboration included the membership of Ljubinko V. Stojković, the director of the Institute of Immunology and Virology "Torlak," in an *ad hoc* emergency panel established by the Permanent Section of Microbiological Standardization (PSMSt) of the International Association of Microbiological Societies (IAMS), which met for the first time on 10 October 1967 at the London Medical Research Council Laboratories, Holly Hill, Hampstead, London, UK (47), the transport of MVD convalescent-phase plasma from West Germany to Belgrade in person by G. May and E. Böhle from Frankfurt am Main (47, 65, 66), frequent conversations/communications between Yugoslav and West German experts (47), and finally a joint symposium on MVD in 1970 (75).

Epizootiological/Epidemiological Considerations

The first recorded appearance of MARV and MVD occurred in 1967 (49). It is well established that all human infections that occurred in West Germany and Yugoslavia during this outbreak traced back to infected grivets that had been shipped from Uganda (55–62). However, whether MARV infected the grivets in Uganda or somewhere *en route* is less clear, and how MARV infected grivets is unclear altogether. The recent discovery of MARV and RAVV in Egyptian rousettes in Ugandan caves (7, 8, 10, 13) strengthens the hypothesis that MARV infected the grivets in Uganda. However, it remains unclear how the grivets could have acquired MARV from these bats and why grivet infections, in nature or captivity, have not been documented since 1967. Additional questions arise regarding the initial infection of veterinarian Ž.St. Epidemiological investigations strongly suggest that he accidentally infected himself during grivet necropsies performed on 25 August (Fig. 1). However, it is important to mention that no evidence was obtained that these necropsied grivets actually had been infected with MARV. Gross pathological data were not published and are no longer available (anecdotally, one of the necropsied grivets had a macroscopically "changed" liver) (47), histopathological examinations were not performed, and all virus isolation attempts in grivet Vero cells from any tested grivet failed. The last result remains puzzling as Vero cells are a standard cell line for the isolation and growth of MARV and all other

filoviruses (4). The number of deaths among the imported grivets and the fact that they had direct contact among each other (importantly disputed by Stojković, who argued that there was little contact between grivets [47]) suggest that MARV serially infected animals before Ž.St. became infected. How often and when Ž.St. was in contact with the grivets are unknown, but he performed at least one additional necropsy on 30 August together with a colleague, M.P., who also had performed a necropsy by himself on 28 August. Given the highly infectious nature of MARV (4), it remains curious why no one other than Ž.St., such as animal caretakers or animal intakers and other veterinarians, became infected.

The infection of Ž.St.'s wife, R.St., has been pinpointed epidemiologically to R.St.'s contact with contaminated fomites while tending to her husband on 2 or 6 September 1967 (Fig. 1). However, filoviruses are known to be highly contagious through direct skin-to-skin contact, and it is unlikely that R.St. never touched her husband doing the initial days of his disease. In fact, in 1972, Ž.St. himself reported having had sexual intercourse with his wife on 30 or 31 August 1967, but in interviews with one of us (A.S.G.) prior to 1972, he strongly denied that any sexual intercourse had occurred.

Clinical Considerations

A comparison of the Belgrade patients to those described from Marburg an der Lahn and Frankfurt am Main reveals common themes and differences (Table 1). Generally, the Belgrade cases presented very similar disease characteristics and kinetics, adding seminal data to the first boilerplate description of "typical" MVD that emerged from all three settings, which has stood a 50-year test of time. These descriptions include generally similar incubation times, clinical symptoms and signs, and laboratory findings (although in non-Belgrade MVD patients, AST activities were typically much higher than ALT activities). Often underdiscussed are the prominent neuropsychiatric manifestations seen in these patients, including severe anxiety/agitation, sensory manifestations (dysesthesia, hyperesthesia, and paresthesia), and even hyperacusis in Belgrade patient 1. Of particular interest in the same patient are the late-onset and then persistent symptoms, signs, and ECG findings of myocarditis with a coincident new leukocytosis at a time when adaptive immune responses were likely developing. A similar late-onset myocarditis associated with atrioventricular block and a new leukocytosis were described in two patients from Frankfurt am Main (29). To our knowledge, these are the only two descriptions of these late MVD manifestations in the medical literature. We presume that similar manifestations might occur in African settings but either they are missed in challenging diagnostic settings or they occur only in patients recovering from very severe illness. On the other hand, not documented for the two Belgrade patients but seen in West German cases were late-onset secondary bacterial complications (e.g., bronchopneumonia and empyema) and common second peaks in temperature.

