



Fatal bacterial CNS infections: a systematic review and a forensic case report

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ABSTRACT

Central nervous system (CNS) infections may cause sudden unexpected death when diagnosis is delayed or missed. We report a fatal case of *Streptococcus pyogenes* meningoencephalitis and systematically review post-mortem investigations of fatal bacterial CNS infections. A 57-year-old woman was found dead at home after untreated otalgia, hearing loss, purulent otorrhea, low-grade fever, asthenia, and vomiting. Autopsy showed diffuse cerebral edema, subdural empyema involving the posterior fossa, and cerebellar tonsillar herniation. Histology demonstrated acute suppurative meningoencephalitis with vasculitic injury. *Streptococcus pyogenes* was isolated from purulent material collected from the empyema; toxicological analyses were negative. The systematic review followed PRISMA 2020. PubMed/MEDLINE and Scopus were searched from database inception to 22 August 2026. Sixty-two studies describing 68 fatal bacterial CNS infections were included. The included cases showed a broad spectrum of postmortem-confirmed bacterial infections, including meningitis, meningoencephalitis, ventriculitis, brain abscess, subdural empyema, rhombencephalitis, spinal meningeal involvement, and infectious vascular complications. Postmortem pathogen-directed testing included culture, histochemical stains, antigen detection, immunohistochemistry, PCR, sequencing, MALDI-TOF identification, or equivalent methods. Autopsy remains central to diagnosing fatal bacterial CNS infections. Integration of neuropathology with postmortem pathogen-directed testing improves pathogen identification, cause-of-death determination, reconstruction of the route and mechanism of death, and infectious disease surveillance.

1. Introduction

Central nervous system (CNS) infections, including meningitis, encephalitis, and meningoencephalitis, remain important causes of morbidity and mortality worldwide despite substantial advances in antimicrobial therapy and diagnostic techniques [1,2]. The clinical presentation of these conditions is often heterogeneous and may be nonspecific, particularly in rapidly progressive or fulminant cases, leading to delayed diagnosis or, in some instances, sudden unexpected death before medical evaluation can be completed [1,2].

In fatal CNS infections, autopsy continues to represent the diagnostic gold standard for identifying the underlying pathological process and

clarifying the cause of death. In this context, postmortem microbiology (PMM) plays a crucial complementary role by enabling the identification of causative pathogens and supporting the interpretation of gross and histopathological findings [3,4]. Although PMM has historically been regarded with caution because of concerns regarding contamination, postmortem bacterial translocation, and microbial overgrowth, growing evidence supports its reliability when sampling is performed according to standardized protocols and findings are interpreted within a multidisciplinary framework integrating autopsy, histology, and microbiological data [3,4]. Recent advances in molecular diagnostics, including polymerase chain reaction (PCR), sequencing technologies, and next-generation sequencing (NGS), have further expanded the

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diagnostic potential of forensic microbiology, allowing the detection and characterization of pathogens that may remain undetected by conventional culture-based methods [4,5].

Among bacterial pathogens, *Streptococcus pyogenes* (group A streptococcus, GAS) is a major cause of invasive infections worldwide and remains associated with substantial morbidity and mortality [6,7]. Although GAS most commonly causes pharyngitis and superficial soft-tissue infections, invasive disease may present as fulminant sepsis, necrotizing soft-tissue infection, pneumonia, or, more rarely, central nervous system involvement [6,7]. Fatal invasive GAS infections may progress rapidly and unexpectedly, sometimes resulting in death before a definitive clinical diagnosis can be established [8]. Recent forensic studies have highlighted the importance of combining autopsy findings, histopathology, and PMM to accurately determine the role of *Streptococcus pyogenes* in unexpected deaths [9].

In this study, we report a fatal case of *Streptococcus pyogenes* meningoencephalitis diagnosed through integrated autopsy, histopathological, and postmortem microbiological investigations. In addition, we performed a systematic review of fatal bacterial CNS infections investigated postmortem, with particular attention to the contribution of PMM and molecular diagnostic techniques in forensic practice.

2. Case-report

A 57-year-old woman was found unresponsive on a sofa at home by her father, who had last seen her alive the previous evening. Emergency medical personnel confirmed death at the scene. Material consistent with vomitus was found in the residence. According to her general practitioner, the woman had no known history of diabetes mellitus, immunodeficiency, or other major chronic medical conditions. Routine blood tests performed approximately three to four months before death were reportedly unremarkable, and she had received seasonal influenza vaccination one month before death.

Approximately two weeks before death, she had developed otalgia and hearing loss, followed by spontaneous purulent otorrhea with partial symptom relief. She had managed the episode at home with warm olive oil, without seeking medical attention or receiving antibiotic treatment. In the days preceding death, she had also experienced low-grade fever, asthenia, and vomiting.

A medico-legal autopsy was subsequently performed. The deceased

was 165 cm tall and weighed 51 kg (body mass index $\approx 18.73 \text{ kg/m}^2$). No noteworthy findings were identified on external examination. At internal examination, the brain weighed 1146 g and showed diffuse cerebral edema, characterized by flattened gyri and narrowed sulci involving both cerebral hemispheres, with marked congestion of the pial vessels [Fig. 1a]. Extensive purulent exudate consistent with subdural empyema was observed over the brainstem, medulla oblongata, and inferior cerebellar surfaces [Fig. 1b]. The cerebellar tonsils displayed grooving at the level of the foramen magnum, consistent with tonsillar herniation secondary to intracranial hypertension. No significant macroscopic abnormalities were identified in organs outside the central nervous system. In particular, there were no findings suggestive of diabetes mellitus, chronic systemic disease, or other conditions commonly associated with impaired immune status.

Histological analysis demonstrated severe acute suppurative meningoencephalitis with multifocal involvement of the brainstem, ventricular structures, cranial nerve VIII, and cerebral cortex. The meninges overlying the pons showed dense inflammatory infiltrates [Fig. 2a]. Sections of the medulla oblongata demonstrated acute and chronic leptomeningeal inflammation with arteritis and inflammatory infiltrates [Fig. 2b]. Inflammatory involvement of the choroid plexus was observed at the level of the fourth ventricle [Fig. 2c].

The vestibulocochlear nerve (cranial nerve VIII) emerging from the pons was involved by inflammatory infiltrates, with chronic inflammatory cells more evident at higher magnification [Fig. 2d, Fig. 2e]. The pontine meninges also showed chronic periarteriolar inflammatory infiltrates [Fig. 2f]. In the right parieto-occipital cortex, intraparenchymal neutrophilic infiltrates were associated with arteriolar wall necrosis [Fig. 2g]. Additional vascular lesions included arteriolitis with inflammatory injury of the arteriolar wall adjacent to the right lateral ventricle [Fig. 2h].

Immunohistochemical analysis demonstrated CD15-positive granulocytes within the pontine meningeal inflammatory infiltrate [Fig. 3].

Overall, the neuropathological findings were consistent with severe acute bacterial meningoencephalitis associated with subdural empyema, complicated by diffuse cerebral edema and intracranial hypertension with cerebellar tonsillar herniation.

Postmortem microbiological examination was performed on purulent material collected from the subdural empyema. Culture of this material yielded *Streptococcus pyogenes*, while testing for yeasts was

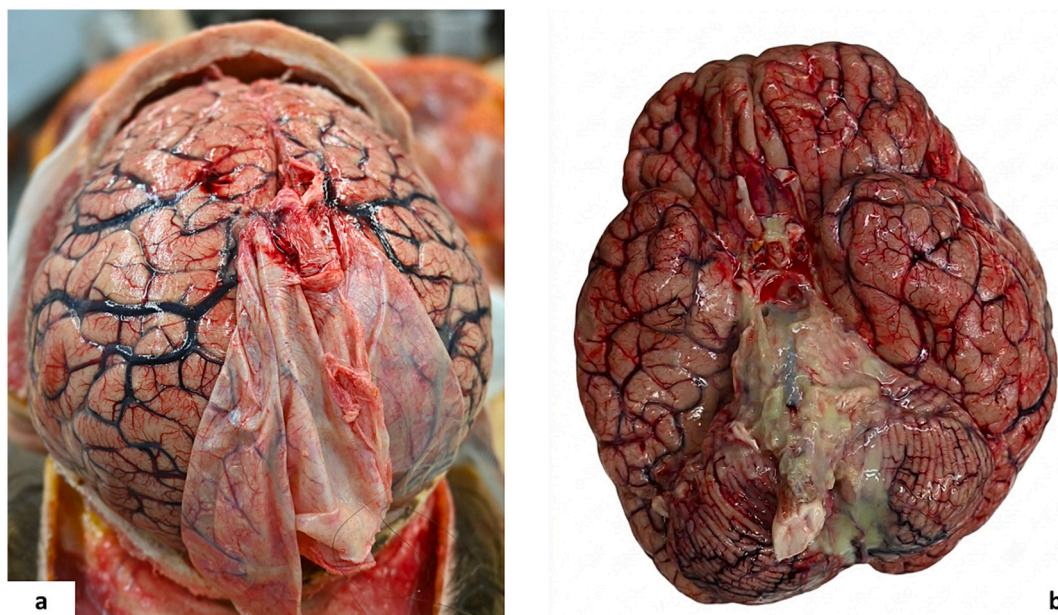


Fig. 1. Gross neuropathological findings. (A) Brain in situ showing diffuse cerebral swelling with flattened gyri, narrowed sulci, and marked congestion of the pial vessels. (B) Inferior view of the brain after removal, showing abundant purulent exudate involving the brainstem, medulla oblongata, and inferior cerebellar surfaces.

