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Tick-borne encephalitis in Europe: a brief update on epidemiology, diagnosis, prevention, and treatment

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ABSTRACT

Tick-borne encephalitis (TBE) is an emerging health threat that is spreading in many parts of Europe. The mix of socio-economical, ecological and climatic factors as well as the presence of more susceptible hosts is actively contributing to the increasing number of TBE reported cases. TBE is an important cause of central nervous system (CNS) infection that can result in long-term neurological sequelae and even death. Diagnosis of TBE relays mainly on high clinical suspicion confirmed by serological and molecular assays both on serum and cerebrospinal fluid (CSF) with an ancillary role for neuroimaging in supporting the diagnosis. No specific antiviral treatment is currently available for TBE; indeed, supportive treatment as well as intensive care and assisted ventilation in severe forms may be needed. Because of limited option for TBE treatment, of crucial importance is effective vaccination to prevent disease-related morbidity and mortality.

Due to expanding proportion of subject possibly exposed to TBE (and new populations such as: unaware travellers to TBE-endemic areas and immunocompromised patients), we performed a comprehensive review of TBE epidemiology, clinical presentation, current available diagnostic tools and treatment.

1. Introduction

Tick-borne encephalitis (TBE) is an important cause of central nervous system (CNS) infection that can result in long-term neurological sequelae and even death [1]. Descriptions of a disease compatible with TBE appeared in Austria in the early 1930s for the first time, although isolation of the responsible virus was not reported until 1937 in the former Soviet Union and 1948 in Europe [2].

TBE is caused by the tick-borne encephalitis viruses (TBEV) serocomplex that consists of three subtypes: (1) the European (TBEV-Eu); (2) Siberian (TBEV-Sib); and (3) Far Eastern (TBEV-FE). TBEV are members of the genus flavivirus, family Flaviviridae, with an unsegmented, positive-stranded RNA genome [2]. The TBEV genomic structure consists of a single open reading frame encoding for one polyprotein, which is the precursor of three structural proteins — E (envelope), C (capsid) and M (membrane) — and seven non-structural proteins [3]. TBEV is mainly transmitted by infected ticks or by unpasteurized dairy products [2]. In the natural environment, TBEV circulates between ticks and various wild vertebrate hosts, such as rodents, hedgehogs and moles that act as reservoirs and amplifier hosts [4]. Horizontal transmission between ticks and vertebrates is necessary for sustained endemicity of TBE; in fact, vertical transovarially transmission is inefficient [4]. Ticks' larvae and nymphs may get infected through viremic animal or by co-feeding next to an infected tick [4]. Vector activity influences the seasonality of TBE, in fact human infections tend to be more frequent in Europe during feeding peak of ticks: from late spring until first months of autumn. TBE is currently endemic in 27 European countries with thousands of human cases each year; however, the actual incidence of TBE is estimated to be significantly higher, because mild cases remain often undiagnosed. Males adults, between 45 and 64, are the most touched by TBE (male:female ratio 1.4:1) probably due to recreational exposure, such as berry and/or mushrooms peaking, and occupational exposure or outdoor sport activities such as biking [5,6]. Between symptomatic patients, around 33% of the infected with TBEV, the most common presentation is aseptic meningitis (50%), follow by meningoencephalitis (40%) or meningoencephalomyelitis (10%) [1,7,8].

From 1974 to 2003, a 400% increase in TBE morbidity had been observed in Europe and TBEV can now be found in regions that were previously unaffected [9,10].

The aim of this article is to give a comprehensive review of TBEV epidemiology, clinical presentation, current available diagnostic tools and treatment.

