Early-Stage Contactin-Associated Protein-like 2 Limbic Encephalitis
Clues for Diagnosis

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Abstract

Background and Objectives
Previous studies suggested that autoimmune limbic encephalitis with antibodies against contactin-associated protein-like 2 (CASPR2-encephalitis) is clinically heterogeneous and progresses slowly, preventing its early recognition. We aimed to describe the onset and progression of CASPR2-encephalitis and to assess long-term outcomes.

Methods
We retrospectively analyzed the medical records of all patients whose CSF tested positive for anti-CASPR2 antibodies in our center between 2006 and 2020. Standardized telephone interviews of all available patients and relatives were conducted, assessing long-term functional independence using the Functional Activity Questionnaire (FAQ) and quality of life using the 36-Item Short-Form Survey (SF36).

Results
Forty-eight patients were included (98% males; median age 64 years), and 35 participated in telephone interviews (73%). At onset, 81% had at least 1 neurologic symptom among the following: limbic (54%), peripheral nerve hyperexcitability (PNH; 21%), and/or cerebellar symptoms (17%). Most of the patients (75%) had initially symptoms of only one of these categories. Limbic symptoms at onset included mostly seizures (33%), while memory disturbances were less frequent (10%). PNH signs were mostly neuropathic pain (9/10 patients). Other symptoms seen at onset included asthenia (33%), mood disorders (25%), and insomnia (21%); 19% of patients did not show any limbic, peripheral, or cerebellar symptom at onset but only asthenia (15%), mood disorders (6%), weight loss (8%), dysautonomia (4%), and/or insomnia (2%). The peak of the disease was attained in median 16.7 months after onset. Over the study period (median follow-up, 58.8 months, range 10.6–189.1), 77% of patients developed ≥3 core CASPR2 symptoms and 42% fulfilled the diagnostic criteria for autoimmune limbic encephalitis, although all patients ultimately developed limbic symptoms. At the last visit, most interviewed patients (28/35 patients, 80%; median, 5 years after onset) had recovered functional independence (FAQ <9) while only the vitality subscore of the SF36 was lower than normative data (mean 49.9 vs 58.0, \( p = 0.0369 \)).
Antibodies against contactin-associated protein-like 2 (CASPR2-Abs) were described in 2010 in patients with autoimmune limbic encephalitis (CASPR2-encephalitis), featuring characteristic limbic symptoms such as anterograde amnesia, temporal lobe seizures, and behavioral changes, as well as in patients with acquired neuromyotonia and Morvan syndrome, a poorly delineated entity that combines signs of peripheral nerve hyperexcitability (PNH) with confusion, insomnia, and hallucinations. Subsequent studies showed that CASPR2-encephalitis is the most frequent of the 3 phenotypes and strongly correlates with the presence of CASPR2-Abs in the CSF. Furthermore, previous publications totaling more than 600 cases revealed that in addition to limbic symptoms, patients with CASPR2-encephalitis can develop nonlimbic features such as cerebellar ataxia, hyperkinetic movement disorders (HMDs), PNH, and/or insomnia. In light of this challenging diversity of symptoms, van Sondersen et al. determined a set of core symptoms to facilitate the identification of these patients. However, because there are no published data on the initial clinical presentation of CASPR2-encephalitis, it is not clear whether these core symptoms are sufficiently sensitive in the early stage of the disease. Moreover, previous reports suggested that the disease can follow a slow and progressive course, which is in contradiction with the recommended clinical criteria for the diagnosis of autoimmune limbic encephalitis. Taken together, these aspects likely make it difficult to recognize CASPR2-encephalitis at the early stage, especially if typical symptoms of autoimmune limbic encephalitis, such as anterograde amnesia, temporal lobe seizure, and behavioral change, are not yet present then. Because timely recognition of the disease is critical for early diagnosis and treatment, it is important to identify which clinical features are prominent at the early stage of CASPR2-encephalitis. We therefore aimed to describe the clinical presentation at the onset and progression of the disease. A cross-sectional analysis of the long-term outcomes was also performed in a subset of the patients.