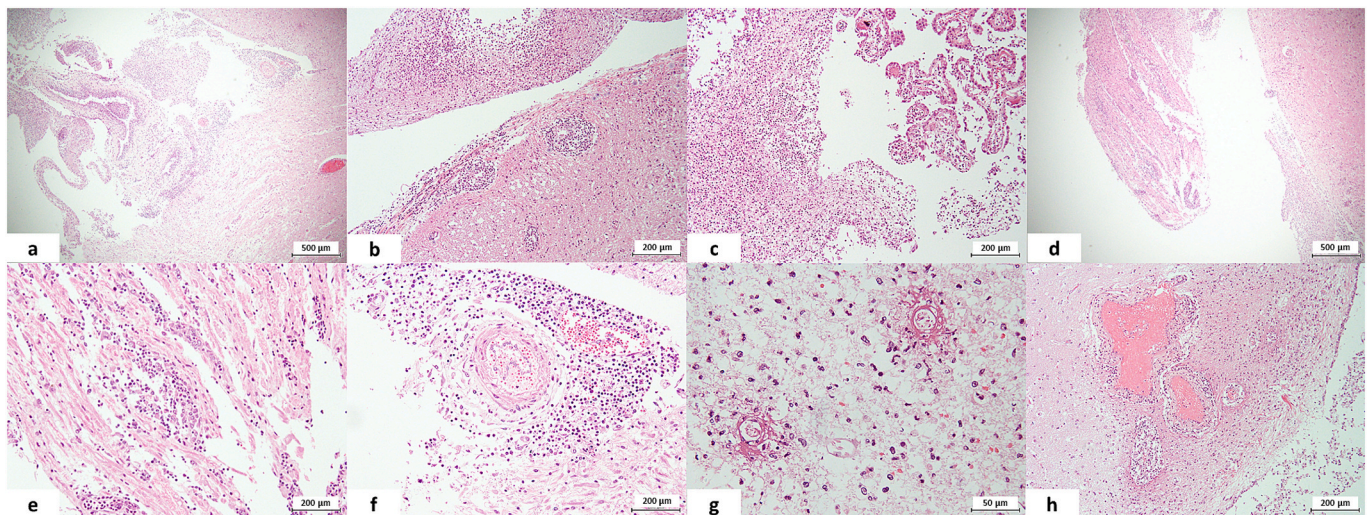


Fig. 2. Histopathological findings. (A) Pons and meninges showing inflammatory infiltrate (H&E, original magnification $\times 4$). (B) Medulla oblongata showing acute and chronic leptomenigeal inflammation with arteritis and inflammatory infiltrates (H&E, original magnification $\times 10$). (C) Fourth ventricle showing inflammatory infiltrate involving the choroid plexus (H&E, original magnification $\times 10$). (D) Vestibulocochlear nerve (cranial nerve VIII) emerging from the pons with inflammatory infiltrate (H&E, original magnification $\times 4$). (E) Vestibulocochlear nerve (cranial nerve VIII) showing chronic inflammatory cell infiltration (H&E, original magnification $\times 20$). (F) Pons and meninges showing chronic periarteriolitis inflammatory infiltrate (H&E, original magnification $\times 20$). (G) Right parieto-occipital cortex showing intraparenchymal neutrophilic infiltrates associated with arteriolar wall necrosis (H&E, original magnification $\times 40$). (H) Right lateral ventricle showing arteriolitis with inflammatory injury of the arteriolar wall (H&E, original magnification $\times 10$).

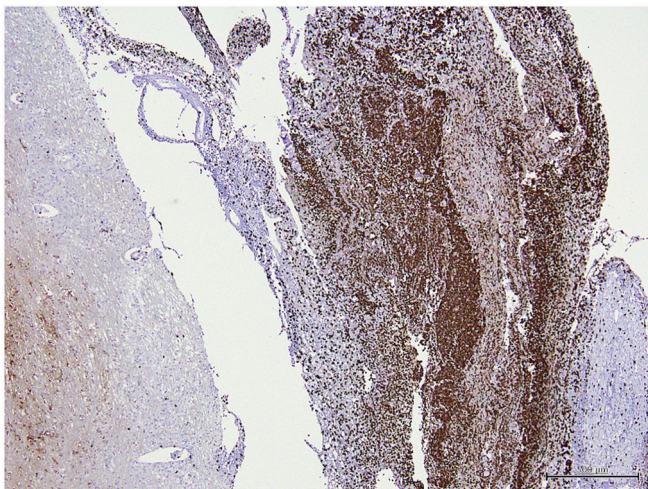


Fig. 3. Immunohistochemical findings. CD15 immunostaining highlighting granulocytes within the pontine meningeal inflammatory infiltrate (original magnification $\times 4$).

negative. Antimicrobial susceptibility testing showed susceptibility to penicillin G, erythromycin, clindamycin, rifampicin, fluoroquinolones, tetracycline, glycopeptides, linezolid, and trimethoprim-sulfamethoxazole, with no evidence of inducible clindamycin resistance. These findings established the diagnosis of fatal streptococcal meningoencephalitis associated with subdural empyema.

Gram staining and other histochemical stains for microorganisms were not available; therefore, direct histopathological demonstration of bacteria within the purulent collection could not be documented. However, the microbiological findings were consistent with the extensive purulent exudate observed at autopsy and with the severe suppurative inflammatory and vascular changes documented on histopathological examination.

Postmortem toxicological analyses performed on blood, urine, brain, and liver samples yielded negative results. Postmortem serological

testing was not performed; therefore, CRP and other inflammatory markers were not available.

The integration of microbiological, gross pathological, histopathological, and toxicological findings supported the attribution of death to acute *Streptococcus pyogenes* suppurative meningoencephalitis associated with subdural empyema, complicated by diffuse cerebral edema, intracranial hypertension, and cerebellar tonsillar herniation.

3. Methods - literature review

This systematic review was designed to identify published fatal bacterial central nervous system (CNS) infections investigated after death through autopsy or postmortem examination, neuropathological assessment, and postmortem pathogen-directed testing. The review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [10]. The objective was to assess the contribution of postmortem investigation to the diagnosis of fatal bacterial CNS infections, with particular attention to autopsy findings, neuropathological features, postmortem identification of the etiological agent, and cause-of-death attribution.

A systematic literature search was performed in PubMed/MEDLINE and Scopus from database inception to 22 August 2026. The search strategy combined terms related to CNS infection, bacterial etiology, and postmortem investigation. Terms referring to meningitis, meningoencephalitis, encephalitis, cerebritis, ventriculitis, brain abscess, subdural empyema, epidural abscess, spinal meningitis, and CNS infection were combined with general bacterial terms and selected bacterial pathogens. These terms were further combined with terms related to autopsy, necropsy, postmortem diagnosis, forensic autopsy, neuropathology, and postmortem investigation. The complete search strings are reported in Supplementary Appendix S1.

Studies were eligible when they reported original human fatal cases in which a bacterial infection involved the CNS and was considered the cause of death or a major contributor to death. Eligible conditions included bacterial meningitis, meningoencephalitis, encephalitis, cerebritis, ventriculitis, brain abscess, subdural empyema, epidural abscess, spinal meningitis or myelitis, and infectious vascular involvement of the CNS. Cases were included only when postmortem examination of the

brain, meninges, spinal cord, or other relevant CNS structures was performed, macroscopic and/or histopathological CNS findings were described, and postmortem microbiological, molecular, histochemical, immunohistochemical, or other pathogen-directed testing contributed to identification of the bacterial agent. Bacterial infections were defined broadly and included pyogenic bacteria, mycobacteria, spirochetes, rickettsiae, actinomycetes, *Nocardia* spp., and other bacterial organisms. Postmortem pathogen-directed evidence included bacterial culture, Gram stain, acid-fast bacilli staining, antigen detection, immunohistochemistry, immunofluorescence, in situ hybridization, polymerase chain reaction, broad-range bacterial PCR, 16S rRNA sequencing, targeted sequencing, metagenomic or next-generation sequencing, MALDI-TOF identification, or equivalent methods. Eligible postmortem samples included cerebrospinal fluid, brain tissue, meninges, spinal cord, abscess material, subdural or epidural pus, ventricular fluid, meningeal or cerebral swabs, blood, or other postmortem specimens. Ante-mortem microbiological findings were recorded when available but were not considered sufficient for inclusion without postmortem pathogen-directed confirmation.

