Chapter 15

Prion Disease

CQ 15-1

What are the clinical features of sporadic Creutzfeldt-Jakob disease (CJD)?

Answer

Sporadic CJD is the most common form of prion disease, constituting approximately 70% of all cases. Classic cases are characterized by a course of rapidly progressive dementia, cerebellar ataxia, pyramidal and extrapyramidal signs, and myoclonus, progressing to akinetic mutism over weeks.

Comments and evidence

The annual incidence of prion disease in Japan is approximately 1 case per 1 million [1, 2]. The mean age at onset is 67.9 years. Typical cases are termed classic CJD, and manifest as rapidly progressive dementia, myoclonus, cerebellar ataxia, visual disturbances, pyramidal signs and extrapyramidal symptoms, progressing to akinetic mutism in 3 to 6 months on average. The diagnostic criteria of sporadic CJD have been reported [3, 4].

The analysis of brain samples from patients with sporadic CJD has led to characterization of the protease K-resistant prion protein (PrP), which is distinguished into type 1 and 2 by Western blot analysis. Combining this typing with the PrP gene codon 129 polymorphism (MM type; homozygous for methionine, MV type; heterozygous for valine, VV type, homozygous for valine), sporadic CJD is classified into 6 types; MM1, MM2, MV1, MV2, VV1 and, VV2. The MM2 type is further classified by clinicopathological findings into MM2-cortical and MM2-thalamic types [5]. MM1 is the most common type of sporadic CJD, with a clinical course of the classic type. For details, see references 5 and 6.

■ References

1) Nozaki I, Hamaguchi T, Sanjo N, et al. Prospective 10-year surveillance of human prion diseases in Japan. Brain. 2010; 133(10): 3043-3057.
2) Nakamaura Y, Ae R, Takumi I, et al. Descriptive epidemiology of prion disease in Japan: 1999-2012. J Epidemiol. 2015; 25(1): 8-14.
3) World Health Organization. WHO Manual for Strengthening Diagnosis and Surveillance of Creutzfeldt-Jakob Disease. Geneva: World Health Organization: 1998.
4) Sanjo N, Mizusawa H. Prion disease: The characteristics and diagnostic points in Japan. Clin Neurol. (Rinsho Shinkeigaku) 2010; 50(5): 287-300. (In Japanese)
5) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases (Research Project for Combating Intractable Diseases) "Study Group on Prion Disease and Late-onset Virus Infections" (ed.) Clinical Practice Guideline for Prion Disease 2017. (In Japanese)
6) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases "Study Group on Prion Disease and Late-onset Virus Infections" (ed.) Prion Disease and Late-onset Virus Infections. Tokyo: Kanehara Shuppan; 2010. (In Japanese)

■ Search formula

PubMed search: June 29, 2015 (Monday)
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CQ 15-2

What are the electroencephalographic, cerebrospinal fluid, and MRI findings of sporadic Creutzfeldt-Jakob disease (CJD)?

Answer

In typical cases, electroencephalogram (EEG) shows slow and/or irregular waves in the early stage, then periodic sharp wave complexes (PSWCs) will emerge when myoclonus appears, and is followed by disappearance of PSWCs and flattening of waves at the end stage. In the cerebrospinal fluid (CSF), the appearance, cell count, and protein level are normal in most cases, while 14-3-3 protein and total tau protein increase. Abnormal prion proteins in the CSF can be detected by real-time quaking-induced conversion (RT-QuIC) method. Further, hyperintensity is observed in the in cerebral cortex and basal ganglia (putamen, caudate nuclei) on diffusion-weighted or FLAIR MRI, and in the medial thalamus in some cases.

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Comments and evidence

In prion disease, the EEG shows slowing and irregularity in the early stage of the disease, then PSWCs emerge at the same time as myoclonus appears. Finally, PSWCs disappear and the EEG flattens in the end stage [1]. Hyperintensity is observed in the cerebral cortex, basal ganglia (putamen, caudate nuclei), and the thalamus in some cases, on diffusion-weighted or FLAIR MRI [2, 3]. CSF examination typically shows a normal appearance and cell count, and protein levels are normal in most cases; however 14-3-3 and total tau proteins are increased in the CSF [4]. In recent years, the RT-QuIC method has been developed, which enables the detection of abnormal prion proteins (PrP^{Sc}) in the CSF with approximately 70% sensitivity [5, 6].