**Methods**

**Patients**

All patients with CSF samples positive for CASPR2-Abs at the French Reference Center on Autoimmune Encephalitis between January 2006 and June 2020 were included. Patients with positive results only in serum were excluded in light of previous results, showing that serum CASPR2-Abs were associated with a wide range of central and peripheral nervous system involvements, while only CSF positivity was reliably associated with limbic encephalitis (eFigure1, links.lww.com/NXI/A752). CASPR2-Abs were considered positive when immunohistofluorescence on rat brain sections and specific cell-based assay gave a concordant result, as previously reported. We retrospectively collected clinical data and diagnostic tests from patients’ medical records; patients for whom medical records were not available were excluded. In addition, telephone interviews were proposed to all patients still alive to complete data collection and to perform a cross-sectional analysis of long-term functional independence and quality of life. Written informed consent was obtained from all patients.

**Telephone Interviews**

The telephone interviews were conducted with the patient and a close relative, when available. The interviews were split into 2 independent parts: one about the mode of onset and course of the disease and the other about current clinical status. Both parts contained open-ended and closed-ended questions. The telephone interviews lasted approximately 60 minutes and were all performed by the same author (J.B.). To ensure patients could undergo the interview, all interviews started by a telephone Mini-Mental State Examination (t-MMSE), as previously reported. After completion of the first part, patients and their relatives were asked whether they wished to postpone the second part. In addition to questions about symptoms, 2 validated questionnaires were administered: the 36-Item Short-Form Survey (SF36) to assess quality of life and the Functional Activities Questionnaire (FAQ) for instrumental activities of daily living. While patients and their family members answered the open-ended and closed-ended questions together, only the patients completed the SF36, and only the family members assessed the FAQ. Patients with no family member assessed their own FAQ. SF36 scores were compared with normative data from a population of French men older than 55 years.

**Data Processing**

Demographic characteristics, diagnostic tests, and treatments were collected exclusively using medical records. Conversely, symptoms at onset, at initial medical appointment, and over
the course of the disease were collected from both medical records and telephone interviews. Information not recalled by the patient during the interview but precisely recorded in the medical file was retained, and, conversely, any information precisely reported by the patient or their relative but not mentioned in the medical chart was retained. Fifteen symptoms previously reported in CASPR2-encephalitis patients, including the core symptoms described by Van Sonderen et al., were reviewed. Mood disorders were defined as unusual anxiety and/or depression. Cognitive impairment combined anterograde memory impairment and/or signs of frontal lobe dysfunction. During interviews, the patient and his/her relative were asked for a noticeable change in mnesic and attentional capacities, behavior, or personality. Ataxia was determined as gait imbalance with no sensitive or motor impairment and/or unusual slurred speech. Motor PNH included fasciculations, myokimia, and/or cramps, with or without electromyographic signs of PNH. The presence/absence of each symptom was precisely reported by the patient or their relative but not recorded in the telephone interviews (a relative was available for all but 2 of them; Figure 1). Forty-seven patients (98%) were male, and the median age at onset was 64 years (range: 46–82). Fifteen patients (31%) had a history of cancer at the last visit (1 had 2 tumors; Table 1); tumor diagnosis ranged from 13 years before to 7 years after the onset of CASPR2-encephalitis (eFigure2, links.lww.com/NXI/A752). No thymoma was detected, and a paraneoplastic origin was not concluded in any of them in accordance with the updated diagnostic criteria for paraneoplastic neurologic syndromes (eTable2, links.lww.com/NXI/A752).

**Clinical Presentations at Onset**

While initial clinical presentations were highly variable in this cohort, at onset, most of the patients (39/48, 81%) had at least 1 neurologic symptom among the following: limbic symptoms (26/48 patients, 54%), symptoms suggestive of PNH (neuropathic pain and/or motor PNH, 10/48 patients, 21%) and intellectual impairment (20/48 patients, 42%).