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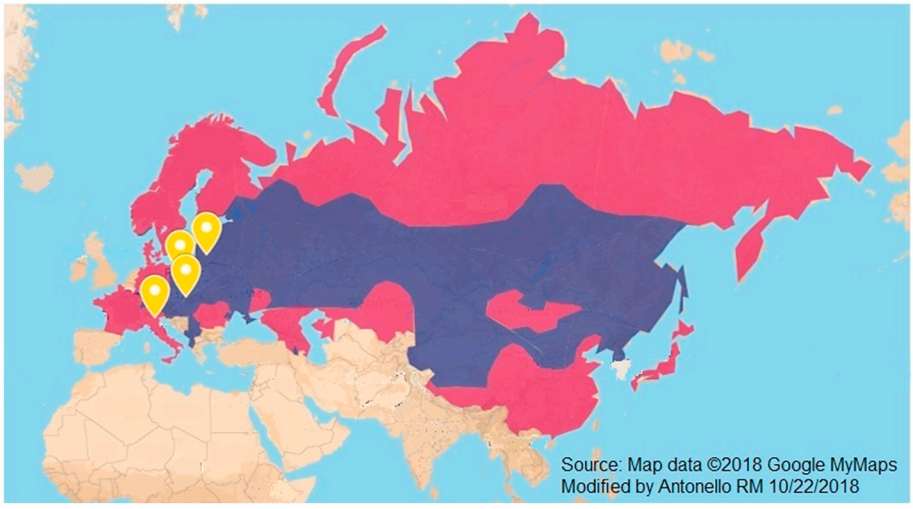

Fig. 1. Epidemiology of TBE: The blue area indicates the so-called "TBE belt". The red area indicates regions at risk. Yellow spots indicate states with an increased number of notifications in the past two years. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

2. Methods

On 17 July 2018 we performed a MEDLINE/PubMed search. The complete search string was as follows: "((Tick-borne) AND encephalitis) AND ("2010/01/01"[Date - Publication]: "3000"[Date - Publication])". Of the 1224 papers identified, 1138 were excluded by title/abstract screening. The full-text of the remaining 86 papers and of their pertinent references (including also articles published before 2010) was then reviewed and discussed, and the final decision about which papers consider for inclusion in the present review was made upon the subjective impression of the authors. The text was ultimately organized in the following major paragraphs: (i) "epidemiology"; (ii) "clinical presentation; (iii)" diagnosis"; (iv) "prevention and treatment".

3. Epidemiology

Tick-borne encephalitis (TBE) is currently endemic in Central Europe, Baltic region, Russia and part of eastern Asia, creating the so-called "TBE belt" [11,12] (Fig. 1). However, due to the mix of socio-economical, ecological (reservoirs and hosts interactions) and climatic factors as well as more susceptible hosts (e.g. such as immunocompromised patients), improved diagnostic capability and medical awareness, the epidemiology of TBE is changing [13,14]. In fact, TBE endemic regions are expanding with an increasing number of reported cases [15]; moreover, because of the high volume of tourists travelling to endemic areas, imported or travel-related TBE is becoming a growing global concern with more patients diagnosed outside commonly affected areas [16,17].

According to the European Centre for Disease Prevention and Control (ECDC), TBE has been notifiable in the EU since 2012 and 2876 cases of TBE were reported in 2016 with 12 fatalities [18].

The most affected nation within Europe were Lithuania, Estonia and Czech Republic with a notification rate of 21.9, 6.1 and 5.4 cases per 100,000 population, respectively [5].

Comparing 2016 ECDC data with the previous year, a sharp increase in the notified cases was observed in Italy (+862%), Slovakia (+111%), Lithuania (91%) and Poland (83%) [5].

TBEV can be transmitted by tick's saliva, rarely by ingestion of unpasteurized milk or milk products derived from viremic livestock [18]. Case reports of TBE after blood transfusions, organ transplantation, in laboratory workers and during breastfeeding can be found in the literature [6].

In Europe, TBE transmission by tick bites is linked with ticks seasonal activity of the two main vectors *Ixodes ricinus* (Western, Central and Eastern Europe) and *Ixodes persulcatus* (from Lithuania and Baltic regions to China and Japan), generally ranging from April to November, with a peak in August, although climate change may favour new infections even during winter months [5,18]. Favourite tick habitats are mainly woodland and mixed forests up to 1500 m of altitude; however, both in peri-urban and urban areas of Germany and Poland, TBE endemicity have been described [19,20].

It has been shown that an increase in daytime and weekly average temperature may affect ticks populations, extend ticks feeding and enhance the chance of TBE transmission [11].

Leisure and professional outdoor activities may pose a threat to travellers visiting endemic areas; in fact, it has been proposed that the risk for travellers visiting European region endemic for TBE may be similar to the risk of developing *Plasmodium vivax* malaria in travellers to India (range between 1:3000–1:25,000 travellers) [21].

