Acute Hemorrhagic Leukoencephalitis: A Case and Systematic Review of the Literature

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Objectives: To present a patient with acute hemorrhagic leukoencephalitis (AHLE) and a systematic review of the literature analyzing diagnostic procedures, treatment, and outcomes of AHLE.

Methods: PubMed and Cochrane databases were screened. Papers published since 01/01/2000 describing adult patients are reported according to the PRISMA-guidelines.

Results: A 59-year old male with rapidly developing coma and cerebral biopsy changes compatible with AHLE is presented followed by 43 case reports from the literature including males in 67% and a mean age of 38 years. Mortality was 47%. Infectious pathogens were reported in 35%, preexisting autoimmune diseases were identified in 12%. Neuroimaging revealed uni- or bihemispheric lesions in 65% and isolated lesions of the cerebellum, pons, medulla oblongata or the spinal cord without concomitant hemispheric involvement in 16%. Analysis of the cerebrospinal fluid showed an increased protein level in 87%, elevated white blood cells in 65%, and erythrocytes in 39%. Histology (reported in 58%) supported the diagnosis of AHLE in all cases. Glucocorticoids were used most commonly (97%), followed by plasmapheresis (26%), and intravenous immunoglobulins (12%), without a clear temporal relationship between treatment and the patients’ clinical course.

Conclusions: Although mortality was lower than previously reported, AHLE remains a life-threatening neurologic emergency with high mortality. Diagnosis is challenging as the level of evidence regarding the diagnostic yield of clinical, neuroimaging and laboratory characteristics remains low. Hence, clinicians are urged to heighten their awareness and to prompt cerebral biopsies in the context of rapidly progressive neurologic decline of unknown origin with the concurrence of the compiled characteristics. Future studies need to focus on treatment characteristics and their effects on course and outcome.

Keywords: leukoencephalitis, immunosuppressive therapy, outcome, mortality, parainfectious disease
INTRODUCTION

Acute hemorrhagic leukoencephalitis (AHLE) is an inflammatory disease of the brain, most often affecting the cerebrum, less commonly the cerebellum, the brain stem, or the spinal cord. Weston Hurst was the first to describe this syndrome in 1941, reporting two adults who developed severe and rapidly progressive encephalopathy due to hemorrhagic lesions of the white matter, histologically characterized by perivascular polymorphonuclear infiltrates, small vessel necrosis, and demyelination.

AHLE is commonly considered to be a variant of acute disseminated encephalomyelitis (ADEM) (1, 2). While the latter is mainly seen in children, the former is more common in adults. Due to the rarity of the disease and the complex diagnostic workup, AHLE is likely to be underrecognized, and underreported.

The etiology of AHLE is unknown. The initial emergence of flu-like symptoms, however, supports the hypothesis of an autoimmune process on the basis of molecular mimicry promoted by mostly viral or bacterial pathogens. In keeping with this, immunosuppressive therapy, mainly with glucocorticoids, is the mainstay of treatment. Based on case reports and small case series, mortality is reported to be as high as 70% (3, 4).

In order to heighten awareness of AHLE and its clinical context, we present an adult patient with typical features of AHLE and a systematic review of the literature aiming to analyze the diagnostic procedures, treatment options, and outcomes of AHLE.

METHODS

The digital databases PubMed and Cochrane were screened by two reviewers using predefined search terms in the advanced search mode. The term “acute hemorrhagic leukoencephalitis” was applied as a MESH term as well as in “title/abstract.” We included all papers meeting each of the following criteria: (1) the papers had to be published after 01/01/2000, (2) the papers had to be describing adult patients (age ≥ 18 years), (3) the publication had to be written in English, and (4) the design had to be either case reports, case series or cohort studies. The results are reported according to the PRISMA-guidelines (http://www.prisma-statement.org).