The Ministry of Health, welfare and Labour Prion Study Group has established a diagnosis support system. Utilization of this system is recommended [7, 8].

References

1) Steinhoff BJ, Racker S, Herrendorf G, et al. Accuracy and reliability of periodic sharp wave complexes in Creutzfeldt-Jakob disease. Arch Neurol. 1996; 53(2): 162-166.
2) Meissner B, Kallenberg K, Sanchez-Juan P, et al. MRI lesion profiles in sporadic Creutzfeldt-Jakob disease. Neurology. 2009; 72(23): 1994-2001.
3) Fujita K, Harada M, Sasaki M, et al. Multicentre, multiobserver study of diffusion-weighted and fluid-attenuated inversion recovery MRI for the diagnosis of sporadic Creutzfeldt-Jakob disease: a reliability and agreement study. BMJ Open. 2012; 2(1): e000649.
4) Nozaki I, Hamaguchi T, Sanjo N, et al. Prospective 10.year surveillance of human prion diseases in Japan. Brain. 2010; 133(10): 3043-3057.
5) Stoeck K, Sanchez-Juan P, Gawinecka J, et al. Cerebrospinal fluid biomarker supported diagnosis of Creutzfeldt-Jakob disease and rapid dementias: a longitudinal multicentre study over 10 years. Brain 2012; 135(Pt 10): 3051-3061.
6) Sano K, Satoh K, Atarashi R, et al. Early detection of abnormal prion protein in genetic human prion diseases now possible using real-time QUIC assay. PLoS One 2013; 8(1): e54915.
7) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases "Study Group on Prion Disease and Late-onset Virus Infections" (ed.) Prion Disease and Late-onset Virus Infections. Tokyo: Kanehara Shuppan; 2010. (In Japanese)
8) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases (Research Project for Combating Intractable Diseases) "Study Group on Prion Disease and Late-onset Virus Infections" (ed.) Clinical Practice Guideline for Prion Disease 2017. (In Japanese)

Search formula

PubMed search: June 29, 2015 (Monday)

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CQ 15-3

What are the types and features of genetic prion disease in Japan?

Answer

Genetic prion diseases are classified as genetic Creutzfeldt-Jakob disease (CJD), Gerstmann-Sträussler Scheinker (GSS) disease, and fatal familial insomnia (FFI). In Japan, genetic prion diseases commonly include V180I (CJD), P102L (GSS), E200K (CJD), and M232R (CJD) mutations of the prion protein gene (*PRNP*). CJD with V180I and M232R are found more commonly in sporadic cases; therefore, genetic testing is required for diagnosis. Patients with V180I mutation often have late onset and typically manifest slowly progressive dementia. Patients with P102L mutation have cerebellar ataxia at onset with slow progression, and patients with E200K mutation show a clinical course similar to classic sporadic CJD. In recent years, one type with autonomic failure as the main symptom has been reported.

Comments and evidence

In Japan, the common mutations of *PRNP* include V180I (CJD), P102L (GSS), E200K (CJD), and M232R (CJD). The frequencies of these mutations differ significantly from those in Europe and America [1, 2]. V180I is the most common mutation in Japan and Korea, and M232R and P105L (GSS) mutations are unique to Japan [3, 4]. Genetic prion disease is usually autosomal dominant, and almost all cases with P105L mutation are familial. However, genetic testing is required for diagnosis of cases with V180I and M232R mutations because these rarely exhibit a family history.

For details, refer to reference 5.

References

1) Nozaki I, Hamaguchi T, Sanjo N, et al. Prospective 10-year surveillance of human prion diseases in japan. Brain. 2010; 133(10): 3043-3057.
2) Nakamaura Y, Ae R, Takumi I, et al. Descriptive epidemiology of prion disease in Japan: 1999-2012. J Epidemiol. 2015; 25(1): 8-14.
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Search formula

PubMed search: June 30, 2015 (Tuesday)

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CQ 15-4

What are the types and features of acquired (infectious) prion disease in Japan?