Studies were excluded when they reported non-fatal cases, infections without documented CNS involvement, cases lacking postmortem

examination of the CNS, or cases without postmortem pathogen-directed evidence of bacterial etiology. Viral, fungal, protozoal, amoebic, parasitic, prion-related, and non-infectious inflammatory conditions were excluded. Cases based only on clinical, radiological, ante-mortem laboratory, or nonspecific histopathological findings were excluded. Reviews, editorials, conference abstracts, experimental animal studies, and publications without original individual human fatal cases were also excluded. When multiple cases were reported within the same publication, eligibility was assessed at the individual case level.

All retrieved records were imported into a reference management file, and duplicates were removed. Titles and abstracts were screened for relevance, and potentially eligible articles were assessed in full text. Uncertain cases were reassessed with attention to CNS involvement, postmortem neuropathological findings, the postmortem biological matrix tested, the diagnostic method used, and whether the bacterial etiology was directly demonstrated rather than inferred.

For each eligible case, data were extracted on first author, year, country, age, sex, immune status or underlying conditions, clinical presentation, ante-mortem diagnosis, type of CNS infection, bacterial agent, autopsy extent, macroscopic and histopathological CNS findings, relevant systemic autopsy findings, postmortem sample tested,

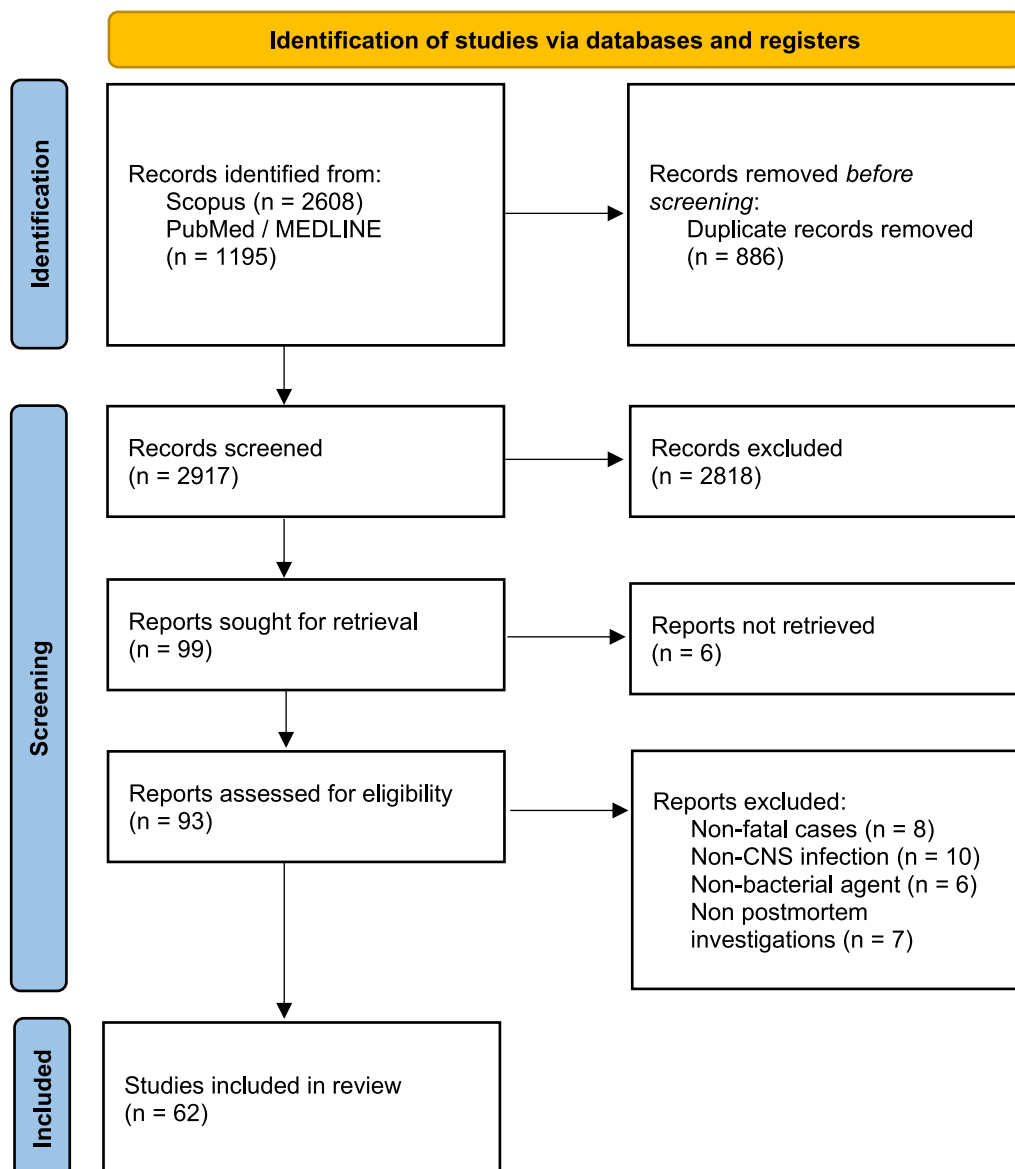


Fig. 4. PRISMA 2020 flow diagram.

diagnostic method, postmortem result, contribution of postmortem investigation, and reported cause of death. The complete extracted dataset is provided in Supplementary Table S2. Extracted data were summarized descriptively and grouped according to CNS infection type and bacterial agent. No meta-analysis was planned, and results were synthesized narratively, with semi-quantitative summaries where appropriate.

4. Results – literature review

4.1. Study selection

The database search identified 3803 records, including 2608 from Scopus and 1195 from PubMed/MEDLINE. After removal of 886 duplicate records, 2917 records were screened by title and abstract. Of these, 2818 were excluded because they were clearly unrelated to the review question. Ninety-nine reports were sought for retrieval, of which six could not be obtained. Ninety-three full-text reports were assessed for eligibility.

After full-text assessment, 31 reports were excluded: eight because they described non-fatal cases, ten because they did not document CNS infection, six because the infection was not bacterial, and seven because no postmortem investigation was reported. Overall, 62 studies were included in the systematic review, providing 68 individual fatal cases of bacterial CNS infection investigated after death [11–72] [Fig. 4].

4.2. Characteristics of included cases

The 68 included cases were published between 1937 and 2026. Most reports were single case reports or small case series, and only a minority included more than one eligible fatal case. The cases came from 21 countries, most frequently the United States, Japan, Italy, the United Kingdom, and the Netherlands. Individual case characteristics are summarized in Table 1.

The included patients were predominantly adults. Age ranged from fetal or neonatal cases to 87 years, with a median age of approximately 48 years. Ten cases involved pediatric patients younger than 18 years, whereas 58 involved adults. Sex was reported in all but one case; 43 patients were male and 24 were female.

4.3. Spectrum of CNS infections

The neuropathological spectrum was broad and included meningitis, leptomenigitis, meningoencephalitis, rhombencephalitis, ventriculitis, brain abscess, subdural empyema, spinal meningeal involvement, and infectious vascular complications. Meningitis, leptomenigitis, or meningoencephalitis represented the most frequent pattern, being present in most included cases. Brain abscesses or cerebral abscesses were also common, either as isolated lesions or in association with meningitis, ventriculitis, or systemic dissemination. Several cases showed mixed or anatomically complex patterns, including meningitis with brain abscess, ventriculitis, subdural empyema, rhombencephalitis, or spinal extension.

Vascular and pressure-related complications were frequently reported. These included cerebral infarction, arteritis, infectious aneurysm or pseudoaneurysm, hemorrhage, delayed cerebral thrombosis, brain edema, hydrocephalus, tonsillar or transtentorial herniation, and brain death. In several cases, the fatal mechanism was related not only to the infection itself but also to its complications, such as herniation, subarachnoid hemorrhage, septic shock, Waterhouse-Friderichsen syndrome, or multiorgan failure.

4.4. Etiological agents

A wide range of bacterial agents was identified. Conventional pyogenic bacteria accounted for the largest proportion of cases.

Streptococcal infections were prominent and included *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus intermedius*, *Streptococcus anginosus*, *Streptococcus equisimilis*, and other non-hemolytic or anaerobic streptococci. *Streptococcus pneumoniae* was the single most frequent species. Other pyogenic or opportunistic bacteria included *Staphylococcus aureus*, *Listeria monocytogenes*, *Klebsiella pneumoniae*, *Serratia marcescens*, *Comamonas testosteroni*, *Pseudomonas aeruginosa*, *Acinetobacter calcoaceticus*, *Escherichia coli*, *Enterobacter* spp., and *Neisseria meningitidis*.

