OVERSIGHT COMMITTEE REPORT ON

Potential Neurological Syndrome of Unknown Cause

February 22, 2022

Transmittal Letter

Hon. K. Dorothy Shephard
Minister of Health

Dear Minister Shephard,

On behalf of the committee appointed to provide expert oversight regarding cases identified as a cluster of a neurological syndrome of unknown cause, we are pleased to submit this report for your consideration in your Public Health investigation.

Respectfully submitted,

Dr. Natalie Banville
Co-Chair, Oversight Committee

Dr. Susan Brien
Co-Chair, Oversight Committee

Investigation into a Neurological Syndrome of Unknown Cause:
Oversight Committee Report

February 22, 2022

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Executive Summary

In the context of a public health investigation led by Public Health New Brunswick (PHNB), the oversight committee, created expressly to provide independent expert oversight and recommendations regarding cases that were identified as part of a cluster with a potential neurological syndrome of unknown cause, presented its findings.

Between August 2021 and February 2022, the committee conducted case reviews, including chart reviews and secondary reviews, for the 48 individuals identified as members of the cluster. These cases were between 18 and 85 years of age (median = 57 years, SD = 18 years), and half were female (24 cases). Most of them were reported to be living in New Brunswick health zones 1 (73%) and 6 (21%) at the time of their referral to the Creutzfeldt-Jakob Disease Surveillance System (CJDSS), which identified them as members of the cluster.

During the in-depth clinical reviews, cases were randomly allocated to pairs of neurologists, who reviewed independently and then presented and discussed their findings with the full committee consisting of six neurologists, co-chairs from Horizon Health Network (HHN) and Vitalité Health Network (VHN), and a Medical Officer of Health acting as a liaison with PHNB.

The committee found that out of 48 cases, none fulfilled the full criteria of the case definition. In light of these findings, the committee concluded that although some of the cases have presentations with unusual symptomology, they do not appear to have a common illness with an unknown etiology and there is no evidence of a cluster of neurological syndrome of unknown cause.

Acronyms

Federal Organizations

CJDSS – Creutzfeldt-Jakob Disease Surveillance System

CFEZID – Centre for Food-born, Environmental and Zoonotic Infectious Diseases

IDPCB – Infectious Diseases Prevention and Control Branch

NML – National Microbiology Laboratory

PHAC – Public Health Agency of Canada

Provincial Organizations

GNB – Government of New Brunswick

PHNB – Public Health New Brunswick

HHN – Horizon Health Network

VHN – Vitalité Health Network

MIND – Moncton Interdisciplinary Neurodegenerative Disease Clinic

Other Acronyms

CFS – Cerebral Spinal Fluid

CJD – Creutzfeldt-Jakob Disease

DNA – Deoxyribonucleic Acid

EEG – Electroencephalogram

MRI – Magnetic Resonance Imaging

Preamble

When disclosing information, Public Health New Brunswick always:

- respects the imperative need to find the right balance between the public's need and right to know and public health duty to protect the privacy of all New Brunswickers
- follows the principle of necessity and proportionality: information is disclosed in a manner that does not permit the identification of affected individuals but is sufficient to fully inform the public

The findings presented in this report follow applicable privacy legislation and best practices to ensure every individual's right to privacy are protected at all times.

Some of the information used for this investigation was collected directly from individuals, who provided their informed consent, which included assurance that no personal or identifying information would be disclosed in the report of findings, and that only de-identified information would be made available to those interested, including participants.

Introduction

In the context of an ongoing public health investigation led by Public Health New Brunswick (PHNB), this committee was appointed with the task of providing independent expert oversight and recommendations regarding the cases identified as members of a cluster with a potential neurological syndrome of unknown cause.

Illnesses of unknown etiology are syndromes or diseases for which little is known about the root causes. As such, these illnesses may be challenging to treat and, in the context of transmissible infections, may represent a risk to the health and safety of the public.

In order to ensure the proper and appropriate care for the individuals identified as members of the cluster and to ensure due diligence with respect to the ongoing public health investigation, the committee was tasked with the formal review of cases and their classification as members of the cluster.

The committee's membership was comprised of co-chairs from the Horizon Health Network (HHN) and Vitalité Health Network (VHN), six independent neurologists who practice within the province and with a variety of subject matter expertise in the field of neurology, and a Medical Officer of Health, acting as a liaison with PHNB (see Appendix B).

The committee's inaugural meeting was held in June 2021, and initially focused on establishing a rigorous and ethical protocol that would allow the committee to proceed with the review while respecting the affected individual's right to privacy and reducing the risk of bias.

In fulfillment of its mandate, the committee presents its findings in the following report, so that they may be considered by PHNB through the course of their public health investigation.

Background

The Creutzfeldt-Jakob Disease Surveillance System (CJDSS) is a federal program that provides conducts prospective national surveillance for human prion disease in Canada. . The CJDSS offers support to collaborating health professionals via consultation, laboratory investigations, logistic support, and education. The CJDSS operates out of the Centre for Food-borne, Environmental and Zoonotic Infectious Diseases (CFEZID)It collaborates with local healthcare providers and assists with the diagnosis of human prion diseases to support epidemiological analysis and public health decision-making. Human prion diseases are provincially reportable and nationally notifiable in Canada.

Through routine case management, a New Brunswick neurologist and the CJDSS noted some common symptoms and similar potential diagnostic profiles among some recent New Brunswick referrals to the surveillance system. These referrals tested negative for Creutzfeldt-Jakob Disease but, due to some noted commonalities in signs and symptoms and the lack of a confirmed diagnosis among cases, the individuals were categorized as being part of a cluster of a potential neurological syndrome of unknown cause by the main referring neurologist and CJDSS who, together, developed the case definition for the cluster.

In late 2020, the New Brunswick neurologist and the CJDSS notified Public Health New Brunswick in writing of these cases. By the end of April 2021, a total of 48 individuals had been formally identified as part of this cluster, 46 of whom had been referred by a single neurologist. Another neurologist referred one of the other cases for investigation of CJD only and was not aware the individual's name had been added to the cluster. A third neurologist referred the remaining case.

At that time, Public Health New Brunswick instigated a two-pronged investigation – an epidemiological investigative survey and a clinical review of the identified cases.

The epidemiological investigative survey commenced in May 2021 and a final report was released in October 2021. The survey did not identify any specific behaviours, foods, or environmental exposures that can be identified as potential risk factors among the cases interviewed.

In June 2021, Public Health New Brunswick commenced the second part of their investigation and announced the creation of an oversight committee to conduct a clinical review of the 48 cases identified as being part of a potential cluster of a neurological syndrome of unknown cause and to support the work of the Moncton Interdisciplinary Neurodegenerative Disease (MIND) Clinic in its objective to provide care and treatment to these patients.