In the aftermath of the EVD outbreak in western Africa in 2013 to 2016, interest in filovirus persistence and clinical sequelae in survivors of filovirus disease has been renewed. Indeed, the first reports on significant sequelae of filovirus disease, virus persistence in the semen after a filovirus infection, and sexual transmission of a filovirus all go back to the 1967 MVD outbreak (17, 28, 29). Though myocarditis and tremor did persist for some weeks into Ž.St.'s convalescence, neither of the Belgrade patients had any symptoms or signs of long-term sequelae on evaluation 2 years later (66). Notably absent was the orchitis or long-term testicular atrophy described in 2/4 Frankfurt am Main male MVD survivors and in at least one male survivor from Marburg an der Lahn (17, 29, 63, 76). However, the extent to which the Belgrade patients were evaluated for long-term sequelae is unclear. For instance, were semen samples taken and evaluated for MARV antigen and full physical examinations performed, or were the patients only interviewed? The Belgrade cases are a reminder that despite severe acute illness, some survivors do not develop significant sequelae, at least in the immediate years after convalescence. Indeed, we have much to learn about the pathophysiology of sequelae after filovirus infection and its possible association with virus persistence (77). For MVD

TABLE 1 Comparison of the clinical presentations of Marburg virus disease during the epidemiologically connected episodes in West Germany and Yugoslavia

	Outbreak (references)		
Parameter	**Belgrade, Yugoslavia**	**Marburg an der Lahn, West Germany**	**Frankfurt am Main, West Germany**
References	47, 65, 66	27, 28, 47, 114	29, 47, 63
Incubation period (days)	6–7	5–7	7–9
Total no./no. with fatal outcome	2/0	24/5	6/2 (death in early organ phase); of 4 remaining, 2 with severe course and 2 with mild clinical course with resolution
No. of primary/secondary cases	1/1	21/3	4/2
Skin rash	From day 6–11 post-symptom onset, diffuse	Initially, head, trunk, hands; later expanding over body	From day 5–12 post-symptom onset; in severe cases, rash was hemorrhagic
Conjunctivitis	Initial sign, lasted 11 days (primary case)	Initial sign	Initial sign
Fever (°C)	High (37.7–39.6)	High	High (39–40)
Exanthema	Presented	Described	Hemorrhagic in a few cases
Liver	Palpable from day 10 of illness, altered enzyme values, jaundice, yellow sclerae; in secondary case, discretely enlarged	Palpable, altered enzyme values	Palpable (except in 1 patient), altered enzyme values
Respiratory signs	Persistent cough, tachypnea (for both patients)	Bronchopneumonia as secondary bacterial infection (1 patient)	Unremarkable
Kidneys	Urine with granular cylinders, albumin, blood; abnormal kidney function test; frequent urination (both patients)	Hematuria, oliguria	Proteinuria, hematuria, and oliguria in 4/6 patients
Lymph nodes	Slightly enlarged cervical lymph nodes	Enlarged cervical, axillary lymph nodes	Enlarged cervical lymph nodes
Fluid disturbances	Facial, skin edema; electrolyte imbalance; dehydration; hemoconcentration	Facial edema	Facial edema (some patients); ascites (1 patient); hypoalbuminemia (all patients)
Hematology	Early leukopenia (shift to the left) followed by leukocytosis, thrombocytopenia (90,000 mm^3), abnormal lymphocytes (6%), basophils (6%), segmented leukocytes (52–68%)	Early leukopenia (shift to the left) followed by leukocytosis, severe thrombocytopenia	Early leukopenia (shift to the left) followed by leukocytosis, severe thrombocytopenia
Gastrointestinal signs	Pharyngeal cramps; from day 7 to peak on day 11 of illness (total of 26 days), profuse, frequent diarrhea with sloughed membranes and melena as noted by positive Adler-Weber test on day 14 of illness; anorexia, hematemesis, nausea	Very persistent diarrhea, initially without blood or mucus; in a few patients followed by constipation; 2 patients with constipation from beginning	Profuse diarrhea with blood (in all except 1 patient)
Hemorrhage	On admission, blood in nostrils; later, mucosal bleeding hematemesis, melena, disseminated intravascular coagulation, uncontrolled bleeding from injection sites, requiring blood transfusion; prolonged coagulation tests	Generalized mucosal bleeding, hematemesis, melena, disseminated intravascular coagulation	Preagonal hemorrhage from all systems (in lethal outcomes)
Genital tract	Male, none; female, erythema, amenorrhea with eventual resumption of menses	Male, reddening without pruritus; female, erythema	Male, sporadic scrotal edema and redness; acute orchitis (in 2 patients)
Cardiovascular signs	From day 10 of illness, sinus tachycardia (120–145 beats/min) with muffled tones; on day 12 of illness, damage to myocardium and increased blood pressure (150/70 mm Hg); signs of myocardiopathy present weeks after discharge	Bradycardia initially; tachycardia only in fatal cases	Bradycardia in all patients; 2 with ECG abnormalities; 1 with congestive heart failure (fatal outcome)
Neurological signs	On admission, fasciculation on hands, tongue, arm tremor, hyperacusis, Kernig's syndrome, increased Babinski's reflex, nystagmus, clouded consciousness	Mental disturbances, hyperesthesia, amnesia	Mild disturbances of consciousness, apathy, somnolence; encephalitis (lethal outcomes)
Differential diagnosis	All samples of urine and stool were free of infectious particles and parasites	Dysentery, severe digestive symptoms (suspicious of *Shigella* sp. infection or leptospirosis)	Yellow fever (due to liver damage)