Details regarding search terms as well as in- and exclusion processes are outlined in Figure 1. Data regarding demographics, clinical and neuroradiologic characteristics were extracted.
FIGURE 2 | Cerebral MRI presenting the temporal evolution within 3 days (from left to right) and EEG excerpt. First row: axial T2-weighted FLAIR images showing increasing bilateral confluent widespread hyperintensities of the supratentorial white matter predominantly on the left. Second row: axial T2-weighted FLAIR images revealing new hyperintensities of the left cerebellar peduncle. Third row: axial SWI demonstrating subtle and small susceptibility artifacts in the splenium of the corpus callosum. Fourth row: axial pre- and post-contrast T1-weighted MPRAGE showing enhancement of the left parieto-occipital region. FLAIR, Fluid-Attenuated Inversion Recovery; SWI, Susceptibility Weighted Imaging; MPRAGE, Magnetization-Prepared Rapid Acquisition with Gradient Echo.
After a temporary slight improvement, the patient deteriorated rapidly with symptoms evolving to mutism, right sided hemiplegia and finally deep coma with a Glasgow coma scale (GCS) of 3 within 4 days. Repeat cerebral MRI 3 days later revealed a progression of the white matter lesions now involving the cerebellum, the ponto-medullar region, and both hemispheres with cerebral edema resulting in a mild midline shift (Figure 2; right part of the first row). In addition, susceptibility artifacts in the splenium of the corpus callosum and the pedunculus cerebelli were consistent with multiple but subtle micro bleeds. The electroencephalogram (EEG) showed intermittent epileptiform activity in both hemispheres with left fronto-temporal predominance (Figure 2; lower part).

A biopsy of the left frontal lobe showed infiltrates with neutrophilic and eosinophilic granulocytes as well as macrophages, acute focal hemorrhages, and vasculitis-like vessel lesions compatible with AHLE (Figure 3A). Despite intensive immunosuppressive therapy including intravenously administered immunoglobulins (IVIG; 0.4 g per kg body weight for 5 days), high dose glucocorticoids (methylprednisolone 2 gram per day for 3 days followed by tapering) and cyclophosphamide (15 milligram per kilogram body weight), the patient showed no improvement and remained deeply comatose with a loss of protective reflexes. Best supportive care was started 13 days after admission and the patient died shortly after.

Autopsy revealed disseminated, mainly perivascular demyelination with focal hemorrhages (Figure 3B) located in both hemispheres, the corpus callosum and the pons with cortical sparing, compatible with AHLE.

RESULTS FROM SYSTEMATIC REVIEW

Of the 255 articles screened from the digital databases PubMed and Cochrane, 43 met our inclusion criteria, each contributing one patient. Males were more commonly affected than females (67 vs. 33%) and patients’ mean age was 38 years. Detailed data extracted from these reports are outlined in Table 1.

As in our patient described above who initially suffered from a respiratory tract infection, infectious pathogens in the context of AHLE were reported in the literature in 35%, including Staphylococcus epidermidis (6), Epstein Barr virus (EBV) (11, 18, 19), Influenza H1N1 (20, 23, 28), Coxsackie B6 (33), Cytomegalovirus (CMV), Human Herpes virus 6 (HHV-6), Herpes simplex (HSV), (Varicella zoster (VZV) (42, 44), Mumps virus (16), Mycoplasma pneumoniae (8, 15, 17, 34), Plasmodium vivax (29), and Mycobacterium tuberculosis (45).

Symptoms of upper respiratory tract infections without identification of the underlying pathogen were described in 19%. In two patients, AHLE occurred after influenza vaccination (37, 41). As in our patient, who suffered from psoriasis, preexisting autoimmune disease is frequently reported in the literature, such as rheumatoid arthritis (30), inflammatory bowel disease (6, 39), primary sclerosing cholangitis (39), multiple sclerosis (1), and polyarteritis nodosa (19) was present in 12%.

Neuroimaging was performed in 91% of all cases. Uni- or bilateral hemispheric lesions were most frequently reported (in
TABLE 1 | Clinical and neuroradiologic characteristics of adult patients with AHLE.