Mycobacterial infections represented an important subgroup and included *Mycobacterium tuberculosis*, *Mycobacterium avium*-intracellulare, *Mycobacterium chimaera*, *Mycobacterium haemophilum*, *Mycobacterium tilburgii*, and a *Mycobacterium mucogenicum*-like microorganism. Actinomycetes and related organisms were also represented, including *Nocardia* spp. and *Actinomyces* spp. Anaerobic or microaerophilic organisms included *Fusobacterium necrophorum*, *Bacteroides* spp., *Peptostreptococcus* spp., and *Clostridium perfringens*. One case of fatal Lyme neuroborreliosis with postmortem molecular evidence of *Borrelia burgdorferi* DNA was also included.

4.5. Postmortem examination and pathogen-directed testing

All included cases underwent some form of postmortem investigation involving the CNS or relevant postmortem specimens. The extent of examination varied from complete autopsy to brain-only autopsy, CNS-restricted neuropathological examination, postmortem lumbar puncture, or targeted postmortem sampling. Macroscopic CNS findings included purulent exudates, basal leptomenigitis, subdural empyema, brain abscesses, ventriculitis, hydrocephalus, cerebral edema, infarction, hemorrhage, granulomatous lesions, and herniation. Histopathological findings, when reported, included acute suppurative inflammation, granulomatous inflammation, necrosis, vasculitis or arteritis, thrombosis, abscess formation, ventriculitis, demyelination, or direct visualization of microorganisms within CNS lesions.

Postmortem pathogen-directed evidence was available in all included cases, as required by the eligibility criteria. Culture was the most frequently reported diagnostic method. Postmortem cultures were obtained from cerebrospinal fluid, ventricular fluid, brain tissue, abscess material, meningeal or cerebral swabs, subdural pus, leptomeningeal exudate, or other postmortem specimens. In several cases, postmortem culture established the diagnosis after negative or non-diagnostic ante-mortem microbiological investigations.

Microscopy and histochemical stains also had an important diagnostic role. Gram stain, acid-fast bacilli staining, Ziehl-Neelsen stain, Grocott or other silver stains, PAS stain, and organism-directed histopathological assessment were used to demonstrate bacteria directly in CNS lesions. Molecular or advanced methods were reported in a smaller but diagnostically important subset of cases, including broad-range bacterial PCR, 16S rRNA sequencing, targeted sequencing, rpoB sequencing, PCR-based mycobacterial identification, MALDI-TOF identification, immunofluorescence, immunohistochemistry, and antigen detection.

4.6. Contribution of postmortem investigation

The contribution of postmortem investigation was substantial across the included cases. In several reports, autopsy established a diagnosis that had not been suspected clinically, particularly when the presentation mimicked stroke, intoxication, sudden unexplained death, eclampsia, abusive head trauma, postoperative deterioration, or non-infectious neurological disease. In other cases, postmortem examination confirmed a clinically suspected bacterial CNS infection, identified the anatomical route of spread, or clarified the fatal complication.

Postmortem investigation was especially relevant in cases with negative or incomplete ante-mortem microbiology. It allowed detection of organisms in brain tissue, meninges, ventricular pus, CSF, subdural

Table 1

Characteristics of included cases of fatal bacterial central nervous system (CNS) infections investigated through postmortem examination.

Study ID	Year	Country	Age	Sex	CNS infection type	Bacterial agent	PM diagnostic specimens	Diagnostic techniques	Reported cause of death
Ali 1977	1977	USA	35 years	Female	Subacute staphylococcal meningitis	<i>Staphylococcus aureus</i>	Purulent cerebrospinal fluid obtained ante-mortem and postmortem.	culture; Gram stain	<i>Staphylococcus aureus</i> meningitis following postpartum endometritis.
Alonso-Vega 1997	1997	Belgium	33 days	Male	Meningoencephalitis	<i>Mycoplasma hominis</i>	CSF; postmortem brain tissue.	culture	Fatal <i>Mycoplasma hominis</i> meningoencephalitis in a full-term newborn.
Aquila 2017	2017	Italy	40 years	Male	Meningoencephalitis with brain abscess and septic thromboembolism	<i>Escherichia coli</i> ; <i>Enterobacter cloacae</i> complex; <i>Acinetobacter baumannii</i> ; <i>Candida albicans</i> also isolated	Sterile swabs from brain and meninges.	culture	Fatal meningoencephalitis/brain abscess with septic thromboembolism due to otitis media.
Banerjee 1979 Case 1	1979	India	40 years	Female	Cerebellopontine angle tuberculoma with tuberculous meningitis and vascular complications	<i>Mycobacterium tuberculosis</i> / tuberculous infection	Meningeal exudate; tuberculoma tissue; pons/basilar artery sections.	AFB/Ziehl-Neelsen	Tuberculous meningitis and vascular complications arising from CNS tuberculoma.
Banerjee 1979 Case 2	1979	India	23 years	Male	Intramedullary spinal cord tuberculoma with terminal tuberculous meningitis	<i>Mycobacterium tuberculosis</i> / tuberculous infection	Intramedullary spinal cord lesion; leptomeningitic exudate around brain and spinal cord; mesenteric lymph nodes.	AFB/Ziehl-Neelsen	Intramedullary tuberculoma complicated by terminal tuberculous meningitis.
Barnicoat 1989 Case 4	1989	United Kingdom	49 years	Male	Multiple cerebral nocardial abscesses with ventriculitis	<i>Nocardia asteroides</i>	Aspirated cerebral pus; brain tissue at postmortem.	culture; Gram stain; Grocott; silver stain	Fatal cerebral nocardiosis with ventriculitis and multiple cerebral abscesses.
Bross 1991 Case 1	1991	USA	68 years	Female	Nocardial meningitis	<i>Nocardia asteroides</i>	CSF obtained before death; pus from radical mastoidectomy; postmortem CNS inflammatory material.	culture; Gram stain	Fatal nocardial meningitis.
Buscemi 2026	2026	Italy	63 years	Male	Ascending spinal and cranial subdural empyema with diffuse acute suppurative meningitis	<i>Streptococcus intermedius</i>	Postmortem purulent material involving brainstem and spinal cord; ante-mortem blood cultures and purulent CSF.	culture; MALDI-TOF	Septic shock secondary to extensive ascending spinal and cranial subdural empyema caused by <i>Streptococcus intermedius</i> , with diffuse acute suppurative meningitis and multiorgan failure
Callea 1985	1985	Italy	49 years	Male	Pontomedullary rhombencephalitis with basal meningitis	<i>Listeria monocytogenes</i>	CSF before death; necropsy brainstem and meningeal spaces.	culture; Gram stain	Fatal CNS listeriosis with pontomedullary encephalitis and basal meningitis.
Capon 1975	1975	Belgium	25 years	Female	Multiple brain tuberculomas with tuberculous meningitis	<i>Mycobacterium tuberculosis</i>	CSF obtained before death; autopsy brain/leptomeningeal/tuberculoma tissue. Premortem abscess fluid; autopsy brain abscess tissue; autopsy abscess fluid; autopsy CSF; lungs, heart valves, kidney, liver also sampled	culture; AFB/Ziehl-Neelsen	Fatal multiple brain tuberculomas with tuberculous meningitis and intracranial hypertension.
Charles 2013	2013	Canada	59 years	Male	Brain abscess	<i>Legionella micdadei</i>		culture; silver stain; PCR/sequencing	Fatal <i>Legionella micdadei</i> brain abscess with axial herniation.
Chatzaraki 2017	2017	Switzerland	48 years	Male	Brain abscess	<i>Streptococcus anginosus</i> ; <i>Staphylococcus hominis</i> also cultured	Liquid content of brain abscess.	culture	Fatal brain abscess originating from chronic frontal sinusitis.
Chung 1982	1982	USA	36 years	Female	Meningitis with brain abscess	<i>Streptococcus equisimilis</i> (Group C beta-hemolytic streptococcus)	Spinal fluid; lung; blood; pus from abscess.	culture	Fatal <i>Streptococcus equisimilis</i> meningitis with brain abscess, septicemia and pneumonia.