The vice-presidents of Medical Affairs for both health networks, Dr. Natalie Banville of Vitalité Health Network and Dr. Edouard Hendricks of Horizon Health Network, who was later succeeded by Dr. Susan Brien, were appointed as co-chairs of the Oversight Committee, which also consisted of six independent neurologists and a Medical Officer of Health from Public Health New Brunswick. The neurologists who formed this committee were: Dr. Sarah Ironside, Dr. Lyle Weston, Dr. Sarmad Al Shamaa, Dr. Mario Alvarez, Dr. Ernest Clevinger and Dr. Byrne Harper (Appendix B).

The role of the neurologists on this committee was to provide peer review and expert oversight of the identified cases, to ensure due diligence and to help determine if there were potential alternative diagnoses or if more investigation is indicated. This work involved, but was not limited to, a comprehensive review of clinical and diagnostic records and information.

Once the reviews were completed, the Oversight Committee sent letters to the individuals' primary care physicians with its conclusions around whether an individual should be included or excluded from the cluster and to provide recommendations for follow-up testing and/or treatment, as applicable. Copies were also provided to the referring physician to ensure that all care providers involved with this patient were made aware of the committee's findings and recommendations. Letters were also sent to the individuals themselves (or their next of kin, where appropriate), advising them to contact their primary care physician to discuss their case.

Objectives

The work of the Oversight Committee consisted of:

1. Clinical review of:
    - medical charts/records of identified affected individuals;
    - relevant data obtained from questionnaires completed by their caregivers; and
    - information obtained from the CJDSS.
2. Identifying patients, or subset of patients, that may need re-interview, new examination/evaluation and further testing.
3. Identifying gaps in the electronic medical records and recommending areas for improvement moving forward.
4. Review of case definition and recommendations for changes.
5. Identifying potential requirements for further laboratory/pathology testing of human samples, including recommendations related to what should be tested for and which samples should be collected.
6. Scan of potentially applicable research.

The overall objective of this work was to determine whether individuals were properly categorized as being part of a cluster of individuals identified as suffering from a neurological syndrome of unknown cause.

Based on its findings from the clinical review of files, the committee did not deem it necessary to pursue changes to the case definition, which the committee found to be vague, overly broad and potentially inclusive of other neurological and medical conditions or diseases. Instead, it reached the conclusion that there was no syndrome to be defined and a case definition was not needed.

In the same vein, the committee did not see the need to identify recommendations for testing of human samples, which would be unnecessarily invasive, given there were no commonalities of conditions found that would indicate the need for this type of testing.

Methods

In June 2021, Public Health New Brunswick announced the creation of an oversight committee to support the work of the MIND Clinic and to conduct a clinical review of the 48 cases identified as being part of a potential cluster of a neurological syndrome of unknown cause. The identification of these cases was based on a perceived common clinical presentation.

The Vice President of Medical Affairs at Vitalité Health Network, and the Vice President of Medical, Academic and Research Affairs for Horizon Health Network were appointed as co-chairs of the Oversight Committee. The committee also consisted of six independent neurologists, all experienced practitioners with a variety of experience in the field of neurology. A Medical Officer of Health served as a liaison with the office of Public Health New Brunswick.

The role of the neurologists on this committee was to provide peer review and expert oversight of the identified cases, to ensure due diligence and to help determine if there were potential alternative diagnoses or if more investigation is indicated. This work involved but was not limited to a comprehensive review of clinical and diagnostic records and information.

The Oversight Committee held its introductory meeting on June 2nd, 2021 and its first full meeting on June 23rd, 2021, when the review process was confirmed. However, due to difficulties in accessing the medical records of patients included in the cluster, the first case reviews were not assigned until the beginning of August 2021.

Despite multiple attempts, PHNB was not able to obtain the needed information from the main referring neurologist. Compounding this, in New Brunswick, individual medical records are contained within various systems that are set up to protect the privacy rights and personal and medical information of its citizens. PHNB does not have access to these records and, as a result, had to seek special approvals for the purpose of conducting this investigation.

Case Definition

The first draft of the case definition was shared with PHNB on December 10th, 2020. In January 2021, the definition, a product of collaboration between the CJDSS and the main referring neurologist, was updated to include confirmed and suspect cases, and was accepted by PHNB. The case definition is as follows:

Confirmed Case:

Progressive neurological syndrome involving rapidly progressing dementia and at least four of the following clinical features, verified directly where possible by a physician:

- Cerebellar ataxia (gait ataxia, truncal ataxia, cerebellar dysarthria or dysmetria), abnormal cerebellar function test or cerebellar symptoms (dysdiadochokinesis, intention tremor etc.)
- Psychiatric symptoms (agitation/irritability, aggressiveness, apathy/withdrawal, anxiety or obsessive behaviour)
- Visual hallucinations, cortical blindness or other cortical visual symptoms
- Pyramidal or extrapyramidal signs, including atypical Parkinsonism
- Myoclonus
- Painful sensory symptoms (limb pain, dysesthesia or paresthesia) persisting for six months or more, in absence of peripheral nervous system dysfunction
- Muscle atrophy

The majority of these should manifest during the first 18-36 months of illness

AND

One or more of the following findings from supporting investigations:

- Atrophy, greater than expected for age on MRI
- EEG slowing or hypoperfusion on SPECT (CT) or hypometabolism on PET-CT scan

AND

Insufficient evidence for an alternative diagnosis, including known forms of human prion disease

Suspect Case:

Progressive neurological syndrome involving at least four of the following clinical features, verified

directly where possible by a health care provider:

- Rapidly progressing dementia
- Cerebellar ataxia (gait ataxia, truncal ataxia, cerebellar dysarthria or dysmetria), abnormal cerebellar function test or cerebellar symptoms (dysdiadochokinesis, intention tremor etc.)
- Psychiatric symptoms (agitation/irritability, aggressiveness, apathy/withdrawal, anxiety or obsessive behaviour)
- Visual hallucinations, cortical blindness or other cortical visual symptoms
- Pyramidal or extrapyramidal signs, including atypical Parkinsonism
- Myoclonus
- Painful sensory symptoms (limb pain, dysesthesia or paresthesia) persisting for six months or more, in absence of peripheral nervous system dysfunction
- Muscle atrophy

The majority of these should manifest during the first 18-36 months of illness.

AND

Insufficient evidence for an alternative diagnosis.

Data Collection and Analysis

Data Collection Tool:

A data collection tool was developed by Public Health New Brunswick to compile the clinical data for each of the 48 patients reviewed by the oversight committee. The data collection tool was developed to assist the reviewers with the available clinical and laboratory information of cases included in the cluster, in a consistent manner. Through this document, patient's data was collected regarding demographic information, presenting complaints, past medical history, social history, family history, treatment history, examination history, and investigations. Extensive information was collected in each category to describe the characteristics (such as onset, site, timing) of the symptoms and signs, their progression, and resolution or ongoing therapy/treatment. In this document, reviewer's comments and recommendations regarding the need of re-examination of the patient by the neurologist or any other clinician and further testing were also collected. This data collection tool was reviewed by the Oversight Committee and approved for this purpose.

