An Exploratory Study on Autoimmune Encephalitis and Comorbidities in the Manitoba Patient Population: 7 Cases and a Review of Literature

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TABLE OF CONTENTS

I. ABSTRACT **Page 3**
II. INTRODUCTION **Page 4**
A. AUTOIMMUNE TARGETS **Page 6**
1. NMDAR **Page 7**
2. DPPX **Page 7**
3. GAD65 **Page 8**
B. COMORBIDITIES/TRIGGERS **Page 9**
1. OVARIAN TERATOMAS **Page 9**
2. OTHER TUMOURS/NEOPLASMS **Page 10**
3. HERPES SIMPLEX VIRUS EXPOSURE **Page 11**
4. SYSTEMIC AUTOIMMUNE DISORDERS **Page 12**
5. BIPOLAR DISORDER **Page 12**
6. INFECTIOUS TRIGGERS **Page 12**
III. PATIENTS AND METHODS **Page 13**
IV. RESULTS **Page 14**
V. DISCUSSION **Page 16**
VI. LIMITATIONS **Page 18**
VII. CONCLUSION **Page 21**
VIII. REFERENCES **Page 22**
IX. TABLES AND FIGURES **Page 24**

I. ABSTRACT

Autoimmune encephalitis is a potentially life threatening, rapidly debilitating disease that is often overlooked or late in diagnosis resulting in lengthy hospital stays and ICU admission. Autoimmune encephalitis may be associated with comorbidities or potential "triggers". The patient population from Health Sciences Center, Winnipeg, Manitoba, was studied to elucidate the comorbidities associated with autoimmune encephalitis in relation to previously identified comorbidities from the medical literature. Charts were reviewed under classification of non-infectious encephalitis category for autoimmune encephalitis, from Jan. 2004-Jan. 2019. Seventy-three charts were evaluated. Seven patients were identified or diagnosed as autoimmune encephalitis. Five out of seven patients were female (71%). The range in length of hospitalization varied from 7 days to 53 days. The mean length of stay (LOS) was 25 days. The 2 male patients had the longest hospitalizations. Common comorbidities were depression, anxiety, neuropsychiatric symptoms, diabetes mellitus with one patient exhibiting multiple concurrent autoimmune morbidities. None of the patients had positive findings for neoplasms, in contrast to the autoimmune encephalitis literature. Autoimmune encephalitis remains a challenging and rare diagnosis. Triggers and/or risk factors predisposing one to this disease may be difficult to identify however, attention to patients presenting with psychiatric symptoms in combination with autoimmune morbidities may allow prompt treatment leading to improved prognosis and decreased hospital stays.

II. INTRODUCTION

Autoimmune encephalitis is a potentially life threatening, rapidly debilitating disease that is often overlooked or late in diagnosis resulting in lengthy hospital stays and intensive care unit (ICU) admissions. Manifestations of the disease are complex and early diagnosis and treatment is significant for recovery. Early prodromal phase is nonspecific and includes flu-like symptoms such as headache, fever, nausea, vomiting, and fatigue.(1) This progresses into a neuropsychiatric phase including confusion, paranoia, hallucinations, anxiety, memory deficits, bizarre behaviour, seizures, and dyskinesia (facial twitching and choreoathetosis) which can quickly deteriorate to intermittent convulsions, weak spontaneous breathing, hypo or hypertension, brady or tachycardia, and loss of consciousness.(2)(3) Due to the neuropsychiatric phase of the disease, many patients are misdiagnosed as having a psychiatric illness and are placed on anti-psychotic medications.(4) The incidence of autoimmune encephalitis is unclear at this time, however, due to improved diagnostics and awareness as well as recent discovery of novel antibodies, increasing number of reports have been documented in the recent years.(5) This exploratory study evaluates some of the demographics, potential comorbidities, and triggers associated with autoimmune encephalitis in the Manitoba patient population and to compare these cases to current literature to help better our understanding of the disease.

There are different pathophysiological mechanisms that can cause autoimmune encephalitis. Antibodies to intracellular antigens, such as anti-Hu, are considered classic paraneoplastic disorders and are strongly associated with cancer.(6) These disorders result in irreversible neuronal death due to T cell targeting neurons.(6) As such, prognosis for the classic paraneoplastic autoimmune encephalitides is poor.(6) A second class involves autoantibodies to

extracellular epitopes. These include N-methyl-D-aspartate receptor (NMDAR), alpha-amino-3-hydroxy-5-methyl-isoazolepropionic acid receptor (AMPAR), gamma-aminobutyric acid (GABA), leucine-rich, glioma inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), metabotropic glutamate receptor 5 (mGluR5), dipeptidyl-peptidase-like protein 6 (DPPX), and Neurexin-3-alpha.(7)(8) These antibodies are considered directly pathogenic and cause reversible effects on synapses with little neuronal death.(6) This class has variable association with neoplasms and patients can completely recover from this class of autoimmune encephalitis with prompt, appropriate treatment.