survivors, this gap in our understanding was obviously present in 1967 and remains 50 years later.

Therapeutic Considerations

In the last 5 decades, specific treatment of MVD patients has not advanced significantly. Despite interest in and progress toward deploying monoclonal antibodies (78, 79), direct antivirals (80–83), and small interfering RNA (siRNA) molecules (84, 85) as countermeasures in animal models, no currently licensed treatment for humans with MVD is available. Indeed, in many ways, the therapeutic milieu in 2020 is not dissimilar to the approach taken in Belgrade in 1967, necessarily focusing on supportive and symptomatic care. Differential case fatality rates in resource-limited settings (86–90) versus those with more capacity (28, 29, 32, 66) suggest a contribution of this care to disease outcome, but, as is the case with EVD (91), robust evidence to inform supportive treatment guidelines is lacking even in 2020.

Of note, the Belgrade MVD outbreak is one of only two historical examples of the use of convalescent-phase sera to ameliorate MVD (two Frankfurt am Main patients also received such sera). Specific details about source patient antibody titers in these 1967 cases are not available, and although all four patients survived, no data support the efficacy of lack thereof of the treatment. The positive outcome in all four cases supports further study of the role of MARV-specific IgG in treatment. In animal models, purified polyclonal IgG from equine antiserum and from vaccinated nonhuman primates was effective in guinea pig models (albeit at very high titers and low virus exposure doses) (92) and nonhuman primates (93), respectively. However, as tailored monoclonal antibody countermeasures are advanced (78, 79), the efficacy and safety of convalescent-phase sera for the treatment of MVD in humans are unlikely to be studied outside the context of a large outbreak. Although one should be cautious with extrapolations from one virus to another, it is of note that a nonrandomized clinical trial of EVD convalescent-phase plasma in Guinea in the setting of the 2013−2016 EVD outbreak failed to show efficacy (94–96). Therefore, the utility of convalescent-phase sera in the treatment of filovirus disease in humans remains unclear. Arguably, the two Belgrade patients may have been among the first and last patients to ever receive such sera for treatment of MVD.