Supplementary documents were also provided to the reviewers, which included the dates, types of laboratory tests, and the results of diagnostic imaging. Results that were solely available in French were translated to English and both were provided to the committee.

Source of Data:

Patient information for the data collection tool was obtained from several sources, including the Government of New Brunswick Electronic Health Record (GNB-EHR) and the Hospital Electronic Medical Records (EMR), where patients were assessed, followed, or received treatment as an outpatient or in patient. Data from the GNB-EHR included the dates, types, and results of investigations such as laboratory tests (chemical tests, hematological tests, blood or blood-product transfusions, microbiological tests, serology, and tests with specific tissues) and diagnostic imaging (x-ray, computerized tomography, ultrasound, magnetic resonance imaging (MRI), and nuclear medicine). The GNB-EHR also includes patients' treatment/therapy summary profiles. Results of testing and medications were entered in the data collection tool in the appropriate data tab.

Data from Hospital EMRs included initial consultation requests by the primary healthcare provider, patient's history and physical examination reports, specialist consultation reports and updates, operative records, family conference reports, discharge summaries, and results from tests and/or reports. These reports included but were not limited to, electroencephalograms (EEGs), electromyograms (EMGs), polysomnograms, attending nurses' notes, and any other applicable allied healthcare provider reports, notes, or data entries.

Data entry and cleaning:

Patients' clinical data was compiled between July and November 2021 by an experienced medical researcher and reviewed by a Medical Officer of Health. All applicable reports were printed and logged with the patient's unique investigation identification number, then all personal information was de-identified, and the documents were scanned and saved as PDFs. Every entry in the data collection tool included the location of the source document (GNB-EHR or hospital EMR), the type of report, the dictation date, the date signed, and the name of the person to whom the data is attributed. As part of a summary review of the data, patient files were reviewed again in December 2021 and any new reports or findings were compiled for the reviewers using the same method described above.

Data analysis:

Descriptive analysis methods were used to analyze the collected information on each case through the data collection tool. The main software used for the analyses was IBM SPSS Statistic Version 26.0. This report contains

descriptive analyses of data collected from all 48 reviewed cases. Analyzed findings were summarized as counts and percentages and presented in tables.

Process for the Review:

The review of cases was completed using a three-step process. First, each case was randomly assigned to two neurologists. Each neurologist independently reviewed the information provided in the data collection sheet and additional documents. On an average, it took about four hours for each doctor to review individual records. Therefore, each case review took up to a total of eight hours.

Secondly, these two neurologists would then meet to discuss and compare their findings. If required, they looked into the EMR or EHR to verify the information provided in the data collection sheet or followed up directly with the physician of record for specific investigations to gain additional insight into the case. In some instances, they requested to see the case for an in-person assessment, or requisitioned additional tests or investigations be completed and provided for review.

As a next step, the two neurologists would present their findings to the committee as a whole and the six neurologists would discuss the findings and decide on final conclusions and recommendations, if applicable. The recommendations, including decisions on the inclusion or exclusion of cases from the potential neurological syndrome of unknown cause was always unanimous. The final step was for the assigned neurologists to submit a written report to the committee.

Throughout the process, the pairs of neurologists were rotated, to avoid unintentional professional bias.

At one Oversight Committee meeting, Dr. Gerald Jansen, lead neuropathologist for CJDSS, presented the results of the autopsies completed on six of the individuals included in the cluster. These findings were included as part of the full review of these cases using the methodology described above. These results were subsequently received from CJDSS on September 9th, 2021.

All written clinical review reports were received by the Oversight Committee by January 2022. As reports were received, a letter was sent to each individual included in the cluster (or their next of kin, if applicable), informing them of the general findings of the committee, specifically whether they continue to be included in a cluster of an unknown neurological syndrome, and to encourage them to contact their primary care provider or the MIND Clinic (Moncton Interdisciplinary Neurodegenerative Diseases Clinic) to further discuss their health care plan. A letter was also sent to their primary care provider and copied to the MIND clinic with recommendations for further care, treatment, or investigation as applicable.

Results

Results:

This report describes the findings from the clinical reviews of 48 individuals who have been identified as having a potential neurological syndrome of unknown cause in New Brunswick, Canada. It highlights the results of the reviews by the oversight committee completed using the information collected in the data collection tool, specifically developed for this purpose, by Public Health New Brunswick. The data collection tool collected information on topics related to demographics, patient's history, clinical presentations, investigations, treatment/therapy, and neurologists' comments and recommendations.

Demographic Information of cases:

Information on all the cases (n=48) included in the line list of the potential neurological syndrome of unknown cause, provided by the CJDSS, were reviewed by the six neurologists in the Oversight Committee. This review started on August 3rd, 2021 and was completed in February 2022. Among the 48 cases, 10 (21%) individuals are deceased.

Twenty-four of the reviewed cases were male (50%) and 24 were female (50%). Ten patients (21%) were aged 40 or younger at time of referral. The median age for all cases was 57 years (range 18-85 years). The average age of males was 62 years (Mean: 62, SD: 15, range 28-85), and the average age of females was 52 years (Mean: 52, SD: 19, range 18-84). Overall, there were more females in younger age groups and more males in older age groups.

At the time of referral, most of the cases were living in areas in southeastern New Brunswick around the Moncton area (Zone 1; n=35, 73%), followed by the northeastern region around the Acadian Peninsula (Zone 6; n=10, 21 %). The rest of the patients were living in Health zones 2, 5, and 7 (one patient in each zone). At the onset of symptoms, most of the cases' residence were in urban areas (n=29, 60%). It should be noted that the geographic distribution of cases is consistent with the service area of the referring neurologist