**Statistical Analysis**

The Fisher exact test was used to compare categorical data, and the Mann-Whitney U test was used for continuous data. Statistical significance was set at \( p < 0.05 \). All analyses were performed using the R software (R Core Team, 2014. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. R-project.org) and GraphPad Prism 7 software (GraphPad Inc., San Diego, CA).

**Data Availability**

Because of space limitation, not all data could be provided in the article. Data not provided in the article will be shared at the request of other investigators for purposes of replicating procedures and results.

**Results**

**Patients**

After exclusion of patients who tested positive for CASPR2-Abs only in serum, we identified 52 patients testing positive for CASPR2-Abs in the CSF between January 2006 and June 2020 (for all but 1 patient, serum results were also tested positive). Of note, clinical features differed in patients who tested positive only in serum compared with patients who tested positive in the CSF, as previously observed (eTable1, links.lww.com/NXI/A752). Four were excluded from analysis because of insufficient data (Figure 1), and therefore, 48 were included, of whom 35 (73%) participated in the telephone interviews (a relative was available for all but 2 of them; Figure 1). Forty-seven patients (98%) were male, and the median age at onset was 64 years (range: 46–82). Fifteen patients (31%) had a history of cancer at the last visit (1 had 2 tumors; Table 1); tumor diagnosis ranged from 13 years before to 7 years after the onset of CASPR2-encephalitis (eFigure2, links.lww.com/NXI/A752). No thymoma was detected, and a paraneoplastic origin was not concluded in any of them in accordance with the updated diagnostic criteria for paraneoplastic neurologic syndromes (eTable2, links.lww.com/NXI/A752).

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**Figure 1 Flowchart of the Study**

- Patients whose CSF tested positive for anti-CASPR2 antibodies (N = 52)
  - Excluded (n = 4):
    - No available data (4)
- Patients included (n = 48)
  - Not interviewed (n = 13):
    - Deceased (8)
    - Refused interview (2)
    - Lost to follow-up (5)
- Patients participated in telephone-based interviews (n = 35)
Autoimmune encephalitis was not initially suspected in any of the patients; therefore, none received the appropriate tests for the fulfillment of the Graus criteria then. The commonest of limbic symptoms at onset were seizures (16/48 patients, 33%; tonic-clonic seizures, 8 patients; and focal seizures, 8 patients), usually without any other symptom of limbic encephalitis (except 3 patients with behavioral changes and 1 patient with anterograde amnesia). Behavioral changes (irritability, apathy, and/or hyperemotivity) affected 10/48 patients (21%), 6 without further sign of limbic encephalitis, while cognitive impairment was reported in 5/48 patients (10%, anterograde amnesia with disorientation, 3 patients; short-term memory impairment, 1 patient; and autobiographical amnesia, 1 patient). We did not identify any patient at onset with all the 3 typical signs of limbic encephalitis (seizures, amnesia, and behavioral change). PNH symptoms consisted in neuropathic pain (9/10 patients) and/or motor PNH (2/10 patients). Cerebellar symptoms at onset were episodic (5/8 patients) and/or permanent (5/8 patients, including 2 patients with episodic exacerbations, Table 2). Symptoms not included in the aforementioned categories were observed in 22/48 patients (46%), including asthenia (16/48, 33%), mood disorders (12/48, 25%), insomnia (10/48, 21%), weight loss (6/48, 13%), hyperhidrosis (3/48, 6%), and tremor (1/48, 2%; Table 2). Nine patients (19%) did not show limbic impairment, signs suggestive of PNH, or cerebellar symptoms at onset, presenting instead with asthenia (7/9 patients), mood disorders (3/9 patients), insomnia (1/9 patient), weight loss (4/9 patients), and/or dysautonomia (2/9 patients).