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Table 1 (continued)

Study ID	Year	Country	Age	Sex	CNS infection type	Bacterial agent	PM diagnostic specimens	Diagnostic techniques	Reported cause of death
Dwork 1994	1994	USA	18 months	Male	Intracerebral mycobacterial infection / CNS involvement by disseminated MAI	<i>Mycobacterium avium-intracellulare</i>	Blood and urine cultures during life; autopsy brain tissue and systemic organs.	culture; AFB/Ziehl-Neelsen	Disseminated <i>Mycobacterium avium-intracellulare</i> infection with intracerebral involvement in pediatric AIDS.
Engelen-Lee 2018 Patient 1	2018	Netherlands	39 years	Male	Pneumococcal meningitis with delayed cerebral thrombosis	<i>Streptococcus pneumoniae</i>	CSF culture during life; autopsy brain/meningeal tissue.	culture; IHC/IF/antigen	Delayed cerebral thrombosis after pneumococcal meningitis with multifocal infarction
Engelen-Lee 2018 Patient 2	2018	Netherlands	52 years	Male	Pneumococcal meningitis with delayed cerebral thrombosis	<i>Streptococcus pneumoniae</i>	CSF culture during life; autopsy brain/meningeal tissue.	culture; IHC/IF/antigen	Delayed cerebral thrombosis after pneumococcal meningitis with extensive infarction, arterial inflammation, small abscess and ventriculitis
Engelen-Lee 2018 Patient 3	2018	Netherlands	73 years	Male	Pneumococcal meningitis with delayed cerebral thrombosis	<i>Streptococcus pneumoniae</i>	CSF culture during life; autopsy brain/meningeal tissue.	culture; IHC/IF/antigen	Delayed cerebral thrombosis after pneumococcal meningitis with multifocal infarction and active meningeal/arterial inflammation
Engelen-Lee 2018 Patient 4	2018	Netherlands	68 years	Female	Pneumococcal meningitis with delayed cerebral thrombosis	<i>Streptococcus pneumoniae</i>	CSF culture during life; autopsy brain/meningeal tissue.	culture; IHC/IF/antigen	Delayed cerebral thrombosis after pneumococcal meningitis with basilar artery inflammation/thromboembolism and multifocal infarction
Eon 2026	2026	Belgium	45 years	Male	Rhombencephalitis/diffuse CNS involvement due to disseminated atypical mycobacterial infection	<i>Mycobacterium tilburgii</i>	Cerebrospinal fluid; brain biopsy specimens; lymph node biopsy; liver, spleen and cervical lymph nodes at autopsy.	AFB/Ziehl-Neelsen; PCR/sequencing	Fatal disseminated <i>Mycobacterium tilburgii</i> infection with severe neurologic complications, refractory status epilepticus, cerebral edema and bilateral uncus herniation
Ferrara 1977	1977	Italy	44 years	Male	Purulent basal leptomeningitis with Waterhouse-Friderichsen syndrome	<i>Acinetobacter calcoaceticus</i> (Mima polymorpha)	Unfixed fragments of brain and spinal cord with leptomeninges; pus from pontine cistern; kidney, lung and spleen.	culture	Sudden death due to Waterhouse-Friderichsen syndrome and purulent leptomeningitis caused by <i>Acinetobacter calcoaceticus</i> .
Fujimoto 2002 Patient 1	2002	Japan	51 years	Female	Bacterial subdural empyema / meningoencephalitis	<i>Streptococcus intermedius</i>	Postmortem CSF; leptomeningeal pus; sputum and blood cultures.	culture; Gram stain	Death from bacterial empyema caused by <i>Streptococcus intermedius</i> in a patient undergoing chronic hemodialysis.
Gimenez-Munoz 2015	2015	Spain	40 years	Male	Rhombencephalitis / necrotizing meningoencephalitis	<i>Listeria monocytogenes</i>	Blood cultures from last febrile peak; necropsy encephalon tissue.	culture; Gram stain	Fatal rhombencephalitis due to <i>Listeria monocytogenes</i> .
Mata Gonzalez 1980	1980	Spain	73 years	Female	Tuberculous brain abscess with basilar tuberculous meningitis	<i>Mycobacterium tuberculosis hominis</i>	Surgical abscess pus and capsule; CSF; autopsy brain/meninges and systemic organs.	culture; AFB/Ziehl-Neelsen	Tuberculous brain abscess complicated by basal tuberculous meningitis and disseminated miliary tuberculosis; death from aspiration bronchopneumonia.
Havlik 2006	2006	USA	38 years	Male	Bacterial meningitis with ruptured cerebral artery aneurysm	<i>Staphylococcus aureus</i>	Postmortem CSF, posterior neck purulent fluid, and blood.	culture	Ruptured cerebral artery aneurysm due to pyogenic meningitis and osteogenesis imperfecta.
Heninger 2013	2013	USA	31 years	Female	Acute pneumococcal meningitis	<i>Streptococcus pneumoniae</i>	Swab of brain surface.	culture	Acute bacterial meningitis with methamphetamine use as significant condition.
Hensby-Bennett 2019	2019	New Zealand	73 years	Female	Acute pneumococcal meningitis	<i>Streptococcus pneumoniae</i>	Postmortem urine; bacterial brain swab from subarachnoid space.	culture; Gram stain; IHC/IF/antigen	Pneumococcal meningitis.
Hodges 1937	1937	USA	9 years	Female	Acute purulent meningitis with ventriculitis	Nonhemolytic/gamma streptococcus	Ante-mortem spinal fluid cultures; postmortem brain/	culture	Acute purulent meningitis of brain and cord due to nonhemolytic/gamma streptococcus.

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Table 1 (continued)

Study ID	Year	Country	Age	Sex	CNS infection type	Bacterial agent	PM diagnostic specimens	Diagnostic techniques	Reported cause of death
Hori 1982	1982	Germany	35 weeks gestation	Not reported	Intrauterine purulent leptomeningitis	Streptococci / Gram-positive cocci	cord/ventricular exudate; left middle ear culture. Postmortem fetal brain/leptomeninges; placenta and umbilical cord.	Gram stain	Stillbirth with intrauterine purulent leptomeningitis.
Jacobs 1993	1993	Netherlands	5 years	Female	Purulent leptomeningitis / leptomeningoencephalitis	<i>Fusobacterium necrophorum</i> subsp. <i>necrophorum</i>	CSF; intracranial pus and brain tissue fragments obtained at autopsy. Postmortem CNS tissue/subarachnoid purulent CSF; paranasal sinus tissue.	culture	Fatal meningitis due to <i>Fusobacterium necrophorum</i> subsp. <i>necrophorum</i> .
Janega 2022	2022	Slovak Republic	36 years	Female	Purulent meningitis secondary to acute sinusitis	Gram-positive diplococci, presumptive <i>Streptococcus pneumoniae</i>	Postmortem CNS tissue/subarachnoid purulent CSF; paranasal sinus tissue.	Gram stain	Purulent meningitis complicating acute sinusitis.
Jevon 1994	1994	USA	8 years	Female	Purulent group A streptococcal meningitis	Group A beta-hemolytic <i>Streptococcus</i> / <i>Streptococcus pyogenes</i>	CSF; lung tissue; vesicular fluid; autopsy tissues.	culture; Gram stain; IHC/IF/antigen; PCR/sequencing	Fatal group A streptococcal meningitis with toxic shock-like syndrome.
Jin 2008	2008	USA	54 years	Male	Diffuse purulent meningitis	<i>Comamonas testosteroni</i>	Postmortem swabs from brain surface.	culture	Fatal <i>Comamonas testosteroni</i> meningitis.
Johnson 1998	1998	United Kingdom	83 years	Male	Purulent meningitis with multiple brain abscesses	<i>Serratia marcescens</i>	Postmortem meningeal pus.	culture; Gram stain	Fatal <i>Serratia marcescens</i> septicemia with meningitis, brain abscesses and myocarditis.
Kano 1999	1999	Japan	49 years	Male	Brain abscesses associated with primary CNS lymphoma	<i>Streptococcus</i> group F	Autopsy brain abscess samples.	culture; IHC/IF/antigen; PCR/sequencing	Fatal brain edema/respiratory arrest in primary CNS lymphoma with streptococcal brain abscesses.
Karakitsos 2009	2009	Greece	42 years	Male	Listerial rhombencephalitis / CNS infection	<i>Listeria monocytogenes</i>	Blood and postmortem brain tissue.	culture	Fatal listerial CNS infection with severe brain damage/brain death.
Khatib 2000	2000	USA	55 years	Male	Meningitis and multiple brain abscesses	<i>Streptococcus intermedius</i>	Lung biopsy specimen; autopsy brain abscesses/meninges.	culture; Gram stain	Fatal <i>Streptococcus intermedius</i> infection with lobar pneumonia, meningitis and multiple brain abscesses.
Koda 2003	2003	Japan	48 years	Male	Actinomycotic basilar meningitis with infectious arteritis	<i>Actinomyces</i> species	Postmortem basilar brain/meninges and left lung lesion.	culture; PAS; Grocott	Sudden death attributed to lethal cardiac arrhythmia triggered by subarachnoid hemorrhage secondary to actinomycotic necrotizing arteritis.
Koskiniemi 1982	1982	Finland	37 years	Female	Purulent meningitis / brain-stem meningoencephalitis	Microaerophilic <i>Streptococcus</i> and <i>Bacteroides</i> spp.	Pus around leptomeninges at autopsy.	culture	Fatal brain-stem meningoencephalitis with purulent meningitis.
Kristopaitis 1999	1999	USA	76 years	Male	Acute cranial and spinal meningitis with choroid plexitis	<i>Clostridium perfringens</i>	Autopsy cranial/spinal meninges; blood and incision-site swab cultures reported after death. Postmortem cardiac bioprosthesis and multiple organs; brain examined histologically; no brain specimen sent for culture.	culture; Gram stain	Fatal postoperative <i>Clostridium perfringens</i> meningitis.
Lau 2020 Patient 2	2020	Canada	75 years	Male	Granulomatous encephalitis	<i>Mycobacterium chimaera</i>	Postmortem cardiac bioprosthesis and multiple organs; brain examined histologically; no brain specimen sent for culture.	culture; AFB/Ziehl-Neelsen	Fatal <i>M. chimaera</i> encephalitis with likely central respiratory failure due to brainstem involvement.
Lau 2020 Patient 3	2020	Canada	73 years	Female	Granulomatous encephalitis	<i>Mycobacterium chimaera</i>	Postmortem brain tissue, cardiac bioprosthesis and other organs.	culture; AFB/Ziehl-Neelsen	Fatal <i>M. chimaera</i> encephalitis with likely central respiratory failure due to brainstem involvement.
Manso 1997	1997	Spain	65 years	Male	Listeria meningitis with systemic cardiovascular infection	<i>Listeria monocytogenes</i>	Postmortem pericardial pus; tricuspid valve vegetation; ante-mortem CSF/blood.	culture; Gram stain	Fatal purulent pericarditis/tamponade in disseminated <i>Listeria monocytogenes</i> infection with meningitis and endocarditis.
Martin 2006	2006	Antigua and Barbuda	16 years	Female	Brain abscess	Methicillin-resistant <i>Staphylococcus aureus</i>	Postmortem brain abscess.	culture; Gram stain	Fatal community-acquired MRSA brain abscess.