Answer

Two types of acquired prion diseases have been confirmed in Japan; variant Creutzfeldt-Jakob disease (variant CJD; vCJD) and dura mater graft-associated CJD. Cases of dura mater graft-associated CJD in Japan constitute over half of all cases worldwide. Surprisingly, some cases showed disease onset over 30 years after dura mater transplantation. Two-thirds of these cases are the non-plaque type and show a clinical feature similar to classic CJD. One-third of the cases are plaque-type and manifest as relatively slowly progressive ataxia.

Comments and evidence

Acquired prion diseases are classified into Kuru, vCJD, and iatrogenic CJD [1, 2].

Variant CJD exhibits a younger onset compared with the other prion diseases, with a mean age at onset of 29 years. Patients manifest psychiatric symptoms such as frustration and depression at an early stage; therefore, the disease is often misdiagnosed as psychiatric diseases. As the disease progresses, cognitive impairment and motor symptoms such as ataxic gait, gradually emerge. Hyperintensity in the medial-dorsal thalamus (pulvinar sign) is observed on diffusion-weighted MRI. Periodic sharp wave complexes (PSWCs) on EEG are typically not observed.

In Japan, all cases of acquired CJD, except one case of vCJD, are dura mater grafting-associated CJD, with 154 confirmed cases (Surveillance Committee, September 2017). The dura mater used in all identifiable cases was cadaveric dura mater Lyodura® from B. Braun, Germany. The cases in Japan constitute over half of the cases worldwide [3]. After Lyodura® was discontinued (March 1997), the disease has not been found in patients who undergo dura mater grafting. Although the incidence of patients with dura mater grafting-associated CJD has decreased, some cases have presented with disease up to 30 years after surgery [3]. Two-thirds of dura mater grafting-associated CJD cases have clinicopathological findings similar to classic CJD, and one-third of the cases manifest an ataxic gait with relatively slow progression, and no PSWCs is observed on electroencephalogram in the early stage. Pathological examination of the brain shows plaque-like deposition of abnormal prion protein [4].

For patients with CJD caused by dura mater grafting, the patient/family association has set up a CJD support network (http://www.cjdnet.jp/). Utilization of this network is recommended.

■ References

1) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases. Study Group on Prion Disease and Late-onset Virus Infections and Study Group Related to Surveillance and Infection Control of Prion Disease. Clinical Practice Guideline for Prion Disease 2017. (In Japanese)
2) Health Welfare and Labor Sciences Research Grant for Research Project for Combating Intractable Diseases. "Study Group on Prion Disease and Late-onset Virus Infections" (ed.) Prion Disease and Late-onset Virus Infections. Tokyo: Kanehara Shuppan: 2010. (In Japanese)
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PubMed search: June 30, 2015 (Tuesday)

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CQ 15-5

What are the infection control measures and effective sterilization methods for prion disease?

Answer

For medical devices that have been used in high-risk procedures for patients known to have prion disease (see Guideline [1]), the currently recommended method is to remove as much as possible the blood and tissue fragments attached to the device, then immerse in 3% sodium dodecyl sulfate (SDS) solution and boil at 100°C for 3-4 minutes. After washing manually or in a washer-disinfector, sterilize in a pre-vacuum autoclave at 134°C for 10 minutes.

Comments and evidence

Prion disease can be transmitted not only after disease onset but also during the incubation period via medical devices that have been in contact with high-risk infectious sites or through blood (for variant CJD). The Japanese guidelines for prevention of prion disease currently recommend disinfection and sterilization methods for surgical instruments that have been used in patients with prion disease (http://prion.umin.jp/guideline/cjd_2008all.pdf) [1].

■ References

1) Health Welfare and Labor Sciences Research Grant; Research Project for Combating Intractable Diseases. Study Group on Prion Disease and Late-onset Virus Infections. Guidelines for Prevention of Prion Disease (2008 edition).
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■ Search formula

PubMed search: June 30, 2015 (Tuesday)
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