Diagnosis of autoimmune encephalitis is based on a patient's serum and CSF for specific antibodies, characteristic clinical signs and symptoms, head MRI changes, and response to immunotherapy.(2) Autoimmune encephalitis is often confused with viral encephalitis in the early stages and patients are generally started on an antiviral therapy, such as Acyclovir, upon presentation. Results for viral polymerase chain reaction (PCR) can take days and usually only after failed response to antivirals and a negative PCR for viral deoxyribonucleic acid (DNA) is a diagnosis such as autoimmune encephalitis entertained. Interestingly, autoimmune encephalitis occurs more frequently in immunocompetent patients compared to immunosuppressed patients.(9) Outcomes vary from full recovery to institutionalization, to death after lengthy hospitalization.(10)(11)(12) Twenty five percent of patients remain severely disabled and mortality is estimated at 7%.(3)(11) Early diagnosis and confirmation of autoimmune encephalitis is necessary in achieving early treatment and improving patient prognosis.

The number of cell surface and intracellular antigens that are targets for autoimmunity continue to expand as research advances.(13) Anti-NMDAR and anti-DPPX are novel antibody

immune-mediated illnesses that can cause encephalitis involving the limbic system.(2)(8) Glutamic acid decarboxylase 65 (GAD65) 65 is an autoantibody targeting an intracellular synaptic protein that is linked to some cases of autoimmune encephalitis.(14) Of the known autoimmune encephalitis targets, the NMDAR is most abundant in the body which may explain why documented prevalence of anti-NMDAR encephalitis is higher compared to other autoimmune antibodies.(15)

There are very few facilities in North America that specialize in the diagnostic testing of these autoimmune antibodies further adding to the obstacles in diagnosing this challenging disease. The two facilities most frequently used by physicians in MB is Mitogen Advanced Diagnostics Laboratory located at the University of Calgary and Mayo Clinic Laboratories located in the United States.

A. AUTOIMMUNE TARGETS

1. NMDAR

The NMDAR plays a critical role in learning and memory and is also the major mediator of excitotoxicity.(10) These receptors are located in the hippocampus and the forebrain. In the disease state, the NR1 subunit of the receptor is targeted by antibodies which facilitate internalization of the receptors into the cell, thereby decreasing NMDAR synapses causing dysregulation and subsequent psychiatric, behavioural, and neurological symptoms (Figure 1).(2) The disease is more prevalent in females compared to males with a ratio of 3:1 and an average age of onset of 21 years, however, the disease has been documented in those aged 8 months to 85 years.(16)(17)(18) It has recently been reported that the etiology of encephalitis in young

adults is more frequently associated with anti-NMDAR antibodies compared to Herpes Simplex Virus (HSV), Varicella Zoster Virus, and West Nile Virus.(16) The first description of anti-NMDAR encephalitis was in 1997 describing two isolated female cases with psychiatric manifestations and ovarian teratomas.(19) The first reported case of anti-NMDAR encephalitis was in 2005 (20) and was first named by Dalmau *et al.* in 2007.(10) A report by Viaccoz *et al.* (2014) states that most anti-NMDAR encephalitis patients with partial seizures and mouth-face-tongue involuntary movements were male.(21) It is, therefore, important to test those patients with mental disorders, seizures, and involuntary mouth-face-tongue movements for anti-NMDAR antibodies in the serum and cerebral spinal fluid (CSF) to rule out a reversible cause.(2) Anti-NMDAR encephalitis diagnosis is mainly through the detection of anti-NMDAR antibodies. Patients with anti-NMDAR encephalitis generally present with no changes in the routine biochemistry of the CSF, mononuclear/lymphocyte hyperplasia, mild to moderate protein elevation, elevated IgG, or presence of oligoclonal bands.(2) Early MRI findings are non-specific; however, late MRI findings can show abnormal signals in the medial temporal lobes, high abnormal signals in the basal ganglia, cortex, brainstem, and cerebellum indicating demyelination, mild meningeal enhancement, or transient lesions.(2) Large doses of steroids and gamma globulin are first line therapy for anti-NMDAR encephalitis.(22) Second line therapy includes cyclophosphamide and rituximab.(17)