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Table 1 (continued)

Study ID	Year	Country	Age	Sex	CNS infection type	Bacterial agent	PM diagnostic specimens	Diagnostic techniques	Reported cause of death
Mathews 2014	2014	USA	87 years	Female	Rhomboencephalitis / brainstem abscess	<i>Listeria monocytogenes</i>	Postmortem brain abscess tissue; ante-mortem blood cultures.	culture; Gram stain	Fatal <i>Listeria monocytogenes</i> rhomboencephalitis.
McCann 1985	1985	United Kingdom	53 years	Male	Pyogenic meningitis	<i>Klebsiella pneumoniae</i>	Postmortem swabs of meninges and lungs; blood cultures.	culture; NGS/mNGS	Fatal <i>Klebsiella pneumoniae</i> pyogenic meningitis with gram-negative septicemia.
Motoi 1997	1997	Japan	64 years	Male	Necrotizing leptomeningeal infection / meningitis	<i>Bacillus cereus</i>	Postmortem brain/leptomeninges, choroid plexus/ventricles, stomach and liver; ante-mortem blood culture.	culture; Gram stain; PAS; Grocott; EM	Fatal necrotizing <i>Bacillus cereus</i> leptomeningeal infection with diffuse subarachnoid hemorrhage and terminal coma/respiratory arrest.
Mularski 2019	2019	Poland	2 years	Male	Meningococcal meningitis / severe meningococcal disease	<i>Neisseria meningitidis</i> group W	Postmortem CSF and blood; body fluids/tissues sampled at autopsy.	PCR/sequencing	Septic shock associated with severe meningococcal disease and Waterhouse-Friderichsen syndrome caused by group W <i>Neisseria meningitidis</i> .
Natanti 2021 Case 1	2021	Italy	77 years	Male	Disseminated mycobacterial CNS involvement	<i>Mycobacterium chimaera</i>	Postmortem bone marrow, lymph nodes, spleen, brain and liver samples.	culture; AFB/Ziehl-Neelsen	Fatal disseminated <i>M. chimaera</i> infection with progressive multiple organ failure.
Natanti 2021 Case 2	2021	Italy	70 years	Female	Granulomatous brain involvement / disseminated mycobacterial CNS involvement	<i>Mycobacterium chimaera</i>	Postmortem lymph nodes, spleen, brain and peri-prosthetic tissue.	culture; AFB/Ziehl-Neelsen	Fatal disseminated <i>M. chimaera</i> infection.
Ogg 1997	1997	United Kingdom	44 years	Male	Cerebral abscesses	<i>Nocardia asteroides</i>	Postmortem cerebral abscess material.	culture	Fatal cerebral nocardiosis in AIDS.
Okon 2013	2013	USA	71 years	Male	Clostridial meningitis	<i>Clostridium perfringens</i>	Postmortem CSF and blood cultures.	culture; Gram stain	Fatal <i>Clostridium perfringens</i> meningitis with <i>Plesiomonas shigelloides</i> sepsis.
Oksi 1996 Patient 1	1996	Finland	51 years	Female	Lyme neuroborreliosis / chronic inflammatory CNS involvement	<i>Borrelia burgdorferi</i> sensu lato	Autopsy brain tissue specimens; CSF, plasma and bone marrow specimens during life.	culture; IHC/IF/antigen; PCR/sequencing	Fatal Lyme neuroborreliosis with inflammatory/demyelinating brain changes.
Ong 2009	2009	Australia	9 months	Female	Acute bacterial meningitis	Group A <i>Streptococcus pyogenes</i>	Postmortem brain/ meninges and optic nerve sheaths; blood culture.	culture; Gram stain	Bacterial meningitis, with significant contribution from congenital disorder of glycosylation.
Onoda 1992	1992	Japan	44 years	Male	Diffuse suppurative meningitis	Group A <i>Streptococcus</i>	Postmortem cerebrospinal fluid.	culture; IHC/IF/antigen	Cerebral herniation due to acute streptococcal meningitis complicating invasive prolactinoma.
Orzechowska 2007	2007	United Kingdom	49 years	Male	Bacterial meningitis	<i>Klebsiella pneumoniae</i>	Postmortem meningeal tissue/pus and pancreatic tissue/pus.	culture	Fatal <i>Klebsiella pneumoniae</i> bacterial meningitis secondary to infected pancreatic pseudocyst.
Pacholec 2020	2020	USA	65 years	Male	Multiple brain abscesses	<i>Mycobacterium haemophilum</i>	Postmortem brain abscesses and skin samples; wrist/right finger cultures.	culture; AFB/Ziehl-Neelsen	Fatal disseminated <i>Mycobacterium haemophilum</i> infection involving CNS.
Protonotariou 2015	2015	Greece	41 years	Male	Bacterial meningitis	<i>Streptococcus agalactiae</i>	Postmortem CSF.	culture; Gram stain	Fatal <i>Streptococcus agalactiae</i> meningitis with multiple organ failure.
Sariol 2009	2009	Puerto Rico	42 years	Male	Granulomatous meningoencephalitis	<i>Mycobacterium mucogenicum</i> -like microorganism	Postmortem brain/encephalon tissue samples, including temporal lobe specimens.	PCR/sequencing	Fatal granulomatous meningoencephalitis associated with <i>M. mucogenicum</i> -like microorganism.
Senard 2018	2018	France	12 years	Male	Disseminated cerebral/cerebellar abscesses with meningitis and ventriculitis	<i>Nocardia elegans/aobensis/africana</i> complex	Postmortem brain abscess tissue; renal cyst aspirate and CSF cultures during life.	culture; Grocott; PCR/sequencing; MALDI-TOF	Fatal cerebral herniation due to disseminated nocardiosis with brain abscesses/meningitis/ventriculitis.

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Table 1 (continued)

Study ID	Year	Country	Age	Sex	CNS infection type	Bacterial agent	PM diagnostic specimens	Diagnostic techniques	Reported cause of death
Shinoyama 2012	2012	Japan	56 years	Male	Tuberculous meningitis	<i>Mycobacterium tuberculosis</i> / tubercle bacilli	Brain autopsy exudates/tissue; CSF cultures during course.	culture; AFB/Ziehl-Neelsen; PCR/sequencing	Fatal fulminant tuberculous meningitis.
Shintaku 2020	2020	Japan	72 years	Male	Actinomycotic brain abscess with ventriculitis and leptomeningitis	Actinomyces species	Postmortem brain abscess and lung/bronchial lesions.	culture; Gram stain; AFB/Ziehl-Neelsen; PAS; Grocott	Fatal acute actinomycotic brain abscess in the setting of respiratory insufficiency.
Shintaku 1991	1991	Japan	46 years	Male	Purulent mycobacterial meningitis	Acid-fast bacilli, probably <i>Mycobacterium tuberculosis</i>	Postmortem brain/ meningeal tissue.	AFB/Ziehl-Neelsen; IHC/IF/antigen	Fatal acute purulent mycobacterial meningitis in AIDS.
Williams 2019	2019	Australia	81 years	Female	<i>Pseudomonas</i> meningoencephalitis	<i>Pseudomonas aeruginosa</i>	Postmortem brain/ meningeal material, not further specified.	Postmortem examination; microbiological basis not fully detailed in extracted text.	<i>Pseudomonas aeruginosa</i> meningoencephalitis with concurrent pulmonary emboli/DVT.
Wolfe 1998	1998	USA	23 years	Female	Acute meningitis and cerebritis	Beta-hemolytic group B <i>Streptococcus</i> / <i>Streptococcus agalactiae</i>	Postmortem meninges/ brain histology; placenta culture.	culture; Gram stain	Fatal maternal beta-hemolytic group B streptococcal meningitis.
Wong 2006	2006	Hong Kong	33 years	Male	Klebsiella meningitis	Klebsiella species	Postmortem meningeal/ skull-base pus swab.	culture	Klebsiella meningitis.
Yamamoto 2017	2017	Japan	73 years	Male	Meningitis, ventriculitis and brain abscess	<i>Nocardia araoensis</i>	Postmortem pus from the left lateral ventricle.	culture; PCR/ sequencing	Fatal transtentorial herniation due to <i>N. araoensis</i> meningitis/ventriculitis/ brain abscess.
Yoshikawa 1975 Addendum case	1975	USA	62 years	Female	Bilateral subdural empyema	Peptostreptococcus intermedius	Postmortem sinus and subdural fluid; antemortem blood cultures.	culture	Fatal bilateral frontoparietal subdural empyemas associated with purulent sinusitis.
Zahed 2022	2022	USA	24 years	Male	Right frontal brain abscess with suppurative meningitis	<i>Streptococcus intermedius</i> and coagulase-negative <i>Staphylococcus</i>	Autopsy cultures and cultures at presentation.	culture	Brain death/uncal herniation due to brain abscess and suppurative meningitis secondary to chronic rhinosinusitis.