TBE patients with chronic disease and/or on immunosuppressive treatment may experience a more severe outcome and it is important to raise awareness of the disease in such populations as well as to screen organ donors in TBE endemic areas [6,20].

Of note, case series of patients treated with rituximab, a chimeric monoclonal antibody that primarily affects lymphocyte B-cell leading to their profound depletion (up to 12 months), have shown TBE related severe and fatal outcomes, underlying the need of patients' tick-bite protection, preventive vaccination and possibly checking for protective level of antibody in TBE vaccinated patients before administering rituximab [11,21].

To our knowledge, the existence of an increased risk of development or worsening of TBE in patients treated with monoclonal antibodies other than rituximab has not been reported so far, but it cannot be excluded. Certainly, this issue merits dedicated investigation in light of the increasing use of such agents for different diseases and conditions [22].

4. Clinical presentation

The clinical spectrum of TBE may range between seroconversion without prominent morbidity and fatal encephalitis; however, just about one patient on three will develop symptoms of TBE infection [23]. The disease typically follows a biphasic pattern in 72–87% of patients and the median incubation period is 8 days (range, 4–28 days) after tick bite [23].

Nonspecific symptoms of mild fever, malaise, headache, nausea, vomiting and myalgias may be present as first manifestation of the disease and spontaneously resolve within 1 week [24].

If the first phase is symptomatic, the majority of patients has no further symptoms; however, the progression to more severe illness,

after a median of 2–8 days (range, 1–20 days), may experience recrudescence of fever, headache and vomiting [24].

The second phase, especially in children, may be characterized by an aseptic meningitis, or it may present as a meningoencephalitis form, poliomyelitic form with flaccid paralysis, or a polyradiculoneuritic form with a Guillain-Barré–like paralysis; all these form tends to resolve spontaneously [24,25].

Neurologic infections are commonly more benign in children, while it may be more severe in elderly and immunocompromised hosts (Fig. 3, from panel 1b to 1d shows example of neurological involvement during TBE infection). In fact, even if both Far Eastern and Siberian subtype of TBEV have a more severe outcome (probably due to a more aggressive neurovirulence/neurotropism), the European subtype of TBE accounts for 1% to 2% of fatal infection [25,26]. Encephalitis manifestations are typical of central nervous system involvement, with altered consciousness, focal signs as well as seizures [20,26]. The most usually affected voluntary muscles are shoulder girdle and upper limb musculature; also autonomic functions, such as urinary bladder continence, may be compromised. Cranial nerves as well can be affected, leading to produces gaze and peripheral facial paralysis and dysphagia. When paralysis, paresis or limb weaknesses are present myelitis or radical neuritis should be suspected due to lower motor neuron involvement that may proceed to permanent weakness and muscular atrophy [25,26]. Sequelae and complications related to prolonged hospitalization (due to profound iatrogenic sedation with intubation) are common (40 to 60% of patients with neurological involvement) and may present with health acquired pneumonia or health failure [25,27,28,29] (Table 1, [30,31]). Post-encephalitic syndrome (PES) has been linked to TBE virus with mutation in NS1 gene and a defective T-cell host response. Of note, both cases of PES due to the European strain reported in the literature had unfavourable outcome [32,33].

5. Diagnosis

Diagnosis of TBE relays mainly on high clinical suspicion confirmed by serological and molecular assays both on serum and cerebrospinal fluid (CSF) (Fig. 2).

5.1. Molecular and serological assays

In the first phase of illness, polymerase chain reaction (RT-PCR) on serum can be use to detect viral-RNA; while in the second phase, when neurological involvement is manifested, RT-PCR can be used on CSF, with lower sensitivity (> 50 copies/ml), and again on serum to try to detect cases of progressive disease [34,35,36]. Indeed, in the second phase of the disease TBEV-immunoglobulin M (IgM) and usually TBEV-immunoglobulin G (IgG) antibodies are present on serum and they are diagnostic for TBE infection [16,36]. IgM and IgG may be detected on CSF as well, but they appear later in time than on serum. Antibody index may be used as an adjunctive tool to help diagnose active TBE infection [37]. Recently, a new ELISA kit for detection of TBEV-IgM showed promising results preserving good sensitivity (94.1%) and specificity (98.1%), but with lower cross-reactions with other flavivirus; thus, it could be commercially implemented in endemic areas [38]. TBEV-IgG avidity represents an additional serologic marker that can be used when IgM are borderline or negative and remains high-clinical suspicion or when IgM and IgG are both positive and it is necessary to rule out possible cross-reaction due to polyclonal IgM activation [39].