| Ref. No. | Year of publication | Age | Sex | Infectious and non-infectious associated conditions | Neuroimaging findings associated with AHLE | Pathological CSF findings | Immunosuppressive treatment | Outcome |
|----------|---------------------|-----|-----|---------------------------------|---------------------------------|-----------------------------|--------------------------|---------|
| (5), 2000 | 34 Male | Not reported | Frontal, temporal and parietal lobe, right basal ganglia | WBC 64 (mainly mononuclear), RBC 124, protein 1.25 | Not reported | Dexamethasone 24 mg/d | full recovery |
| (6), 2001 | 41 Female | Sepsis with Staph. epidermidis | Diffuse swelling in the posterior fossa, no focal lesion (CT) | RBC 4880, protein 1.09 | Not reported | death (AHLE diagnosed post-mortem) |
| (7), 2001 | 44 Female | Upper respiratory tract infection 1 week prior | Bilateral hemispheres | WBC 103 (mainly polynuclear), protein 0.98 | Dexamethasone 15 mg/d, later Methylprednisolone 1 g/d, EVD | full recovery |
| (8), 2002 | 28 Male | Mycoplasma pneumoniae | Right hemisphere | Not reported | Decompressive craniectomy, glucocorticoids | survival (minor hemiparesis left, homonymous hemianopia to the left, neglect) |
| (9), 2003 | 19 Male | Upper respiratory symptoms 2 weeks prior | Bilateral posterior hemispheres, splenium of corpus callosum | Not reported | Dexamethasone | death |
| (10), 2004 | 57 Female | Flu-like symptoms 7 days prior | Frontal and temporal lobes | WBC 58 (mainly mononuclear), protein 2.85 | Methylprednisolone 1 g/d | survival (global aphasia, tetraparesis) |
| (11), 2004 | 28 Male | EBV (EBV DNA in CSF and brain biopsy) | Bilateral temporal lobes, thalamus | WBC 24 (mainly mononuclear), protein 0.65 | Dexamethasone 16 mg/d | death |
| (12), 2005 | 43 Male | Upper respiratory tract infection 2 weeks prior | Frontal and temporal lobes, generalized edema | RBC 37, protein 0.75 | Dexamethasone, EVD | survival (mild left hemiparesis) |
| (13), 2005 | 42 Female | Not reported | Bilateral frontal lobes, corpus callosum, left thalamus, capsula interna | WBC 2100 (mainly polymorphonuclear), protein 1.76 | Prednisolone | survival (with residual neurological deficits) |
| (14), 2006 | 22 Female | Not reported | Bilateral hemispheres | Not reported | Methylprednisolone 1 g/d | full recovery |
| (15), 2007 | 31 Male | Mycoplasma pneumoniae | Not reported | Elevated myelin basic protein, cell count, and protein not reported | Dexamethasone, plasmapheresis, EVD, decompressive craniectomy | survival (slight upper extremity tremor) |
| (16), 2009 | 30 Male | Mumps | Parieto-occipital lobes, thalami, cerebellum, brainstem | Not reported | Methylprednisolone | death |
| (17), 2009 | 62 Male | Mycoplasma pneumonia 2 weeks prior | Right cortex, left corpus callosum, pons, mesencephalon | Normal | Dexamethasone 32 mg/d, plasmapheresis | survival (left hemiplegia) |
| (18), 2010 | 20 Male | EBV (PCR brain biopsy) | Right temporal lobe | WBC 14 (mainly mononuclear), protein 1.6 | Decompressive craniectomy, EVD | full recovery |
| (19), 2010 | 76 Male | EBV (PCR CSF) polyarteritis nodosa | Cerebellum | WBC 10 (mononuclear), protein 0.78 | Methylprednisolone 500 mg/d | survival |
| (20), 2010 | 40 Male | Influenza H1N1 | Bilateral hemispheres | Protein 2.4, RBC 157 | Not reported | survival (severely disabled) |
| (21), 2010 | 21 Male | Not reported | Pons | WBC 25, protein 0.7 | Methylprednisolone 1 g/d, plasmapheresis | death |
| (22), 2011 | 25 Male | Not reported | Bilateral hemispheres, brainstem, and cerebellum | Protein 0.53 | Methylprednisolone | survival with mild left hemiparesis |
| (23), 2011 | 56 Female | Influenza H1N1 | Bilateral cerebral hemispheres, right striatum | RBC 90, WBC 8 (mononuclear), protein 0.51 | Methylprednisolone 500 mg/d | survival (mild action tremor) |