Table 1  Demographic Characteristics and Ancillary Tests Over the Study Period

| Total population | N = 48 |
|------------------|-------|
| Males, n (%)     | 47 (98) |
| Median age at onset, y (range) | 64 (46–82) |
| A history of cancer, n (%) | 15 (31) |
| Abnormal MRI, n/N (%) | 28/45 (62) |
| Bilateral mesio-temporal abnormalities, n/N (%) | 24/28 (86) |
| Unilateral mesio-temporal abnormalities, n/N (%) | 4/28 (14) |
| CSF Normal, n (%) | 20 (42) |
| Cell count >5 cells/μL | 19 (40) |
| Protein, g/L, median (range) | 0.54 (0.2–1.38) |
| Oligoclonal bands, n/N (%) | 14/38 (37) |
| Abnormal EEG, n/N (%) | 28/46 (61) |
| Positive serum anti-CASPR2 antibodies, n/N (%) | 41/42 (98) |

Abbreviation: CASPR2 = contactin-associated protein-like 2.

Figure 2 Progression of CASPR2-Encephalitis

(A) An overlap of the 3 main categories of neurologic symptoms in the patients: limbic (generalized or temporal lobe seizures, behavioral change, and/or memory impairment), peripheral nerve hyperexcitability (PNH), and cerebellar symptoms at the studied time points between onset and peak of the disease; and (B) over the entire study period (left panel) and at the last visit (right panel). The values represent the number of patients in each category. Patients who did not have symptoms of limbic encephalitis, cerebellar ataxia, or peripheral nerve hyperexcitability at 1 time point are not represented in the corresponding diagram. CASPR2 = contactin-associated protein-like 2.
Only 5 patients (10%) had ≥3 of the core CASPR2 symptoms at onset (Figure 3).

**Progression From Onset to Peak of the Disease**

At first medical appointment (median time 58.5 days after onset, range 0–822 days), 37/48 patients (77%) had limbic symptoms, including seizures (30/48, 63%) and cognitive impairment (14/48, 29%); 12/48 patients (25%) featured cerebellar symptoms, mostly episodic ataxia (8/48, 17%); and 10 (21%) experienced PNH symptoms (neuropathic pain, 9/10; motor PNH, 2/10; Figure 2). In addition, asthenia (19/48, 40%), mood disorders (15/48, 31%), and insomnia (12/48, 25%) were also frequently observed (Table 2). The peak of the disease was attained in median in 16.7 months after onset (range 1–134). Then, most patients (35/48, 73%) experienced symptoms belonging to 2 or 3 of the abovementioned categories of neurologic symptoms: limbic impairment, PNH symptoms, or cerebellar ataxia (Figure 2A). In addition, 46/48 patients (96%) presented with asthenia (30/48, 63%), mood disorders (37/48, 77%), insomnia (23/48, 48%), weight loss (19/48, 40%), and/or dysautonomia (18/48, 38%). Most of the patients (33/48 patients, 69%) were functionally dependent (mRS score ≥2; Figure 4A). In some patients, seizures and asthenia resolved before the peak of disease was attained (Table 2).

**Cumulative Symptoms Over the Study Period**

Over the entire course of disease, all patients developed limbic symptoms, 22/48 patients (46%) had signs suggestive of PNH, and 34/48 (71%) had cerebellar symptoms (Figure 2B; Table 2). Other symptoms, such as mood disorders (40/48, 83%), dysautonomia (22/48, 46%), asthenia (34/48, 71%), weight loss (24/48, 50%), and sleep disorders (27/48, 56%), were also frequent. Only HMDs were uncommon (3/48 patients, 6%; including tremor, choreiform movements, and myoclonus–each in 1 patient; Table 2).