The titre of anti-TBE virus neutralizing antibodies can be measured to distinguish TBE from other pathogens (E.g. West-Nile virus or Dengue virus) in endemic areas [40]. Moreover, the neutralizing antibodies titre can be useful to discriminate between past TBE infection and TBE vaccination (being higher and without age-dependent decrease in the former) [40].

Table 1
Potential tick-borne encephalitis (TBE)-related sequelae.

TBE-related sequelae and complications	Frequency, if available in the literature [ref]
Prolonged asthenia	85% [27]
Persistent headache	29% [27]
Decreased concentration	33% [27]
Memory difficulties	20% [27]
Tremor and movement disorders	16% [27]
Ataxia and incoordination	4–5% [28]
Depression	3% [27]
Cranial nerves paresis	2% [28]
Anxiety	1% [28]
Flaccid paralysis	-
Chronic encephalitis process	-
Dysphasia	-
Hemorrhagic syndrome	-
Mood disorders	-
Psychoorganic symptoms	-
Sleep disorders	-

5.2. Neuro-imaging and other diagnostic instruments

Neuro-imaging, especially magnetic resonance (MRI), and electroencephalogram (EEG) are becoming useful tools to detect localized lesion and quantify the burden of neurological involvement; however, both MRI and EEG modifications are unspecific and currently not diagnostic [16]. MRI is the imaging of choice to support the diagnosis of TBE [41]. Fig. 3 (Panel 1a) shows a MRI of a TBE fatal case occurred in a 36 years old patient undergoing post-transplant immunosuppression. TBE virus has a peculiar predilection for basal ganglia and thalamus localization has shown by post-mortem evaluation [41,42]. After 10 days from the infection, inflammatory changes in the CNS peaks and may be visible at MRI, nicely correlating with anti-TBE IgM and IgG detectability in CSF [43].

Moreover, TBEV has a special affinity to anterior horn cells of the spinal cord and spinal MRI may be able to detect pathological changes elucidating the basis of symptoms [42,44].

6. Prevention and treatment

Because of limited option for TBE treatment, of crucial importance is effective vaccination to prevent disease-related morbidity and mortality. In Europe and Russia are currently licensed 5 type of vaccine by three different pharma-company, namely GSK-Encepur (Germany), Pfizer (Austria), Microgen (Russia) and Chumakov Institute (licensed just in Russia) [45]. The route of administration is intramuscular for all the vaccine, however the schedule varies from 3 sequential administration (time 0, 1–3 months and 12 months) for the European made vaccines to 2 administration for (time 0, 5–7 months) for the Russian made ones [45]. In case of planned immunosuppression or a temporally close trip to endemic areas, the second doses Pfizer's vaccines may be administrated 2 weeks after the first dose, in order to have a more rapid immune-response [45,46]. GSK-Encepur and Chumakov Instiute vaccines have an accelerate scheduled in case of need as well [45].

It is important to underline that if the vaccination is done during or after immunosuppression, the antibody answer may be not efficient enough to protect the patient from TBE-infection. A prospective, multicentre study from Sweden has shown as in patients with rheumatoid arthritis (RA) treated with tumour necrosis factor-inhibitors and/or methotrexate, serum anti-TBE antibody level were protective in 39% and 79% in patients with RA and healthy controls, respectively [47]. Improved vaccines' immunogenicity and more frequent schedules may be used to reach protective antibody title in patients with established risk factors and in travellers at risk of TBE.