(Continued)
| Ref. No. Year of publication | Age | Sex | Infectious and non-infectious associated conditions | Neuroimaging findings associated with AHLE | Pathological CSF findings | Immunosuppressive treatment | Outcome |
|-----------------------------|-----|-----|----------------------------------------------------|------------------------------------------|--------------------------|-----------------------------|---------|
| (24), 2011 70 Male          | 70  | Male | Non-specific abdominal pain with fever 1 week prior | Both cerebral hemispheres, brainstem, medulla oblongata | WBC max. 267 (mainly polymorphonuclear), RBC max. 400, protein max. 72 | Methylprednisolone 1 g/d, IVIG | death |
| (25), 2011 37 Male          | 37  | Male | Not reported | Cerebellum, medulla oblongata | WBC max. 700 (mainly mononuclear), RBC max. 100, protein max. 1.56 | Glucocorticoids survival (right-sided weakness, ataxia and dysarthria) | death |
| (26), 2011 23 Male          | 23  | Male | Not reported | Pons, medulla oblongata, proximal spinal cord | WBC 20 (mononuclear), protein 0.69 | Methylprednisolone 1 g/d, followed by prednisolone 40 mg/d | death |
| (27), 2012 51 Male          | 51  | Male | Gastroenteritis 2 weeks prior | Bilateral hemispheres | Not reported | Dexamethasone death | |
| (29), 2014 27 Male          | 27  | Male | Influenza H1N1 | Bilateral occipital and parietal lobes | WBC 1400 (mainly polymorphonuclear), protein 1.2 | Prednisolone death | |
| (29), 2013 75 Male          | 75  | Male | Rheumatoid arthritis, hypothyroidism | Medulla oblongata, pons, cerebellum | WBC 90 (mainly polymorphonuclear), RBC 101, protein 1.84 | Not reported death | |
| (30), 2014 39 Male          | 39  | Male | Flu-like symptoms 3 days prior | Normal (CT) | WBC 365 (mainly mononuclear), RBC elevated, protein 4.66 | Not reported death | |
| (3), 2014 24 Female         | 24  | Female | Autoimmune myopathy | Right frontal lobe | Not reported | Decompressive craniectomy dexamethasone, plasmapheresis survival (severely disabled) | |
| (3), 2015 48 Male           | 48  | Male | Pneumonia, viral myocarditis | Not performed | Not performed | Not reported death (found dead) | |
| (1), 2015 21 Female         | 21  | Female | Multiple sclerosis | Bilateral basal ganglia | Protein 1.2 | Not reported survival (severely disabled) | |
| (3), 2016 34 Female         | 34  | Female | Upper respiratory symptoms 6 weeks prior possibly due to Coxsackie B6 virus | Pons, right cerebellum, fronto lobe, bilateral hippocampi | Protein 0.48 | Methylprednisolone, IVIG death | |
| (34), 2016 27 Male          | 27  | Male | Mycoplasma pneumoniae (PCR of brain biopsy) | Right frontal and parietal lobe | Not reported | Dexamethasone 12 mg/d, decompressive craniectomy, partial frontal lobectomy, EVD death | |
| (35), 2016 44 Male          | 44  | Male | Snake bite (Russell's viper) | Frontal, parietal and temporal lobes | Not reported | Not reported full recovery | |
| (36), 2013 25 Female        | 25  | Female | Upper respiratory tract infection 2 weeks prior | Brainstem, corpus callosum | Protein 0.65 | Methylprednisolone 1 g/d, plasmapheresis, mannitol survival (severely disabled) | |
| (37), 2014 33 Female        | 33  | Female | Influenza vaccination 2 weeks prior | Spinal cord (C7−T11) | WBC 55, RBC 2050 | Methylprednisolone 1 g/d, IVIG survival (paraplegia) | |
| (38), 2014 33 Female        | 33  | Female | None | Right fronto-parietal and temporoparietal lobes | Normal (after 26 days of treatment) WBC 45 (mainly polymorphonuclear), few RBCs, protein 0.51 | Methylprednisolone 16 mg/d, Dexamethasone survival (left-sided apraxia) | |
| (4), 2017 19 Male           | 19  | Male | Isolated fever for 2 weeks | Left parietal, occipital and frontal regions, corpus callosum, left basal ganglia | | Methylprednisolone, IVIG, cyclophosphamide, rituximab, plasmapheresis, craniectomy, hypertonic saline death | |
TABLE 1 | Continued