Virological Considerations

In Yugoslavia, MARV isolation from grivets in cell culture (grivet Vero cells) failed, and virus isolation from patient samples in cell culture was not reported. Virus was, however, undoubtedly isolated in guinea pigs experimentally infected with patient sera or coagula, as evidenced by electron microscopic images of MARV-characteristic virions. By means of guinea pig isolation, at least four MARV isolates were obtained: from serum and coagulum taken from Ž.St. on the day of hospital admission (day 7 after symptom onset) and from serum and coagulum taken from R.St. on day 2 of symptomatic disease (64, 65). These isolates were then passaged four more times in guinea pigs, resulting in ever shorter and more lethal disease, as has been observed previously and subsequently in other laboratories (64, 65). Such passaging results in guinea pig-specific genomic adaptations in the MARV genome (97–99). Therefore, the Belgrade MARV isolates were probably guinea pig adapted.

Genomic sequencing technologies did not yet exist in 1967, and all samples from the Belgrade outbreak were destroyed during outbreak containment efforts under the guidance of the World Health Organization (WHO). Thus, while partial or complete genome sequences were determined later on for West German MARV isolates (such as MARV/Hesse isolates Cieplik [Ci67], Ratayczak, and Poppinga [Popp]) (100–102), no such sequences were determined for the Belgrade isolates. However, before the Belgrade samples were destroyed, sera from the infected guinea pigs were shared with Charles Edward Gordon Smith (1924–1991) at the Microbiological Research Establishment (MRE) (today the Defense Science and Technology Laboratory [Dstl]), Porton Down, Salisbury, Wiltshire, UK (A.S.G., personal observation) and from there with eminent

Soviet virologist Mihail Petrovič Čumakov (Чумаков Михаил Петрович) (1909–1993) at the Soviet Academy of Sciences' Institute of Poliomyelitis and Viral Encephalitides (Институт полиомиелита и вирусных энцефалитов АМН СССР) (today the Chumakov Federal Scientific Center for Research and Development of Immune and Biological Products of the Russian Academy of Sciences [Федеральный научный центр исследований и разработки иммунобиологических препаратов им. М.П. Чумакова РАН]) in Moscow, USSR (71). Whereas published records on possible UK experiments with Belgrade MARV isolates have not been uncovered, two abstracts shed some very limited light on Soviet follow-up work (71, 72). Čumakov had already received West German MARV isolates, in particular isolates Hilberger, Lüdicke, and Popp (71). In 1968, Čumakov et al. wrote:

> "Кроме того, в нашей лаборатории проводилось, с участием докт. Борджосски, серологическое исследование еще двух штаммов вируса ЦГЛ от случаев в Белграде, изолированных на морских свинках проф. Стойковичем и Боджосски [In addition, in our laboratory and with participation of Dr. Borđoški, we conducted a serological examination of two more strains of Cercopithecus hemorrhagic fever virus from the Belgrade cases isolated in guinea pigs by Profs. Stojković and Borđoški]" (71).

Čumakov et al. further elaborated that studies were performed to determine, among other things, (i) the pathogenicity of MARV to, and pathogenesis features in, nonhuman primates of two species and rodents of several species, (ii) MARV particle characteristics using electron microscopy, (iii) the effects of MARV on tissue cultures, (iv) the stability of MARV in the presence of chloroform, ether, or sodium deoxycholate, and (v) the feasibility of producing a formalin-inactivated MARV vaccine. However, whether Belgrade MARV isolates were used for any of these studies is unclear (71). The role of Borđoški in these studies is also unclear—all that can be stated today with certainty is that Borđoški officially visited Moscow in 1968 (A.S.G., personal observation).

The second Soviet abstract, published in 1971 by V. Â. Karmyševa et al. (72), emphasized again that

> "В Институте полиомиелита и вирусных энцефалитов АМН СССР в 1967–1968 гг. было выведено и изучено несколько штаммов вируса ЦГЛ (Марбург-вирус по Siegert'у) из секционных материалов от людей, умерших во Франкфрурт-те-на-Маийне, или из крови людей, заболевших в Белграде" [From 1967 to 1968, several Cercopithecus hemorrhagic fever virus (Marburg virus, according to Siegert) strains were isolated at the Soviet Institute of Poliomyelitis and Viral Encephalitides from sectional materials from people who died in Frankfurt am Main and from the blood of people who were infected in Belgrade].