Abbreviations: AFB, acid-fast bacilli; CNS, central nervous system; CSF, cerebrospinal fluid; EM, electron microscopy; IF, immunofluorescence; IHC, immunohistochemistry; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; mNGS, metagenomic next-generation sequencing; NGS, next-generation sequencing; PCR, polymerase chain reaction; PM, postmortem.

empyema, abscess material, or systemic postmortem specimens. It also clarified pathogenetic pathways, including otogenic spread, sinus-related intracranial extension, postoperative or traumatic inoculation, hematogenous dissemination, contiguous spread from skull-base lesions, and healthcare-associated infection after cardiac surgery.

Overall, the included literature shows that fatal bacterial CNS infections investigated after death form a heterogeneous group of conditions in which postmortem examination and pathogen-directed testing frequently provide decisive diagnostic information. The available evidence remains mainly descriptive, deriving predominantly from case reports and small case series; therefore, no meta-analysis was performed. A semi-quantitative synthesis of the main demographic, microbiological, pathological, and diagnostic variables is provided in Table 2, and reporting completeness is summarized in Supplementary Table S3.

5. Discussion

Streptococcus pyogenes remains a major human pathogen responsible for a broad spectrum of diseases ranging from uncomplicated pharyngitis and skin infections to severe invasive infections associated with substantial morbidity and mortality [6]. Invasive group A streptococcal (iGAS) disease may manifest as bacteremia, necrotizing soft-tissue infection, streptococcal toxic shock syndrome, pneumonia, and, more rarely, CNS involvement [6,7]. Although meningitis and meningoencephalitis represent uncommon manifestations of iGAS infection, they are associated with high mortality and may progress rapidly despite the absence of prominent prodromal symptoms [2,7]. Furthermore, severe iGAS infections are characterized by the potential for fulminant clinical deterioration, and fatal cases may occur before a definitive diagnosis can be established [8].

The present case exemplifies these challenges. Approximately two weeks before death, the decedent had developed otalgia and hearing loss, followed by spontaneous purulent ear discharge, strongly suggesting an untreated suppurative otitis. In the days preceding death, she also experienced low-grade fever, asthenia, and vomiting, but did not undergo medical evaluation or receive specific treatment before being found dead at home.

Although the primary infectious focus could not be definitively established, the temporal sequence of symptoms strongly supports a probable otogenic origin. Otitis is a recognized extracranial focus of bacterial meningitis and may result in intracranial infection through direct extension across the temporal bone structures or through hematogenous dissemination. Recent data from a nationwide cohort of 2548 adults with community-acquired bacterial meningitis showed that otitis was present in approximately one-quarter of cases, confirming its relevance as a potential route of CNS infection [73]. In the present case, the combination of otalgia, hearing loss, purulent otorrhea, inflammatory involvement of the vestibulocochlear nerve, and extensive purulent involvement of the posterior fossa and subdural space provides converging evidence of a probable otogenic pathway. Nevertheless, in the absence of documented suppurative involvement of the middle ear, mastoid, or temporal bone, this route cannot be established with certainty.

Beyond pathogen identification, the present case highlights the diagnostic value of detailed neuropathological examination in reconstructing the mechanisms leading to death. Gross examination demonstrated diffuse cerebral edema, flattening of the cerebral gyri, narrowing of the sulci, and marked congestion of the pial vessels. An extensive purulent collection within the subdural space overlying the brainstem, medulla oblongata, and inferior cerebellar surfaces documented a subdural empyema associated with severe suppurative meningoencephalitis. Cerebellar tonsillar grooving at the level of the foramen magnum indicated downward herniation secondary to intracranial hypertension, identifying the immediate mechanism responsible for the fatal outcome.

Histopathological examination further characterized the severity

Table 2

Semi-quantitative synthesis of fatal bacterial CNS infections investigated post-mortem ($N = 68$).

Domain	Variable	Cases, n/N (%)
Included evidence	Unique studies	62
	Included cases	68
Study design	Case report / brief report / letter	57/68 (83.8%)
	Case series / case series-review	7/68 (10.3%)
	Autopsy study	4/68 (5.9%)
Demographic characteristics	Male	43/68 (63.2%)
	Female	24/68 (35.3%)
	Sex not reported	1/68 (1.5%)
	Pediatric (<18 years)	10/68 (14.7%)
	Adult (≥ 18 years)	58/68 (85.3%)
	Age, median (IQR), years	48 (35.8–65); range: newborn/fetal to 87
CNS infection pattern	Meningitis / leptomeningitis / meningoencephalitis	52/68 (76.5%)
	Brain abscess / cerebral abscess	18/68 (26.5%)
	Ventriculitis	5/68 (7.4%)
	Subdural / epidural empyema	3/68 (4.4%)
	Spinal CNS involvement	10/68 (14.7%)
	Rhombencephalitis / brainstem involvement	17/68 (25.0%)
	Tuberculoma / granulomatous CNS involvement	8/68 (11.8%)
	Infectious vascular complication	20/68 (29.4%)
Etiological category	Streptococci (including <i>S. pneumoniae</i> , GAS/GBS, viridans/anginosus group)	22/68 (32.4%)
	Staphylococci	5/68 (7.4%)
	<i>Listeria monocytogenes</i>	5/68 (7.4%)
	Mycobacteria / nontuberculous mycobacteria	14/68 (20.6%)
	<i>Nocardia</i> spp.	5/68 (7.4%)
	Actinomyces / actinomycetes	7/68 (10.3%)
	Anaerobes / clostridia / fusobacteria / bacteroides	5/68 (7.4%)
	Other Gram-negative bacteria	10/68 (14.7%)
	Other bacteria	3/68 (4.4%)
Postmortem investigation	Forensic/medicolegal autopsy	8/68 (11.8%)
	Brain-only/CNS-restricted or neuropathological autopsy	13/68 (19.1%)
	Autopsy/necropsy/postmortem examination, any extent	68/68 (100.0%)
Postmortem diagnostic specimens*	CSF / ventricular fluid	29/68 (42.6%)
	Brain tissue / brain abscess material	46/68 (67.6%)
	Meninges / leptomeninges / meningeal swabs	25/68 (36.8%)
	Subdural / epidural pus or empyema	1/68 (1.5%)
	Spinal cord / spinal material	10/68 (14.7%)
	Blood	16/68 (23.5%)
	Other systemic postmortem specimens	23/68 (33.8%)
Postmortem diagnostic techniques*	Culture	59/68 (86.8%)
	Gram stain / bacterial morphology	22/68 (32.4%)
	Acid-fast / Ziehl-Neelsen stain	14/68 (20.6%)
	Histochemical stains (PAS/Grocott/Warthin-Starry/etc.)	6/68 (8.8%)
	Immunohistochemistry / immunofluorescence / antigen test	10/68 (14.7%)
	PCR / 16S rRNA sequencing / targeted sequencing	10/68 (14.7%)
	MALDI-TOF	2/68 (2.9%)
	Metagenomic / next-generation sequencing	1/68 (1.5%)
	Electron microscopy	2/68 (2.9%)

Abbreviations: AFB, acid-fast bacilli; CNS, central nervous system; CSF, cerebrospinal fluid; EM, electron microscopy; GAS, group A *Streptococcus*; GBS, group B *Streptococcus*; IHC, immunohistochemistry; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; mNGS,

metagenomic next-generation sequencing; NGS, next-generation sequencing; PCR, polymerase chain reaction.