| Ref. No. Year of publication | Age | Sex | Infectious and non-infectious associated conditions | Neuroimaging findings associated with AHLE | Pathological CSF findings | Immunosuppressive treatment | Outcome |
|-----------------------------|-----|-----|-----------------------------------------------|-------------------------------------------|---------------------------|----------------------------|---------|
| (39), 2017                  | 36  | Female | Pregnancy, colitis ulcerosa, primary sclerosing cholangitis | Frontal lobes, corpus callosum, basal ganglia | RBC 110, protein 0.52 | Methylprednisolone, plasmapheresis | death |
| (40), 2017                  | 36  | Male | Not reported | Not performed | Not reported | None | death (AHLE diagnosed post-mortem) |
| (41), 2018                   | 70  | Male | Influenza revaccination 3 days prior | Bilateral hemispheres, corpus callosum, posterior brain stem | WBC 199, (mainly polymorphonuclear), protein 1.74; follow-up CSF acellular, protein 8.53 | Methylprednisolone 1 g/d, plasmapheresis | death |
| (2), 2018                   | 25  | Female | Flu-like symptoms 3 weeks prior | Cerebellum | WBC 13 (mononuclear), protein 2.86 | Glucocorticoids, plasmapheresis, decompressive craniectomy, VP-shunt | survival (nystagmus, minimal dysarthria) |
| (42), 2019                  | 63  | Male | HSV (PCR from CSF) | Bilateral fronto-temporo-parietal hemispheres | WBC 58 (mainly polymorphonuclear), RBC 70, protein 0.7 | Dexamethasone 0.15 mg/kg body weight/day, methylprednisolone 1 g/d | survival (severely disabled) |
| (43), 2019                  | 42  | Male | Cough and fever about 1 week prior | Brainstem, especially right pons, right temporo-occipital hemorrhage | Not reported | Not reported | death |

Units: cell count (RBC/WBC), number per microliter; protein, gram per liter.
CSF, cerebrospinal fluid; WBC, white blood cells; RBC, red blood cells; IVIG, intravenous immunoglobulins; EVD, external ventricular drainage; VP-shunt, ventriculo-peritoneal shunt; PCR, polymerase chain reaction.

65%), whereas isolated lesions of the cerebellum, the pons, the medulla oblongata, or the spinal cord without concomitant hemispheric involvement were rare (16%).

CSF analysis was reported in 72%. As seen in the CSF of our patient, the most frequent finding reported in the literature was an increased protein level (87%). WBC was elevated in 65% (of which 50% mainly mononuclear and 40% mainly polymorphonuclear), RBC in 39%.

A histologic diagnostic work-up was performed in 58% of patients (biopsy in 26%, autopsy in 35%, both biopsy and autopsy in 1 patient). In all cases providing histologic work-up, the findings supported the diagnosis of AHLE.

Treatment was described in 79%. Glucocorticoids were the most common immunosuppressive therapy applied (97%), followed by plasmapheresis (26%), and intravenous immunoglobulins (12%). In one patient, the use of cyclophosphamide and rituximab was reported. However, a clear temporal relationship between immunosuppressive therapy and the patients' clinical course could not be established in most case reports.

Overall mortality was 46.5%. Fourteen percentage of patients made a full recovery, whereas 39.5% survived with mild to severe neurological impairment.

Table 2 presents a comparison of clinical, neuroradiologic, and laboratory differences between AHLE and ADEM based on the data of our systematic review and recent case reports and reviews regarding ADEM.

DISCUSSION

AHLE is a rare disease with a rapidly progressive course and prompt recognition is crucial. However, since no evidence-based diagnostic criteria exist, diagnosis is challenging. The limited number of cases described in the literature, likely reflecting the low incidence and/or underreporting, calls for heightened awareness in the context of patients developing acute cerebral inflammation of unknown origin. Since we could not identify formal studies and our insights are based on case reports only, the level of evidence regarding the clinical, neuroimaging, and laboratory characteristics remains very low. However, as mentioned above, our patient presented many of the typical clinical features of AHLE as described in the literature that may assist in the diagnostic workup as follows:

First, a preceding or concomitant infection is reported in more than 50%, with different viruses being the most commonly reported pathogens, for example EBV, mumps, VZV, HSV, HHV-6, and influenza. In 19% of all patients with AHLE, symptoms of a non-specific upper respiratory tract infection without identification of an underlying pathogen are described, as was the case in our patient.