| Table 2 Distribution of Symptoms Over the Study Period |
|------------------------------------------------------|
| **Total population N = 48** | Onset | First appointment | Diagnosis | Peak | Last visit | Cumulative symptoms |
| **Median time from onset d (interquartile range; range)** | — | 58.5 [6.5–121.5] (0–822) | 313 [156.8–631.8] (31–2,634) | 502 [181.3–760.5] (30–4,019) | 1764 [946.3–2,684.8] (320–5,675) | — |
| **Categories of neurologic symptoms, n (%)** | | | | | | |
| Limbic | 26 (54) | 37 (77) | 47 (98) | 48 (100) | 40 (83) | 48 (100) |
| Cerebellar | 8 (17) | 12 (25) | 29 (60) | 32 (67) | 26 (54) | 34 (71) |
| Peripheral nerve hyperexcitability | 10 (21) | 10 (21) | 18 (38) | 18 (38) | 13 (27) | 22 (46) |
| **Symptoms, n (%)** | | | | | | |
| Cognitive impairment | 5 (10) | 14 (29) | 43 (90) | 45 (94) | 33 (69) | 46 (96) |
| Seizures | 16 (33) | 30 (63) | 41 (85) | 40 (83) | 12 (25) | 45 (94) |
| Behavioral disorder | 10 (21) | 13 (27) | 33 (69) | 35 (73) | 25 (52) | 42 (88) |
| Episodic ataxia | 5 (10) | 8 (17) | 17 (35) | 17 (35) | 7 (15) | 21 (44) |
| Cerebellar ataxia | 5 (10) | 6 (13) | 19 (40) | 25 (52) | 20 (42) | 25 (52) |
| Neuropathic pain | 9 (19) | 9 (19) | 11 (23) | 13 (27) | 10 (21) | 15 (31) |
| Motor signs of peripheral nerve hyperexcitability | 2 (4) | 2 (4) | 9 (19) | 9 (19) | 5 (10) | 13 (27) |
| Dysautonomia | 3 (6) | 5 (10) | 13 (27) | 18 (38) | 12 (25) | 22 (46) |
| Insomnia | 10 (21) | 12 (25) | 19 (40) | 23 (48) | 15 (31) | 27 (56) |
| Asthenia | 16 (33) | 19 (40) | 33 (69) | 30 (63) | 19 (40) | 34 (71) |
| Weight loss | 6 (13) | 7 (15) | 18 (38) | 19 (40) | 14 (29) | 24 (50) |
| Mood disorders | 12 (25) | 15 (31) | 35 (73) | 37 (77) | 21 (44) | 40 (83) |
| Hyperkinetic movement disorders | 1 (2) | 1 (2) | 1 (2) | 3 (6) | 3 (6) | 3 (6) |
In retrospect, 37/48 patients (77%) had ≥3 core CASPR2 symptoms and 27/48 (56%) ≥4 (Figure 3). Only 20/48 patients (42%) fulfilled Graus criteria for autoimmune limbic encephalitis (subacute onset criterion, 8/48, 17%; MRI criterion, 24/45 patients, 53%; CSF criterion, 28/48 patients, 58%; and EEG criterion, 28/48 patients, 58%, Figure 3). Regarding EEG, second reading of 50 recordings from 11 patients (143 hours of recording in total) showed abnormal findings in 4/11 patients (36%), most commonly in temporal regions: slow waves (4/11, 36%), IEDs (4/11, 36%), and ictal events (4/11, 36%); the latter consistently triggered by hypopnea (eFigure3; eTable3, links.lww.com/NXI/A752).

**Clinical Status at Last Visit**

The median follow-up was 58.8 months after disease onset (range, 10.6–189.1). All patients received immunotherapy, in median 10.8 months after onset (range, 1–88.6), including steroids (33/48, 67%), IV immunoglobulins (37/48, 77%), rituximab (26/48, 54%), IV cyclophosphamide (23/48, 48%), plasma exchange (4/48, 8%), mycophenolate mofetil (4/48, 8%), azathioprine (4/48, 8%), methotrexate (1/48, 2%), and mitoxantrone (1/48, 2%). The median follow-up after the onset of immunotherapy was 41.1 months (range 2.9–162.5). Sixteen patients (33%) experienced a neurologic relapse a median 22 months (range, 10–108) after disease onset. All but 3 relapses (81%) were resurgences of previous symptoms, and most of them (10/16; 63%) occurred within the 3 months after full or partial withdrawal of immunotherapy. Eight patients (17%) died during follow-up, at a median age of 71 years (range 64–84) and after a median time of 3 years after disease onset (range 1–14). Causes of death were metastatic cancer, cardiac arrest, and progression of CASPR2-encephalitis—each in 1 patient, and were unknown for 5 patients. Among survivors, 30/40 (75%) had an mRS score ≤2 at the last visit. We did not observe any correlation between mRS score at the last visit and delay to the first immunotherapy. Mild short-term memory impairment persisted at the last visit in 33/48 patients (69%) and lacunar autobiographical amnesia in 10 other patients (21%; Table 2). Other symptoms at the last visit included seizures (12/48, 25%), cerebellar symptoms (26/48, 54%), and PNH symptoms (13/48, 27%). Thirty-five patients (73%) also experienced additional symptoms such as insomnia, asthenia, weight loss, and/or mood disorders (Figure 2B; Table 2).