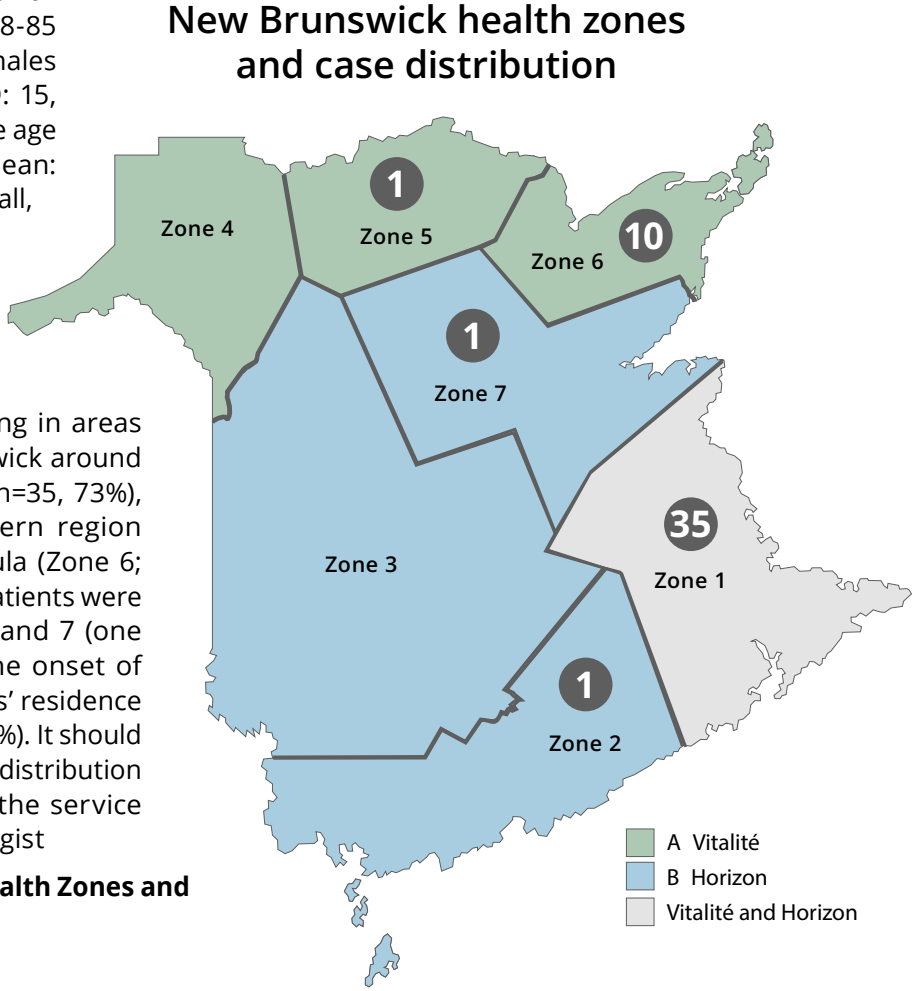

Figure 1: New Brunswick Health Zones and Case Distribution

Table 1: Demographic Information

Demographic Information	Notes
Patients, n (%)	48 (100%)
Patient age (median years at referral)	57 (SD 18) Range 18-85 years
Age 40 or younger at referral, n (%)	10 (21%)
Patient Sex, n (%)	
Male	24 (50%)
Female	24 (50%)
Mean age, females at referral (n = 23)	52 (SD 19) Range 18-84
Mean age, males at referral (n = 25)	62 (SD 15) Range 28-85
Health zone at the time of referral, n (%)	
Zone 1	35 (73%)
Zone 6	10 (21%)
Zone 2	1 (2%)
Zone 5	1 (2%)
Zone 7	1 (2%)
Patients' residence classification time of referral n (%)	
Urban	29 (60%)
Rural	19 (40%)

Referral Timeline:

Most of the patients were referred for CJD assessment in 2020 (n= 18, 38%), followed by 2019 (n=15, 31%), 2021 (n=9, 19%), and 2018 (n=4, 8%). In 2017 and 2014, one patient each was referred. It was following the CJD review process, and once CJD was excluded as a diagnosis, that these cases were later grouped as a cluster of a potential syndrome of an unknown cause.

Documented Symptoms/signs:

Most of the cases included in the list of the potential neurological syndrome of unknown cause presented with several symptoms and signs at the time of referral, including generalized symptoms (such as headache, fatigue, dry skin, constipation), specific neurological symptoms/signs [such as lack of muscle control or coordination of voluntary movements (ataxia), quick and involuntary muscle jerks (myoclonus), dysmetria (overstepping or under stepping, or the lack of coordination of movement resulting in undershooting or overshooting of intended position of arm, leg or eye), seeing things that are not there (visual hallucinations) and other visual disturbances, difficulty in speech (dysarthria), abnormal muscle tone, muscle weakness, painful sensory symptoms (e.g.: burning or prickling sensation)], and psychiatric symptoms (e.g.: irritability, anxiety, depression). Clinical charts from the first referral visit showed that in 2019, 17 cases had first symptoms, followed by 9 cases each in 2018 and 2020, 4 cases in 2016, 3 cases each in 2014 and 2017, 2 cases in 2013, and 1 case in 2010.

In clinical notes, lack of muscle control or coordination of voluntary movements or ataxia was the most common symptom/sign documented (n=43, 90%), followed by quick and involuntary muscle jerks or myoclonus (n=42, 88%), psychiatric symptoms (n=38, 79%), seeing things that are not there or visual hallucinations (n=23, 48%), difficulty in speech or dysarthria (n=22, 46%), slowness of movement or bradykinesia (n=19, 40%), overstepping or under stepping or dysmetria (n=19, 40%), muscle atrophy (n=19, 40%), and burning or prickling sensation or paresthesia (n=17, 35%) were noted. Out of the 48 cases, only 25 cases had documented dementia that manifested and progressed within two years of the of the diagnosis, recorded as having rapidly progressing dementia. The clinical notes also documented some pre-existing conditions among those cases: sleep disorder (n=21, 44%), head trauma (n=19, 40%), depression (n=15, 31%), and anxiety (n=14, 29%) were most commonly documented.

Table 2: Common Clinical Signs and Symptoms

Clinical Features	Cases = 48 (100%)
Ataxia	43 (90%)
Myoclonus	42 (88%)
Psychiatric Symptoms	38 (79%)
Visual Hallucinations	23 (48%)
Dysarthria	22 (46%)
Bradykinesia	19 (40%)
Dysmetria	19 (40%)
Muscle Atrophy	19 (40%)
Paresthesia	17 (35%)

Investigations:

Data from the GNB-EHR showed that all cases included in the list of the potential neurological syndrome of unknown cause had extensive investigations performed. Those investigations included laboratory tests (chemistry, hematology, coagulation, transfusion medicine, microbiology, serology, and cytopathology) and diagnostic imaging (x-ray, Computed tomography (CT) scan of the brain, ultrasound, magnetic resonance imaging (MRI), and electroencephalography (EEG), Single-photon emission computed tomography (SPECT-CT), and genetic test). It is to be noted here that most of the cases had primary investigation and follow-up investigations, where the same tests were redone to identify the changes over time or after or before the treatment/therapy. Among the neurological condition specific investigations, Magnetic Resonance Imaging (MRI) was performed in all cases (n=48, 100%), followed by electroencephalography (EEG) (n=46, 96%), Spinal fluid analysis (n=44, 92%), Computed tomography (CT) scan of the brain (n=40, 83%), Single-photon emission computed tomography (SPECT-CT) (n=37,77%), and genetic test (n=15, 31%). The Montreal Cognitive Assessment (MoCA) was also completed on 34 (71%) cases to assess their cognitive function. It is to be noted here that most of the investigations were done more than once based on the recommendations of the consulting specialists. 29 (60%) of the MRI's conducted were reported to have abnormal findings such as atrophy, greater than expected for age or unexplained atrophy. Of those who had an EEG, 38 (83%) were found to have mild to moderate regional or generalized slowing of brain activity. All the cases who had a SPECT-CT (n=37, 77%) showed variable degrees of hypoperfusion (moderate to diffuse hypoperfusion) in one or more regions of brain. Hypoperfusion can be a non-specific finding that can be seen across many different conditions. Of the cases with an available CT scan (n=40, 83%), 17 (43%) of those reported abnormal findings (variable degrees of atrophy of different regions of brain and prominence of the ventricles). Cerebrospinal fluid analysis for protein markers for Prion disease was done on 44 cases (92%), all of which were negative. Genetic tests for Hereditary Prion disease was completed on 15 cases (31%), which were negative.