Second, the fact that the illness emerged in a male adult person is typical. In contrast to ADEM, which is more common in children and teenagers (33), AHLE mainly affects adult patients. Moreover, our literature review shows a male preponderance of 67%.
### TABLE 2 | Comparison of main clinical, neuroradiologic, and laboratory characteristics between AHLE and ADEM.

|                      | ADEM                                                                 | AHLE                                                                 |
|----------------------|----------------------------------------------------------------------|----------------------------------------------------------------------|
| **Epidemiology**     | - More common in children                                           | - More common in adults                                              |
|                      | - Incidence 0.3–0.6 per 100,000 per year (46)                        | - Incidence unknown                                                  |
|                      | - Male predominance (46)                                             | - Male predominance (see Table 1)                                    |
|                      | - More common in children and teenagers (33)                         |                                                                      |
| **Clinical findings**| **Symptoms**                                                         |                                                                      |
|                      | - Focal neurological symptoms according to the location of lesions   | - Focal neurological symptoms according to the location of lesions   |
|                      | - Unspecific encephalopathy (12)                                     | - Symptoms and signs of elevated intracranial pressure possible (12) |
| **Radiological**     | **FLAIR**                                                            |                                                                      |
|                      | - Hyperintense lesions of the white matter (12)                      | - Larger lesions, confluent                                          |
|                      | **SWI/T2**                                                           | - Significant edema with space-occupying effect (9, 12)              |
|                      | - no data                                                            | - (Petechial) hemorrhages (12)                                       |
| **Laboratory and**   | **CSF**                                                              |                                                                      |
|                      | - Protein increased in 23–62% of pediatric patients (46)             | - Granulocytic pleocytosis (12)                                      |
|                      | - Lymphocytic pleocytosis (12, 25)                                   | - Elevated protein in 87% (see Table 1)                              |
|                      |                                                                     | - Normal glucose (12)                                               |
|                      |                                                                     | - Possibly erythrocytes/ferritin elevated                            |
|                      |                                                                     | - Neutrophil-predominant leukocytosis (12)                            |
|                      |                                                                     | - Necrosis of small vessels (12)                                     |
|                      |                                                                     | - Perivascular fibrin exudation (31)                                  |
|                      |                                                                     | - Hemorrhages (“ring-and-ball”) (9)                                  |
|                      |                                                                     | - Infiltration with neutrophils and macrophages (31)                 |
|                      |                                                                     | - Demyelination in later stages (31)                                 |
| **Peripheral blood** | - No leukocytosis (12)                                               | - Possible thrombocytopenia                                           |
| **Histopathology**   | - Perivascular demyelination with lymphocytic infiltration (9)      | - Unfavorable                                                        |
|                      |                                                                     | - Complete remission in 14% (see Table 1)                            |
|                      |                                                                     | - Surviving patients with significant neurological sequelae (12)     |
|                      |                                                                     | - Mortality 46.5% (see Table 1)                                      |

**Treatment options**

- Glucocorticoids
- IVIG
- Plasmapheresis
- Cyclophosphamide, rituximab
- Mortality 1–3% (48)
- Complete remission in 60–80% (12)
- Partial remission in 11% (12)

**Prognosis**

- Mortality 1–3% (48)
- Complete remission in 60–80% (12)
- Partial remission in 11% (12)

ADEM, acute disseminated encephalomyelitis; AHLE, acute hemorrhagic leukoencephalitis; FLAIR, Fluid attenuated inversion recovery; SWI, susceptibility weighted imaging; CSF, cerebrospinal fluid; IVIG, intravenously administered immunoglobulins; numbers in brackets, corresponding references.

Third, the clinical course with rapid neurological decline eventually leading to coma and death also suggests AHLE. In the literature, mortality is mentioned to be as high as 70% (3, 4). However, in our review of the literature, we found an overall mortality of 46.5%, which is substantially lower. Moreover, 14% of patients made a full recovery and returned to their premorbid neurological baseline (3, 5, 7, 14, 18, 35), and 11% survived with only minor neurological sequelae (2, 12, 15, 23, 38). The reason for the better outcome in this systematic review compared to previous studies (3, 4) remains unclear. The fact that aggressive immunosuppression was described in a large proportion of cases, however, suggests a treatment-related improvement. Unfortunately, if and to what extent aggressive immunosuppression influences outcome cannot be determined by our data and other factors that may play an important role regarding disease control remain to be uncovered.