**Cross-sectional Analysis of the Long-term Outcomes**

All 35 patients who participated in the telephone interviews also underwent the SF36 questionnaire to accurately assess their long-term quality of life, while their relatives estimated their functional autonomy through the FAQ standardized questionnaire (2 patients with no relative available rated their own FAQ). t-MMSE was also performed to ensure the patients were able to answer these questionnaires (median score, 25/26; range, 18–26). Telephone interviews were performed in median 64.0 months (range 15–189.2) after disease onset. Patient characteristics were similar between those included or not in this cross-sectional analysis, except for less treatment with azathioprine, less frequent cerebellar symptoms at onset and seizures at the last visit, and more frequent neuropathic pain at onset in those included (eTable4, links.lww.com/NXI/A752). Moreover, 8 patients were not included because they had died during follow-up (Figure 1), whereas all patients included were still alive at the last visit. Only 7 patients (20%) were dependent in 3 or more activities (FAQ score ≥9).
Compared with functionally independent patients (FAQ score<9), cerebellar ataxia persisting during the telephone interview was significantly more frequent in the dependent group of patients (FAQ score ≥9, n = 5/7, 71% vs n = 7/28, 25%, *p* = 0.033). The SF-36 quality of life scores of this cross-sectional cohort were similar to those of the normative population, except for moderate reduction of the vitality subscore (mean score 49.9 vs 58.0, *p* = 0.037; Figure 4B).

**Discussion**

This study highlights the diagnostic challenge that CASPR2-encephalitis represents at its early stage and its mostly favorable long-term prognosis. Although previous studies describe the many different symptoms encountered at any time point over the disease course, none describe precisely the symptoms present at onset and their further development.3,5,9-13 (Illustrated in eFigure 4, links.lww.com/NXI/A752). It is of importance that it was found in this cohort that the clinical presentation at onset of the disease was highly heterogeneous and did not initially suggest autoimmune limbic encephalitis. In particular, typical limbic encephalitis symptoms, especially anterograde amnesia, were missing at onset in most cases. When present at onset, seizures were usually initially isolated (not accompanied by cognitive disturbances), before other symptoms appeared, as reported recently in a study focusing on seizure outcome.23 Subsequently, the disease tended to develop progressively, the median time to peak largely exceeded 1 year from the first symptom. This is in contrast to other autoimmune encephalitides; for instance, the development of the full clinical picture usually takes less than 1 month in N-Methyl-d-Aspartate receptor-encephalitis24 and never more than 1 year in leucine-rich glioma inactivated protein 1-encephalitis (median, 5.5 months).11 The initial course of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor-encephalitides and gamma-aminobutyric acid B receptor-encephalitides also seems faster than in CASPR2-encephalitis; the times to diagnosis are reported to be 6.525 and 4.5 weeks,26 respectively. As a result of the slow progression of CASPR2-encephalitis, the
core CASPR2 symptoms were rarely present at onset, and the Graus criteria were not fulfilled in more than half of the patients. In addition, diagnostic tests (brain MRI and EEG) were often normal. Taken together, the slow progression, the frequent absence of limbic symptoms at onset, and the normal MRI and EEG results make the diagnosis of CASPR2-encephalitis particularly challenging, especially at the earliest stage. Timely diagnosis is important because early immunotherapy may improve the patients' long-term outcomes, and in the patients included in this study, the diagnosis and initiation of immunotherapies were strikingly late (almost a year in following disease onset for most of the patients) compared with that reported in other autoimmune encephalitis (the median time ranging from 21 days in N-Methyl-d-Aspartate receptor-encephalitis to 26 weeks in leucine-rich glioma inactivated protein 1-encephalitis). The absence of correlation between delay to immunotherapy and functional outcome in our cohort might be due to the limitations of the mRS score as assessment of follow-up clinical status in autoimmune encephalitides. It is also likely that because the diagnosis is challenging, some cases are not recognized and are therefore not adequately treated. It is of importance that the results presented in this study indicate that at least 1 of 3 symptoms can be identified in most patients at the early stage, before diagnosis: seizures (generalized or focal), cerebellar ataxia, and/or neuropathic pain. These early neurologic signs were often associated with other, less specific symptoms, such as insomnia, asthenia, weight loss, and/or mood disorders. These findings suggest that the onset of these neurologic signs—otherwise unexplained—are compatible with early stage of CASPR2-encephalitis, especially in men older than 50 years who also develop the other symptoms described earlier; testing for anti-CASPR2 antibodies should be performed in such cases.