Table 3: Investigations

Investigations and Results		
Name of Investigation	**Percentage**	**n**
Montreal Cognitive Assessment (MoCA)	34 (71%)	n = 48
Electroencephalography (EEG)	46 (96%)	n = 48
Abnormal EEG	38 (83%)	n = 46
SPECT CT	37 (77%)	n = 48
Abnormal SPECT CT	37 100%)	n = 37
Brain CT	40 (83%)	n = 48
Abnormal Brain CT	17 (43%)	n = 40
Brain MRI	48 (100%)	n = 48
Abnormal Brain MRI	29 (60%)	n = 48
Cerebrospinal fluid analysis	44 (92%)	n = 48
Results: Negative EP-QuIC	44 (100%)	n = 44
Genetic Tests (various)	15 (31%)	n = 48
Autopsy results	6 (13%)	n = 48
Confirmed known condition(s)	6 (100%)	n = 6

Autopsy results: Ten patients out of the 48 (21%) are deceased, 6 of them had autopsies completed. For the ten patients who are deceased, post-mortem diagnoses were confirmed by autopsy, or, the review of medical records has provided sufficient evidence of an alternative diagnosis. These diagnoses included such conditions as Alzheimer's disease, Lewy body disease, or cancer.

Neurologists' report findings:

After completing the review of records, neurologists provided potential alternative diagnoses for 41 patients (85%). The alternate diagnoses provided included some known conditions like Alzheimer's disease, Lewy body dementia, mixed dementia, diabetic or inflammatory polyneuropathy, Parkinson disease dementia, fronto-temporal dementia, alcohol related cerebellar dysfunction, post-concussion syndrome, chronic traumatic encephalopathy, paranoid schizophrenia, chronic Fatigue Syndrome, Chronic severe anxiety disorder, and cancer.

Most of these cases were recommended to have additional consultations with their treating neurologists or other neurologists (such as behavioral or movement disorder neurologists). In addition, the neurologists also recommended consultations with neurophysiologists, medical geneticists, geriatricians, psychiatrists, ophthalmologists, rheumatologists, concussion specialists, psychologists, cardiologists, and gastroenterologists.

The reviewing neurologists also recommended further investigations for many of the cases. These included tests and evaluations such as a neuropsychology evaluation, psychiatric evaluation, genetic testing, Magnetic resonance imaging (MRI), computed tomography (CT) scan, polysomnography, DaT scan (a specific type of single-photon emission computed tomography (SPECT) imaging technique), blood tests, Cerebrospinal fluid (CSF) analysis, cardiac work-up.

Of the 48 total cases, the committee also made recommendations for specialist consultation and/or further investigation for 29 cases (60%). Of those, 15 were recommended to have both consultation from a specialist and further investigation, 9 and 5 were recommended for only consultation or further investigation, respectively. The summary of these recommendations is available in the following table.

Table 4: Summary of Neurologists' Recommended Actions

	Total	
Recommended Actions	**N**	**%**
Consultation and investigation	15	31%
Consultation only	9	19%
Investigation only	5	10%
No additional follow-up	19*	40%
Grand Total	**48**	**100**%

**These 19 individuals include the 10 who are deceased*.

Discussion

The clinical data that had been collected was reviewed and all documented clinical features and results from supporting investigations were compiled and then analyzed to identify cases meeting the case definition (see Appendix B). In accordance with the provided case definition, a confirmed case must involve rapidly progressing dementia, at least four clinical features of which the majority manifested within the first 18-36 months of the illness, one or more supporting investigation, and insufficient evidence for an alternative diagnosis including known forms of human prion disease.

Out of 48 cases, none fulfilled the full criteria of the case definition. Twenty-five out of 48 cases met the criteria for rapidly progressing dementia, 19 of those had at least four of the clinical features mentioned in the definition, which were verified directly by a physician. Out of those 19 cases, those symptoms did not manifest during the first 18-36 months of illness in one case. In addition, one case did not fulfill the criteria for supporting investigations (in MRI, EEG, and SPECT-CT) as an alternative diagnosis was provided. There was no evidence of a known prion disease in any of these cases. The reports of the reviewing neurologists of these remaining 17 cases were then reviewed to determine whether there was sufficient evidence for alternative diagnoses (or potential alternative diagnoses), concluding there was sufficient evidence for an alternative diagnosis in all of the17 cases. These diagnoses include Alzheimer's disease, Lewy Body Disease, Post-concussion Syndrome and others. In summary, of the 48 cases reviewed, none met the case definition as developed by the main referring neurologist and CJDSS. The findings are shown in a flow chart below.

Table 5: Summary of Case Definition Analysis

Case Definition Criteria	Cases = 48
Number of cases meeting the full case definition	0 (0%)
Number of cases with rapidly progressing dementia (within 2 years)	25(52%)
Number of cases with clinical features manifesting within 3 years	19 (40%)
Number of cases presenting with at least 4 clinical features	18 (38%)
Number of cases with one or more findings supporting investigation	17 (35%)
Number of cases with suggested alternative diagnoses/diagnoses	17 (35%)