The most frequently discussed pathomechanistic hypothesis is an autoimmune process promoted by cross reactivity (i.e., molecular mimicry) between human myelin and viral or bacterial antigens, but the exact mechanisms remain to be elucidated (33).

Diagnosis of AHLE mainly relies on neuroimaging, cerebrospinal fluid (CSF) analysis and histopathology. Due to the lack of formal studies, guidelines defining diagnostic algorithms are lacking, and cannot be drawn from current data. Furthermore, most clinical scenarios described in the literature encompass symptoms and signs that may prompt the clinician to suspect ADEM. While single clinical characteristics do not reliably differ between AHLE and ADEM, the concurrence of multiple symptoms, and signs may facilitate the distinction between these two entities. In this context, Table 2 presents a compilation of different symptoms and diagnostic findings that are most discriminative between AHLE and ADEM. However, as the syndromatic appearance and clinical course of AHLE and ADEM are often indistinguishable, treatment options are equal, and the body of evidence regarding the latter is limited for both entities, the need for a reliable differentiation seems questionable.

Brain MRI is crucial and typically reveals confluent white matter lesions with significant edema, space-occupying effects, and petechial hemorrhages (12, 38). The location of the lesions seems highly variable. Uni- or bilateral hemispheric involvement is seen in nearly two third of patients, but other distributive patterns have been described. The most useful aspect on cerebral MRI in differentiating AHLE from ADEM is, however, the presence of intraparenchymal hemorrhages.

Third, the clinical course with rapid neurological decline eventually leading to coma and death also suggests AHLE.
While infectious encephalitides are more frequent and may represent an important differential diagnosis to AHLE, their diagnosis is usually less challenging, as multiplex PCR assays and whole genome sequencing approaches in the cerebrospinal fluid allow rapid detection of several infectious pathogens including HSV type 1, the most commonly identified cause of sporadic encephalitis worldwide that mostly affects the temporal lobe and limbic region (47). A study of adult immune competent patients with encephalitis who had temporal lobe abnormalities found that bilateral temporal lobe involvement was associated with lower odds of HSV encephalitis compared to all other etiologies (48). Moreover, patients with Herpes encephalitis were more likely to be older and white, and to present acutely and with fever, seizures, and upper respiratory symptoms. In addition to the bilateral temporal lobe involvement, lesions outside the temporal lobe or limbic region suggested alternative diagnoses and thus may also help to differentiate Herpes encephalitis from AHLE. Early recognition is crucial, as treatment of the former entity is effective with the intravenous administration of aciclovir, as well as screening for and treatment of limbic seizures and status epilepticus—both well-known complication of Herpes encephalitis (49).

Although histopathologic examination was only described in 58% of the cases included in our review, typical features include infiltration with granulocytes and macrophages, necrosis of small vessels and hemorrhages in a “ring and ball” pattern (9, 12, 50). Circumscribed perivascular demyelination seems to occur in cases with a prolonged course of disease, whereas in patients with a fulminant development of AHLE leading to death within 1–2 days from onset, demyelination is usually not (yet) present (31).

Treatment aims at attenuating the autoimmune process believed to cause AHLE, at avoiding secondary neurological damage due to intracranial hypertension and breakdown of the blood-brain-barrier, and at preventing infectious complications, such as pneumonia due to aspiration, that may further promote systemic inflammation.

CONCLUSION

Although our systematic review of the literature revealed a lower mortality than previously reported, acute hemorrhagic leukoencephalitis remains a life-threatening neurologic emergency with high mortality. Diagnosis is challenging as the level of evidence regarding the diagnostic yield of clinical, neuroimaging, and laboratory characteristics remains very low. Hence, clinicians are urged to heighten their awareness and to prompt cerebral biopsies in the context of rapidly progressive neurologic decline of unknown origin with the concurrence of the compiled characteristics. Future studies need to focus on treatment characteristics and their effects on course and outcome.

ETHICS STATEMENT

Written informed consent was obtained from the patient’s family for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

PG, MS, and RS planned the work, acquired the data, and wrote the manuscript. GD, KT, SR, SM, and JF interpreted the data, revised the manuscript and substantially contributed to the inaugural draft. All authors approved the final submitted version.

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