The remainder of the abstract clarifies that nonhuman primate experiments were performed with MARV, but again, clarification on whether Belgrade isolates were used is lacking. After 1971, all research with filoviruses was moved from Moscow to a highly classified military laboratory in Zagorsk (today Sergiev Posad) and from there to several other institutes within the clandestine Soviet biological warfare program (103, 104). Publications on Soviet/Russian MARV research were first published again at the end of the 1980s. The Belgrade isolates have not been mentioned in the Russian literature since 1971, but there is still a chance that live viruses or inactivated, but still sequenceable, samples exist somewhere in British or Soviet repositories for future study.

APPENDIX

Institute of Virology, Vaccines and Sera "Torlak"

The Institute of Virology, Vaccines and Sera "Torlak" (Institut za virusologiju, vakcine i serume "Torlak"/Институт за вирусологију, вакцине и серуме "Торлак") is a research institute in Belgrade, Serbia (previously part of Yugoslavia) (105). The institute

has its origins in the Central Institute of Hygiene (Centralni higijenski zavod/Централни хигијенски завод) in Belgrade, which was established in the mid-1920s (106, 107) to work on the eradication of typhus and other infectious diseases within its jurisdiction. After World War II, the Central Institute of Hygiene was transformed into three federal institutes, including the Federal Epidemiological Institute (Savezni epidemiološki institut/Савезни епидемиолошки институт). On 20 September 1950, the Committee for the Protection of National Health of the Socialist Federal Republic of Yugoslavia established the Department of Virology and Immunology as part of the Federal Epidemiological Institute (107) under the leadership of Aleksandar Terzin/Александар Терзин (1911–1987) starting in 1951. Marko Borđoški/Марко Борђошки (1908–1982) headed the department starting in 1953 (108, 109). Later, the Federal Epidemiological Institute was merged with the Epidemiological-Bacteriological Institute of Serbia in Belgrade (Epidemiološko-bakteriološki institut Srbije/Епидемиолошко-бактериолошки институт Србије) as the Hygienic Institute of Serbia (Higijenski institut Srbije/Хигијенски институт Србије). The Department of Virology and Immunology was renamed the Virology Department. Routine diagnostic work on viral, leptospiral, and rickettsial infections began at that department in 1952, and the department also took on a role as the Regional Influenza Center of the WHO in Yugoslavia (108–110). Work on poliovirus vaccines started in the Virology Department in 1958 under the leadership of Ljubinko Stojković/Љубинко Стојковић (1920–1997). In 1959, the poliovirus activities were split off as a separate Enterovirus Department. Around 1961, both departments moved into a new building in Belgrade close to Torlak Hill, giving rise to the Virology Sector of the Institute of Health Protection of the Republic of Serbia (Zavod za zdravstvenu zaštitu SR Srbije/Завод за здравствену заштиту СР Србије) headed by Stojković. At the end of 1969, this sector morphed into the Institute of Immunology and Virology "Torlak"/Institut za Imunologiju i Virusologiju "Torlak"/Институт за Имунологију и Вирусологију "Торлак") (107, 108, 111), which in 2006 assumed its final name, the Institute of Virology, Vaccines and Sera "Torlak." Until the end of the last century, this sector/institute was one of the most important European manufacturers of poliovirus vaccine. During this period, "Torlak" exported poliovirus vaccine and other vaccines or serum products to more than 35 countries all over the world. As in other poliomyelitis vaccine production facilities, vaccine production at "Torlak" was based primarily on growing poliovirus in nonhuman-primate-derived primary kidney cell cultures. To establish these cell cultures, "Torlak" annually imported approximately 1,000 to 2,000 nonhuman primates caught in the wild in Africa, Asia, and South America. The animals were euthanized for kidney collection to establish cell cultures following procedures widely used at the time (trypsinization of tissues, filtration, and cell cultivation). Importation of wild nonhuman primates was already known to present a potential risk for public health, as they were known to harbor "exotic" pathogens (i.e., pathogens not endemic in Europe) that could cause human infections. Consequently, all imported animals were transported and placed into quarantine in accordance with established WHO recommendations and rules before enrolling them into the vaccine production process (112, 113). Marko Borđoški and Ljubinko Stojković both became prominent coauthors on several publications describing the MVD outbreak in Yugoslavia in 1967 (64, 65, 67–69).

SUPPLEMENTAL MATERIAL

Supplemental material is available online only.

SUPPLEMENTAL FILE 1, PDF file, 0.3 MB.

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