It is of note that the clinical findings were in accordance with previous studies investigating CASPR2-encephalitis; the population was composed mainly of men older than 50 years, limbic involvement was present in all patients, and there were frequent extralimbic features such as cerebellar ataxia, neuropathic pain, asthenia, sleep disorders, weight loss, and dysautonomia. Only the prevalence of tumors was unexpectedly high; however, the diversity of tumor types and the timing of tumor and encephalitis diagnoses suggest that cancer associations were fortuitous. At the last visit, functional outcomes were good in most of the patients, in line with previous reports showing 73%–89% of patients with mRS ≤2 at the last visit. By contrast, mortality was relatively high (17%), which is likely explained by the demographics of CASPR2-encephalitis: the 8 deceased patients were among the oldest, and in most cases, death occurred years after disease onset and had no identifiable relation to the neurologic disease. It is of importance that CASPR2-encephalitis might constitute a precipitating factor in elderly patients with comorbidities. Of interest, seizures, although frequent, tended to resolve before the peak of disease and were still present at the last visit in only a quarter of the patients. This is in line with previous findings in other types of autoimmune encephalitis, in which epilepsy is often self-limiting. In addition, the cross-sectional analysis confirmed the preservation of long-term functional independence in most of the patients, with quality of life scores only mildly lower than normative values. Interviews of the patients and relatives did not suggest profound cognitive deficits on the long-term; however, due to the design of the study, we were not able to assess the cognitive status of the patients at the last visit. Remarkably, cerebellar ataxia at the last visit was more frequent in the subset of patients with long-term disability; future studies are warranted to determine whether more aggressive immunosuppression should be considered in patients with CASPR2-encephalitis who develop this sign.

The main limitation of the study lies in its retrospective nature and the shortcomings inherent to telephone interviews. Moreover, the analysis was restricted to patients testing positive for CASPR2-Abs in the CSF to better select the limbic encephalitis cases. This kept out other clinical phenotypes associated with CASPR2-Abs, which will need to be addressed in further studies.

In conclusion, we show that CASPR2-encephalitis is clinically heterogeneous at the early phase and has a slower progression compared with other autoimmune encephalitides, which makes it difficult to recognize. In men older than 50 years, the otherwise unexplained development of limbic symptoms (seizures and behavioral changes), cerebellar ataxia, or neuropathic pain is suggestive of early stage of CASPR2-encephalitis, particularly if associated with recent asthenia, insomnia, or mood disorders. The findings suggest that any such patient should be tested for anti-CASPR2 antibodies.

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**Appendix**

| Name               | Location                                                                 | Contribution                                                                                           |
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**Appendix (continued)**

| Name               | Location                                                                 | Contribution                                                                                           |
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| Name                      | Location                                                                 | Contribution                                                                 |
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