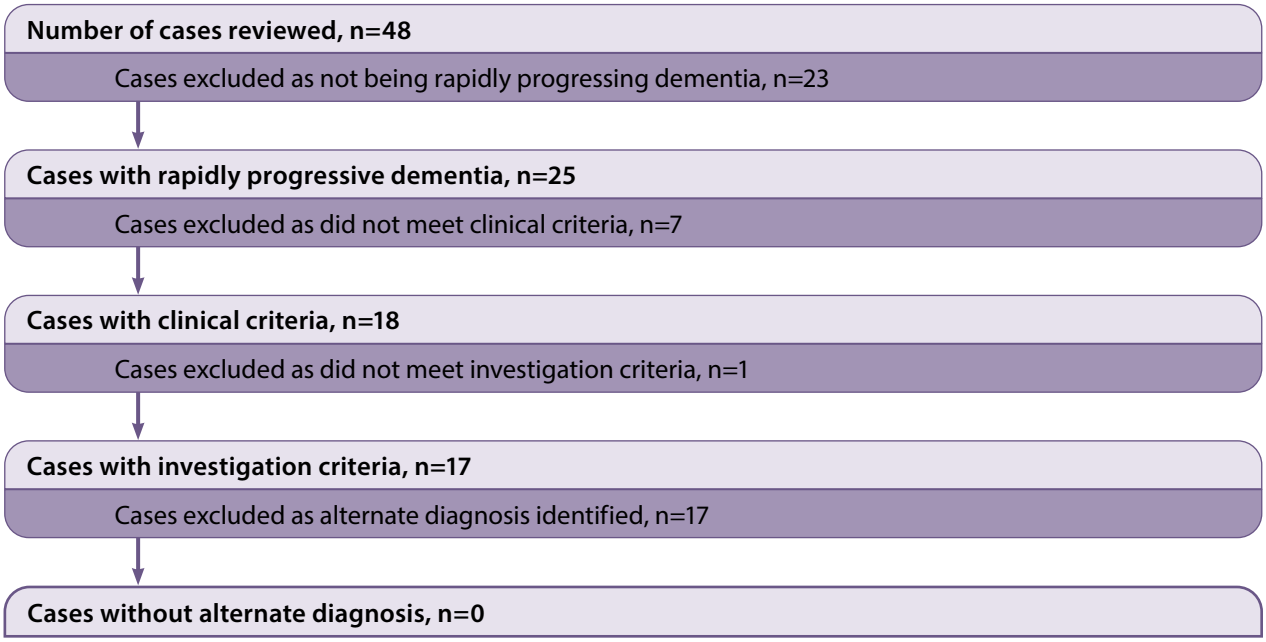

Figure 2: Clinical Review Flow Chart

The data provided here has some limitations. There is the potential for incomplete or missing data as no access was provided to physicians' clinical notes or office records and no way to confirm that all existing records were available on the GNB-EHR and hospital EMRs. Furthermore, the information provided in the consultation reports is the subjective reporting of the dictating physicians and cannot be corroborated by secondary sources. Moreover, there was very limited confirmation from other specialists on some of the clinical findings recorded in the documents.

Nevertheless, data was systematically reviewed and collected according to a standardized process. Details on all source documents were recorded. Reviewers were provided all the available clinical, testing, and treatment information. They could access the actual tests to verify the reporting of the data, e.g., information in an MRI report by a radiologist could be reviewed with the actual MRI and compared with the results described in consultation reports. Investigators could also review and compare multiple reports from various healthcare providers, which allowed for a comprehensive and chronological view of the patients' condition and the progression over weeks, months, and in some cases, years.

This report follows the report entitled "*Investigation into a Neurological Syndrome of Unknown Cause: An Epidemiological Summary of Enhanced Surveillance Interviews*" dated 26th October 2021, which covered the first phase of the investigation into the potential neurological syndrome of unknown cause in New Brunswick. This phase was focused on the review of the clinical and diagnostic information available for those 48 patients by six neurologists. Managed by the Public Health Agency of Canada (PHAC), the CJDSS performs nationwide monitoring of prion diseases, which affect the brain, causing rapidly progressing dementia, movement difficulties, hallucinations, muscle stiffness, pain, and abnormalities showing on diagnostic imaging or on other tests. A growing number of cases reported from New Brunswick were not found to have a known prion disease but were described as presenting in a similar manner. These cases were put under a condition named as the Neurological Syndrome of Unknown Cause. The case definition was developed by three experts: The New Brunswick neurologist who referred 46 of the 48 cases to the CJDSS and two experts/specialists representing the CJDSS and PHAC with additional support from the CJDSS.

PHNB was neither part of the process of determining the clinical content of the case definition nor part of the identification of the cases; however, PHNB has jurisdictional authority over investigations into unusual illnesses in New Brunswick, which are notifiable under the *Reporting and Diseases Regulation* of the provincial *Public Health Act*. The CJDSS process is not meant to usurp this authority but to provide national expertise and surveillance regarding prion disease investigations in Canada. CJDSS does not conduct a retrospective clinical analysis of cases as part of their investigation and relies on clinical information provided solely by referring physicians or the neuropathologist under contract when autopsies are completed.

Since a full review of the case data had not yet been undertaken, a process was established in May 2021 to verify that the first 48 cases met the case definition. This included identifying other potential alternative diagnoses. To accomplish this and ensure due diligence from a clinical perspective, the nine-member oversight committee was enlisted in June 2021 to provide an expert review of the clinical data, recommend next steps, and guide future investigations. From August to December 2021, the oversight committee systematically reviewed the available clinical data for each of the 48 patients. Combined, the data collection and review of each case took approximately 20-25 hours.

The six neurologists on the oversight committee provided expertise and additional perspective on these cases. The quantitative analysis of the clinical data and the findings from the neurologists' review were applied to the case definition, which is the standard of process for investigating a potential new disease. It should be noted that the committee had reservations about the case definition that was developed as it was overly broad and therefore could indicate multiple conditions. Additionally, some of the criteria included in the definition could be open to interpretation. Despite this, after systematically measuring the cases against each element of the case definition, no individual being reviewed met the case definition in full. Additionally, no one specific condition was found to be the probable diagnosis for those individuals for whom an alternate diagnosis was proposed.

Recommendations

Along with its conclusions of the case reviews, the oversight committee would like to make the following recommendations for moving forward.

- **Process recommendations**

    - The review could not conclude that the main referring neurologist had sought second opinions prior to referring individuals to the cluster of suspected cases of an unusual neurological illness with the presence of symptoms that do not fit any recognizable clinical picture. As such, it is the recommendation of the committee that any future cases being considered for a novel syndrome or disease be reviewed by a second specialist (e.g.: neurologist, geriatrician). Should the two physicians not be able to reach a consensus for identifying a patient as potentially having a novel condition, the case would be presented at a board of specialty doctors for determination. This would implement a mechanism of oversight to ensure this due diligence is completed before any further investigations or clustering of cases take place.
    - Given the difficulties experienced in accessing relevant patient information which caused unnecessary delays in the case reviews, it is the recommendation of the committee that written protocols be put into place for the sharing of individual medical information and records with PHNB for the purpose of future investigations that also respect the rights of New Brunswick citizens to privacy and the protection of personal information.

- **Recommendations for patients**

    - This report reveals that patients who were originally included in this cluster have serious known conditions that are impacting their lives in profound ways. Several patients need urgent follow-up assessment and care. Communications have been initiated with the primary care physicians for these patients to inform them of the Oversight Committee findings and the neurologists' recommendations for further testing or re-evaluation. It is the understanding of the committee that these individuals have continued to receive care through their primary care providers, the MIND clinic and/or other specialty providers while the investigation was ongoing.
    - Moreover, many patients and families will have questions regarding their conditions. All the patients involved in this investigation should have access to continued care under the supervision of a specialist.
    - In keeping with the above, the committee further recommends that the MIND clinic continues to provide on-going support to individuals who were identified as part of the cluster and to other citizens of New Brunswick referred to this specialized clinic created for the investigation and treatment of neurodegenerative diseases.

Conclusion

The lack of a defined federal/provincial process for the identification and investigation of a novel disease or condition has caused much speculation and public distrust. Compounding this were experts within their specific fields speculating on causes of a syndrome, the existence of which had not yet been confirmed.

Through this extensive review, the Oversight Committee has unanimously agreed that the individuals who were included in this cluster do not represent a neurological syndrome of unknown cause and has therefore concluded that no such syndrome exists. No individual met the case definition in full and many were found to have other, more probable diagnoses.