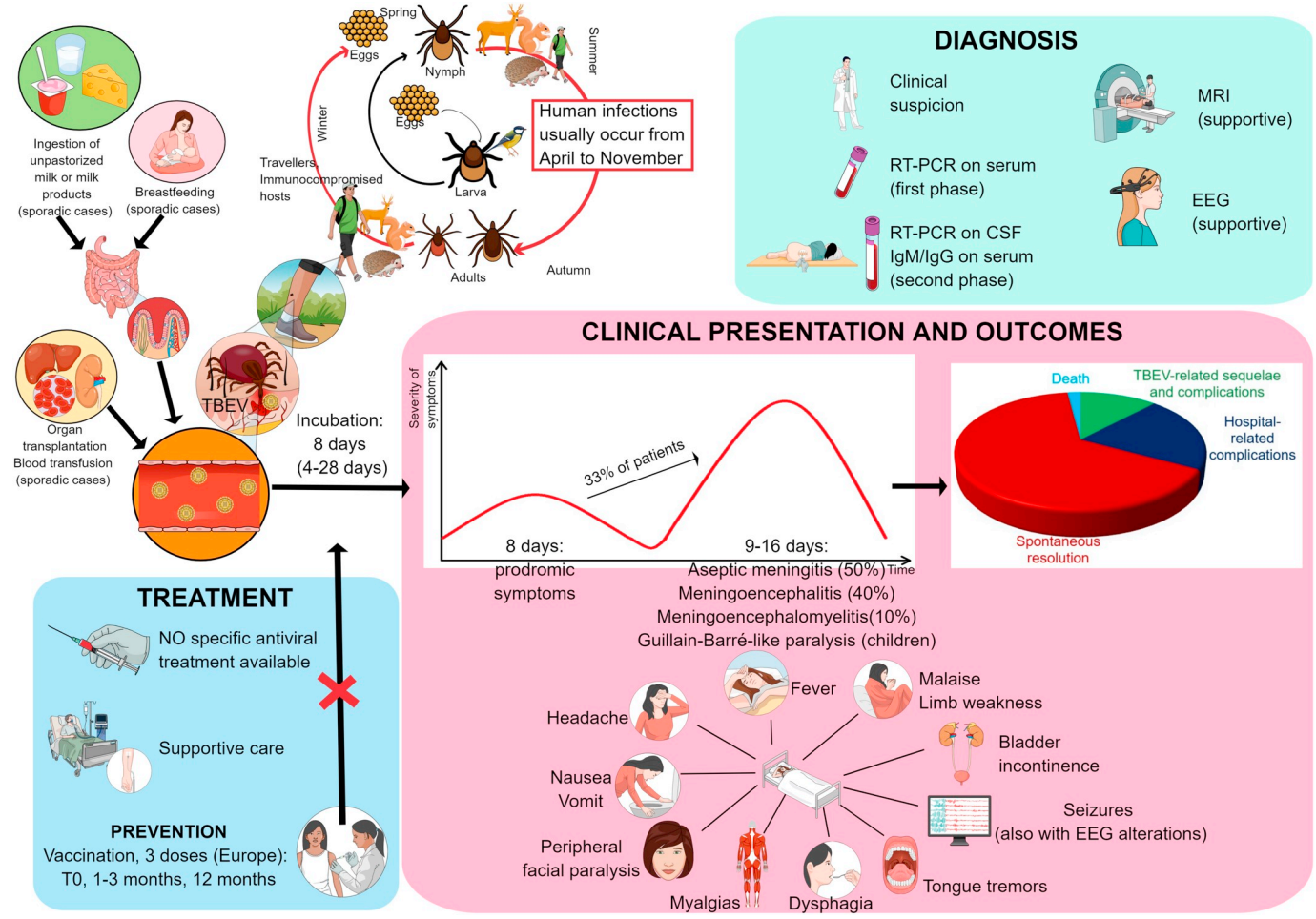

Fig. 2. Diagnosis and clinical presentation of TBE.

Currently, there is no specific available antiviral treatment for TBE; indeed, supportive treatment as well as intensive care and assisted ventilation in severe forms may be needed [6]. Case-reports of steroids treatment have been published, however this practice is not supported by any controlled trial [6]. The nucleoside analogue 7-deaza-2'-*C*-methyladenosine (7-deaza-2'-CMA) has shown good antiviral activity and low cytotoxicity in porcine kidney cells and human neuroblastoma cells and may be a candidate for future investigations [47]. Mannitol can be used in case of cerebral oedema, but must be used carefully due to the risk of severe dehydration, especially in older patients [48,49].