* Percentages may exceed 100% because multiple CNS infection patterns, diagnostic specimens, etiological categories, and diagnostic techniques could be recorded in individual cases.

and extent of the inflammatory process. In addition to dense meningeal, ventricular, cranial nerve, and parenchymal inflammatory infiltrates, vascular involvement was a prominent feature, including arteritis, periarteriolar inflammation, arteriolitis, inflammatory mural injury, and arteriolar wall necrosis. These findings reflect severe inflammation-related vascular injury and likely contributed to blood–brain barrier disruption, tissue damage, and progression of cerebral edema. The isolation of *Streptococcus pyogenes* from purulent material collected directly from the subdural empyema, together with the concordant gross and histopathological findings, strongly supported its etiological significance and minimized the possibility of postmortem contamination or incidental microbial detection. Taken together, the findings support a plausible sequence in which a probable untreated otogenic infection progressed to subdural empyema and acute suppurative meningoen- cephalitis, with severe inflammatory and vascular injury leading to diffuse cerebral edema, intracranial hypertension, cerebellar tonsillar herniation, and death.

The present systematic review provides a focused overview of fatal bacterial CNS infections in which postmortem investigation contributed not only to the documentation of CNS involvement, but also to pathogen-directed etiological confirmation. The included cases demonstrate the broad pathological spectrum of fatal bacterial CNS infections. Meningitis, leptomeningitis, and meningoencephalitis represented the most frequent patterns, but many cases showed anatomically complex disease, including brain abscess, ventriculitis, subdural empyema, rhombencephalitis, spinal meningeal involvement, granulomatous encephalitis, and infectious vascular complications. This heterogeneity is important from both clinical and forensic perspectives, because fatal bacterial CNS infections may not present as classic meningitis and may instead mimic stroke, sudden unexplained death, intoxication, post-operative deterioration, traumatic complications, or non-infectious neurological disease.

The microbiological spectrum was similarly broad. Pyogenic bacteria represented the largest group, with streptococci, including *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus intermedius*, and other streptococcal species, featuring prominently. However, the review also identified a substantial number of infections caused by less common or opportunistic organisms, including *Listeria monocytogenes*, *Nocardia* spp., *Actinomyces* spp., non-tuberculous mycobacteria, *Mycobacterium tuberculosis*, anaerobic bacteria, spirochetes, and other Gram-negative organisms. This finding emphasizes that fatal bacterial CNS infections investigated after death are not limited to common causes of community-acquired meningitis, but include rare pathogens, opportunistic infections, healthcare-associated infections, and infections occurring in immunocompromised or anatomically predisposed hosts.

A central observation of this review is that postmortem pathogen-directed testing frequently provided decisive diagnostic information. In some cases, the causative agent had already been suspected or partially identified during life, but postmortem examination confirmed CNS involvement, defined the extent of disease, or clarified the fatal complication. In other cases, ante-mortem microbiology was negative, incomplete, unavailable, or misleading, and the etiological diagnosis was established only after death through culture, Gram stain, acid-fast staining, histochemical stains, PCR, sequencing, antigen detection, immunofluorescence, or other postmortem tests. This is particularly relevant for slow-growing, fastidious, anaerobic, intracellular, or opportunistic bacteria, for which routine ante-mortem diagnostic workup may fail or may not be performed before rapid clinical deterioration.

The findings also confirm the continuing value of autopsy and neuropathological examination in fatal bacterial CNS infections. Post-mortem examination allowed the identification of purulent exudates, abscesses, ventriculitis, empyemas, granulomatous lesions, necrosis, vasculitis, thrombosis, infarction, hemorrhage, hydrocephalus, brain edema, and herniation. These findings were often essential for reconstructing the mechanism of death. In several cases, death resulted not simply from infection itself, but from secondary complications such as intracranial hypertension, transtentorial or tonsillar herniation, infectious arteritis or aneurysm rupture, delayed cerebral thrombosis, septic shock, Waterhouse-Friderichsen syndrome, or multiorgan failure.

Current forensic guidelines emphasize that PMM should not be considered a standalone diagnostic tool but rather an integral component of a multidisciplinary postmortem investigation combining autopsy findings, histopathology, microbiology, and molecular diagnostics [3,4]. Indeed, microbiological results obtained after death must always be interpreted in the context of pathological findings in order to distinguish true infection from contamination, postmortem translocation, or incidental microbial colonization [3]. The diagnostic value of PMM has also been highlighted by recent forensic studies and systematic analyses, showing that the integration of postmortem microbiological, pathological, and molecular findings can be decisive for identifying the causative pathogen and establishing the infectious nature of death [74–78]. Collectively, these observations reinforce the concept that PMM should be regarded as a fundamental component of modern forensic diagnostics, substantially increasing diagnostic accuracy when interpreted alongside autopsy and histopathological findings [3,4,9].

Another important contribution of postmortem investigation was the clarification of the anatomical route of spread. Several cases were related to otitis, mastoiditis, sinusitis, odontogenic infection, skull-base defects, postoperative contamination, penetrating trauma, hematogenous dissemination, infected prosthetic material, or disseminated opportunistic infection. In this regard, autopsy provided information that is difficult to obtain from microbiology alone: it connected the pathogen to a source, a route of dissemination, the distribution of CNS lesions, and the final pathophysiological event leading to death.

The present review therefore supports a combined diagnostic approach in suspected fatal CNS infection. Macroscopic and histopathological findings remain essential, but they should be integrated with systematic postmortem microbiological and molecular sampling. Depending on the case, relevant specimens may include CSF, ventricular fluid, brain tissue, abscess material, meningeal or cerebral swabs, subdural or epidural pus, spinal samples, blood, and extracranial sites suspected as the source of infection. The reviewed cases show that postmortem culture remains highly informative, but histochemical stains and molecular methods are particularly valuable when cultures are negative, delayed, compromised by antibiotic treatment, or when unusual organisms are involved.

Overall, the present findings emphasize that fatal bacterial CNS infections remain diagnostically challenging and pathologically diverse. Postmortem investigation is not merely confirmatory, but may establish the diagnosis, identify unexpected pathogens, reveal the route of spread, explain atypical clinical presentations, and clarify the mechanism and cause of death. For forensic and clinical autopsy practice, these data support the routine integration of neuropathological examination with targeted postmortem microbiological, histochemical, and molecular testing whenever a fatal CNS infection is suspected or cannot be excluded.

The identification of infectious causes of sudden and unexpected death has implications extending beyond cause-of-death certification. Accurate postmortem diagnosis contributes to epidemiological surveillance, improves estimates of disease burden, and may facilitate the recognition of emerging or previously unrecognized pathogens [4,5,79]. This aspect is particularly relevant for CNS infections, which are often diagnostically challenging and may remain clinically unsuspected until

postmortem investigation is performed. Furthermore, the identification of specific infectious agents may have important public health implications, including outbreak detection, monitoring of pathogen circulation, and implementation of preventive measures for exposed contacts when appropriate [3,79]. The increasing integration of autopsy findings, postmortem microbiology, and molecular diagnostics therefore not only improves diagnostic accuracy at the individual level but also contributes valuable information to broader infectious disease surveillance systems [4,5,79].

5.1. Limitations

This study has several limitations. First, the available evidence consisted predominantly of case reports and small case series, which are inherently susceptible to publication bias and limit the generalizability of the findings. Second, substantial heterogeneity was observed across studies in terms of clinical information, autopsy protocols, postmortem microbiology procedures, specimen collection, and molecular diagnostic approaches. Third, the retrospective nature of the available literature resulted in incomplete reporting of some clinical, pathological, microbiological, and molecular variables. Fourth, only articles published in English were included, introducing a potential language bias. Fifth, the search strategy combined broad syndrome-based and postmortem-diagnostic terms with selected pathogen-targeted terms, but it was not designed as an exhaustive pathogen-by-pathogen search. Therefore, rare cases may have been missed if they were indexed only under highly specific organism names and lacked standard CNS infection-related or postmortem-related terminology. Finally, because of the descriptive nature of the available evidence and the marked heterogeneity of reported variables, quantitative synthesis and meta-analysis were not feasible.

6. Conclusions

The present case and systematic review demonstrate that fatal bacterial CNS infections may present with atypical or rapidly progressive clinical courses and may remain unrecognized before death. Autopsy continues to represent the cornerstone of postmortem diagnosis. Detailed neuropathological examination provides crucial information regarding disease distribution and mechanisms leading to death, while postmortem pathogen-directed testing enhances etiological confirmation and diagnostic accuracy. The findings support a multidisciplinary approach integrating gross pathology, neuropathology, microbiology, histochemical stains, and molecular investigations for the evaluation of suspected fatal bacterial CNS infections. Beyond cause-of-death certification, accurate postmortem diagnosis may contribute to infectious-disease surveillance, recognition of unusual pathogens, and public health monitoring.

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CRedit authorship contribution statement

J.C.: Writing – original draft; Writing – review & editing. M.P.B.: Investigation (histopathological examination); Formal analysis. R.C.: Writing – review & editing. I.V.: Investigation (microbiological analyses). M.M.: Investigation (microbiological analyses). S.R.: Investigation (histopathological examination); Formal analysis. M.C.: Investigation (autopsy). A.L.S.: Investigation (autopsy); Writing – review & editing. All authors read and approved the final version of the manuscript.

Human ethics and consent to participate declarations

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Data availability

All relevant data are within the paper.

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