The Oversight Committee is confident it has conducted its review in a thorough and scientifically sound manner and stands steadfast in support of the quality of its work and analysis provided in this report. As such, it remains willing to share its work and analysis for further national or international peer review by neurological experts should national and provincial public health officials be of the opinion that such a review is warranted.

References

Investigation into a Neurological Syndrome of Unknown Cause (gnb.ca)

Statistics Canada. 2020. Developing Meaningful Categories for Distinguishing Levels of Remoteness in Canada.
https://www150.statcan.gc.ca/n1/pub/11-633-x/11-633-x2020002-eng.htm

Appendix A: Committee Members

Dr. Susan Brien (Horizon Co-Chair)

Dr. Susan Brien is Vice President Medical, Academic and Research Affairs for Horizon Health Network. Originally from New Brunswick and prior to joining Horizon, Dr. Brien served as the Director, Practice and System Innovation at the Royal College of Physicians and Surgeons of Canada. She played an integral part in the Royal College's international initiative as the Vice-President Asia Pacific. Her portfolio included overseeing new regional, national and international projects, facilitating professional development activities such as team training, simulation, performance assessment, simulation accreditation, and curriculum integration. Dr. Brien also held leadership roles including Chief of Neurosurgery at Le Centre de santé et de services sociaux de Gatineau, where she had practiced as a neurosurgeon. She served as the inaugural Director of Operations for Quebec, Eastern Canada and Nunavut with the Canadian Patient Safety Institute, where she was responsible for national patient safety education. Dr. Brien is an Adjunct Professor of Surgery at the University of Ottawa and a faculty lecturer with the Division of Neurology and Neurosurgery at McGill University, where she also served as the UGME Accreditation Lead for the Gatineau Campus. She is a certified physician executive and member of the American Association of Physician Leaders. As Vice President Medical, Academic and Research Affairs, Dr. Brien oversees and ensures systems, policies and procedures support excellence in medical care and champions constant improvement, innovation, and research.

Dr. Natalie Banville (Vitalité Co-Chair)

Dr. Natalie Banville, originally from the North Shore of Quebec, obtained her Doctor of Medicine (MD) from Laval University. She acquired a specialty in Anesthesia and resuscitation at Laval University in 1998, as well as a FRCPC and CSPQ. She worked as an anesthesiologist at the Chaleur Regional Hospital in Bathurst before becoming head of its Anesthesiology Department. Dr. Banville was a member of the Regional Medical Advisory Committee (RMAC) from 2008-2012 and Medical Director of Zone 6, on a part time basis, from 2012 to 2018. She then took on the role of Regional Medical Director of the Vitalité Health Network from 2018 to 2020 and is now Vice-President, Medical Affairs, Vitalité Health Network.

Dr. Sarmad Al-Shamaa (Horizon)

Dr Sarmad Al-Shamaa is a General and Behavioural Neurologist working at the Moncton Hospital within the Horizon Health Network. He attended the College of Medicine/University of Baghdad from1991-1997 where he obtained his MBChB. He is a Fellow of Iraqi Board for Medical Specialization (Neurology), FIBMS 1999-2004 and a Fellow of Royal College of Physicians of Canada (Neurology), FRCPC June 2021 and also holds a Fellowship in Behavioural Neurology from University of Toronto 2017-2019.

Dr. Mario Alvarez (Vitalité)

Dr. Mario Alvarez obtained his Doctor of Medicine (MD) in 1998, specialty certification in Neurology in 2003, and Master of Science (MSc) in Neuroscience in 2011. He received training on neuro degenerations, movement disorders, and functional surgery of movement disorders. Dr. Alvarez provides medical services at the Dr. Georges-L.-Dumont University Hospital and The Moncton Hospital. From 2003 until 2015 he worked at the International Centre for Neurological Restoration (CIREN, Havana, Cuba), as neurologist and director of the Movement Disorders Clinic. Dr. Alvarez has authored and co-authored several peer reviewed publications. He is a member of the College of Surgeons and Physicians of New Brunswick, the American Academy of Neurology, and the International Parkinson's Disease and Movement Disorder Society.

Dr. Ernest Clevinger (Vitalité)

Dr Ernest Clevinger is a neurologist with the Vitalité Health Network.

Dr. Byrne Harper (Horizon)

Dr Byrne Harper obtained a Specialty certification by the Royal College of Physicians and Surgeons of Canada (Neurology) in 1990. Prior to that, he completed a residency in Neurology at the University of Western Ontario in London Ontario and graduated with degree of Doctor of Medicine from Dalhousie University in Halifax, Nova Scotia. Along with being an active staff member at The Moncton Hospital and Consultant at the George Dumont Hospital, he also works as an Associate Professor at Dalhousie University.

Dr. Sarah Ironside (Horizon)

Dr. Sarah Ironside is an Assistant Professor in the Division of Neurology at Dalhousie University and an Assistant Professor in the Faculty of Medicine (Neurology) at Memorial University. She earned her Bachelor of Science (Hons) degree in Biology and Psychology with high distinction followed by her Doctor of Medicine from Dalhousie University. Subsequently, Dr. Ironside completed her Neurology Residency Training program at the University of Toronto and a fellowship in Neuro-Oncology at Sunnybrook Health Sciences Centre, University of Toronto, with funding from the Crolla Family Chair in Brain Tumour Research and the Gord Downie Fellowship in Brain Oncology. She has authored and co-authored several peer reviewed publications. Dr. Ironside is an active member of the Royal College of Physicians and a Diplomate of the Canadian Neurosciences Federation EEG examination.

Dr. Arifur Rahman (Public Health Liaison)

Dr. Rahman is a Regional Medical Officer of Health for the Eastern Region of New Brunswick. He obtained his medical degree from the Dhaka University, Bangladesh and pursued training in Public Health and Internal Medicine. In Bangladesh he worked as a Medical Officer and a Family Physician for more than 7 years. In Canada, he received Post-Graduate Diploma in Clinical Epidemiology and Master's in public health degrees from the Memorial University of Newfoundland in 2014 and 2016, respectively. Since then he worked with the Public Health Agency of Canada and Eastern Health Authority, Newfoundland and Labrador, before joining the Public Health New Brunswick.

Dr. Lyle Weston (Horizon)

Dr. Weston is a New Brunswick born physician. He obtained his medical degree from Dalhousie University and went on to pursue training in Neurology. After successfully passing his Neurology certification examinations he pursued an additional year of training in Neuroelectrophysiology. He has been a practicing physician in Moncton since 1991. He has served in various capacities at The Moncton Hospital including Medical Director of the Neuroelectrodiagnostics Laboratory, Neurological Sciences Department head and most recently as a co-director of the Neuro-Rehab Program. He continues to provide medical services in The Moncton Hospital, Dr. Georges-L.-Dumont University Hospital, Chaleur Regional Hospital and Campbellton Regional Hospital. Dr. Weston is also a past President of the New Brunswick Medical Society as well as the Canadian Neurologic Society.