7. TBE in the future

Milder winters and warmer springs may affect and prolong the period of humans' exposure to ticks as well as tick activity in TBE endemic areas [50]. Similarly, climate changes is extending TBE endemicity, augmenting the distribution of TBE vectors. Low endemic countries may expect an increase in TBE burden in the next years and endemic foci may arise, as already happened in Italy in 2006 and 2013 [51]. Travelling to TBE-endemic areas pose a threat to travellers which, most of the time, are unaware of TBE vaccine availability. Likewise, immunocompromised patients should be carefully counselled about TBE vaccination before travelling to endemic areas. Furthermore, in highly TBE endemic areas, TBE vaccination coverage should be implemented in at risk populations such as environmental service worker, veterinary, immunocompromised-patients, exc. Because of the lack of awareness, travellers that plan outdoor activity during seasonal transmission of TBE in endemic areas should be advised about tick, unpasteurized milk and dairy products avoidance as well as the availability, and actively offered, of an effective vaccine [12,51]. Finally, human population and population density growth may increase exposure to TBE-vectors, demanding a great concerted effort to promote TBE awareness, research on more accurate diagnostic tools, effective treatment and prevention [52,53,54].

8. Conclusion

TBE related health burden is expanding in Europe. Unfortunately, no effective antiviral treatment for TBE is currently available, therefore implementation of awerness and effective vaccination should be expanded in effected areas.

Funding

None.

Conflict of interests

The Authors declare no conflict of interests.

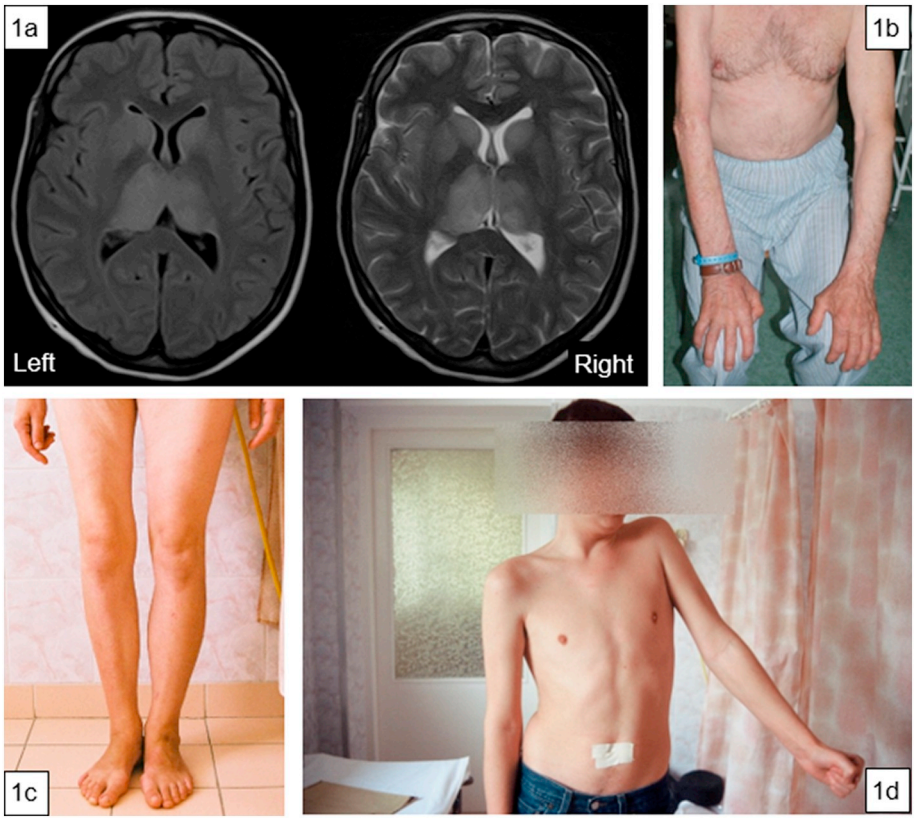

Fig. 3. Possible sequelae in TBE. 1a: 36 years old, fatal case. Axial fluid-attenuated inversion recovery (FLAIR) image (left) and T2-weighted MR image (right) show bilateral hyperintensity of the caudate nucleus, putamen and thalamus. The right side is slightly more involved than the left side. 1b: unilateral plexus brachialis peripheral paresis. Full recovery is extremely rare. 1c: permanent weakness and muscular atrophy of right lower limbs. 1d: bilateral paresis, with reduced ability to elevate the limbs.

Transparency declarations

None to declare.

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