Appendix B: Case Definition

Confirmed Case:

Progressive neurological syndrome involving rapidly progressing dementia and at least four of the following clinical features, verified directly where possible by a physician:

- Cerebellar ataxia (gait ataxia, truncal ataxia, cerebellar dysarthria or dysmetria), abnormal cerebellar function test or cerebellar symptoms (dysdiadochokinesis, intention tremor etc.)
- Psychiatric symptoms (agitation/irritability, aggressiveness, apathy/withdrawal, anxiety or obsessive behaviour)
- Visual hallucinations, cortical blindness or other cortical visual symptoms
- Pyramidal or extrapyramidal signs, including atypical Parkinsonism
- Myoclonus
- Painful sensory symptoms (limb pain, dysesthesia or paresthesia) persisting for six months or more, in absence of peripheral nervous system dysfunction
- Muscle atrophy

The majority of these should manifest during the first 18-36 months of illness

AND

One or more of the following findings from supporting investigations:

- Atrophy, greater than expected for age on MRI
- EEG slowing or hypoperfusion on SPECT (CT) or hypometabolism on PET-CT scan

AND

Insufficient evidence for an alternative diagnosis, including known forms of human prion disease

Suspect Case:

Progressive neurological syndrome involving at least four of the following clinical features, verified directly where possible by a health care provider:

- Rapidly progressing dementia
- Cerebellar ataxia (gait ataxia, truncal ataxia, cerebellar dysarthria or dysmetria), abnormal cerebellar function test or cerebellar symptoms (dysdiadochokinesis, intention tremor etc.)
- Psychiatric symptoms (agitation/irritability, aggressiveness, apathy/withdrawal, anxiety or obsessive behaviour)
- Visual hallucinations, cortical blindness or other cortical visual symptoms
- Pyramidal or extrapyramidal signs, including atypical Parkinsonism
- Myoclonus
- Painful sensory symptoms (limb pain, dysesthesia or paresthesia) persisting for six months or more, in absence of peripheral nervous system dysfunction
- Muscle atrophy

The majority of these should manifest during the first 18-36 months of illness.

AND

Insufficient evidence for an alternative diagnosis.

Appendix C: Data Collection Form

Section	Subsection	Item
Demography and General Information	Demography and General Information	Outbreak ID
		Date of birth
		Date of Referral
		Date of death (if available)
		Sex
		Residence during the onset of the symptoms
		Residence during referral
		Occupation during the onset of symptoms
		Marital status
		Date Reviewed
	Comments	Comments
Presenting Complaints	Presenting Complaints	Presenting complaints
		Site
		Onset
		Characteristics
		Timing/progression
		Exacerbating factors
		Remitting factors
		Associated symptoms
		How it affects patient's life
	Comments	Comments
Past Medical/Injury History	Past Medical History	Medical Illness
		Site
		Onset
		Characteristics
		Timing/progression
		currently present/not
		Any ongoing targeted treatment/ therapy
	History of Injury (Head and Spine)	Injury
		Site
		Time and Mode of injury
		Characteristics
		progression
		Resolved/treated
		Any ongoing targeted treatment/ therapy
	Comments	Comments

Section	Subsection	Item
Systemic Enquiry	Systemic Illness/condition	Name
		Onset
		Characteristics
		Timing/progression
		currently present/not
		Any ongoing targeted treatment/ therapy
	Pregnancy	Currently pregnant/not
		Any previous pregnancy
		Any complication during pregnancy
		Any complication during delivery
		Baby's Health
	Sleep	duration of sleep/day
		Pattern of sleep
		Any change since the onset of other symptoms
		Any previous diagnosis of sleep disturbance/disorder
		Any medication taking for sleep disturbance/disorder
	Comments	Comments

Section	Subsection	Item
Social History	Smoking History	Packs/day
		Current
		Previous
		Never/rare
	Drinking History	Social drinker
		Heavy drinker
		Previous
		Never/rare
	Use of over the counter and illicit drugs	Name
		Current user
		Previous user
		Never/rare
	Use of over the complementary and alternative medicine	Name
		Current user
		Previous user
		Never/rare
	Travel History	Where
		Timing
		Duration of Travel
	Hobbies	What
		Timing
		Any change in activities before the onset of symptoms
		Any change in activities after the onset of symptoms
	Comments	Comments
Family History	Any member of the family/relative has any chronic/genetic disease	Name of the disease/condition
		Relationship with the patient
		Duration
	Comments	Comments

Section	Subsection	Item
Treatment/Medication/Therapy History	Any medication/treatment/therapy for current symptoms/signs	Name of the treatment/medication/therapy
		Targeted S/S/condition
		Start date
		Dose/frequency
		Any changes in the S/S after taking the treatment/medication/therapy
		End date
		Reason of stopping treatment/medication/therapy
	Any medication/treatment/therapy for previous symptoms/signs	Name of the treatment/medication/therapy
		Targeted S/S/condition
		Start date
		Dose/frequency
		Any changes in the S/S after taking the treatment/medication/therapy
		End date
		Reason of stopping treatment/medication/therapy
	Any surgical Procedure	Name of the surgery
		Date
		Reason for the surgery
		Any changes in the S/S after the procedure
	Any Blood donation/receiving history	Blood donation/receiving
		Date
		Reason for the blood donation/receiving
		Any changes in the S/S after the procedure
	Any Organ/tissue receiving history	Type of organ/tissue
		Date
		Reason for the organ/tissue receiving
		Any changes in the S/S after the procedure
	Comments	Comments

Section	Subsection	Item
Examination History	General Examination	Findings
		Progression/Remission
	Examination of Speech	Findings
		Progression/Remission
	Examination of Neck	Findings
		Progression/Remission
	Examination of Cranial Nerves	Site/Cranial Nerve
		Findings
		Progression/Remission
	Examination of the Sensory System	Site/Sense
		Findings
		Progression/Remission
	Examination of the Motor System	Site/Motor Function
		Findings
		Progression/Remission
	Psychiatric Examination	Name of the examination
		Findings
		Progression/Remission
	Examination of Skin	Findings
		Progression/Remission
	Comments	Comments

Section	Subsection	Item
Investigations	Blood Tests	Name of the test
		Initial Date of test done
		Findings
		Follow-up test date
		Findings
	EEG	Initial Date of test done
		Findings
		Follow-up test date
		Findings
	CT/SPEC	Initial Date of test done
		Findings
		Follow-up test date
		Findings
	MRI	Initial Date of test done
		Findings
		Follow-up test date
		Findings
	CSF protein panel	Initial Date of test done
		Findings
		Follow-up test date
		Findings
	Tissue sample testing	Initial Date of test done
		Findings
		Follow-up test date
		Findings
	Genetic testing	Date
		Report Mutation
		Report Genotype
	Brain Autopsy	Date
		Findings
	Comments	Comments
Comments and Recommendations	Recommendation for elaboration of complaints/history	Yes
		No
	Recommendation for Patient re-examination	Yes
		No
	Recommendation for more investigations	Yes
		Name of Investigation
		No
	Comments	Overall Comments