2. DPPX

Dipeptidyl-peptidase-like protein-6 (DPPX) is an important subunit of the Kv4.2 potassium channel. DPPX plays a critical role in voltage-gated ionic currents that mediate signal integration.(8) Immunological alteration of this extracellular target results in neuronal

hyperexcitability.(8) In addition to the psychiatric symptoms and myoclonus also observed in anti-NMDAR encephalitis, patients with autoantibodies to DPPX often have diarrhea or other gastrointestinal symptoms (GI).(13) The cause of the GI symptoms is unclear, but it is suggested it may be due to expression of DPPX in the myenteric plexus.(13)(8) Also, these patients have been reported to have tremor, nystagmus, and hyperkplexia.(13) A plausible explanation for the development of DPPX antibody encephalitis and diarrhea may be from molecular mimicry of DPPX and an unknown infectious agent.(8)

3. GAD65

GAD65 antibody has recently been identified as an important autoantibody possibly associated with autoimmune encephalitis.(14) GAD converts glutamic acid into gamma aminobutyric acid (GABA). GABA is a significant inhibitory neurotransmitter of the CNS. Antibodies to GAD65 is postulated to result in hyperexcitability by increasing the quantity of excitatory neurotransmitters, such as glutamic acid and aspartate.(23) GAD65 antibodies are a marker of type 1 diabetes.(24) They are also found in high titers in many neurological diseases such as stiff person syndrome, resistant epilepsy, progressive encephalomyelitis, and cerebellar ataxia. (14) The presence of low titre GAD65 antibodies in circulation, however, can be found in healthy individuals as well indicating a non-pathogenic role of anti-GAD65 in brain related syndromes.(14) (25) In a review article written by Gagnon and Savard (2016), 58 cases of limbic encephalitis were associated with GAD65 antibodies. In almost half of the cases, a coexisting systemic autoimmune condition was present (mainly diabetes).(14) It was suggested that these patients had a propensity to autoimmunity. GAD65 autoimmunity had no specific type of cancer association. Also, patients diagnosed with GAD65 autoimmune encephalitis did not have

orofacial dyskinesia or brachiofacial dystonia as seen in voltage-gated potassium channel (VGKC) and NMDAR encephalitis.(14)(26) Many of these patients did not recover and were left with severe neurological impairment.(14) Some studies suggest that GAD65 is not a key to pathogenic encephalitis and that instead, other extracellular surface antibodies such as AMPAR and GABA coexist.(14) The presence of GAD65 antibody in the CSF and a causal relationship with encephalitis needs further investigation.

B. COMORBIDITIES/TRIGGERS

There is some evidence showing that autoimmune encephalitis may be associated with other comorbidities or potential "triggers".(10)(7)(15)(3)(14) Some of these comorbidities or triggers were discovered prior to encephalitis onset, some during the workup, and others revealed years after initial presentation.(4) Here, we discuss some of the literature reporting potential comorbidities or triggers associated with autoimmune encephalitis.

1. OVARIAN TERATOMAS

When anti-NMDAR encephalitis was first described in 1997 along with ovarian teratomas, the removal of the teratomas resulted in subsequent significant clinical improvement.(19) Datta Mitra and Afify (2018) describe a 22-year-old patient diagnosed with anti-NMDAR encephalitis subsequently discovered to have bilateral ovarian teratomas.(3) Removal of the tumours along with immunosuppressive therapy resulted in complete recovery. Another study reports a 20-year-old female with a necrotic ovarian teratoma speculated to have released neuronal antigens resulting in the development of anti-NMDAR antibodies.(27) This individual also had a past medical history of Crohn's disease. In 2007, Dalmau *et al.* studied 12 female patients aged 14-44,

11 of which had ovarian teratomas and one who had a mediastinal teratoma.(10) Eight out of 9 patients fully recovered after tumour removal and immunotherapy and 2/3 died without tumour resection. This study highlights the significance of tumour removal for recovery of autoimmune encephalitis.

2. OTHER TUMOURS/NEOPLASMS

Some reports indicate that, although rare, other tumours such as mediastinal and testicular may be implicated in autoimmune encephalitis. (10)(18) Furthermore, a potential association between autoimmune encephalitis and other germ-cell or non-germ cell lines has been postulated.(1)(18)(10) In cases where no detectable neoplasms were identified, it is hypothesized that the trigger may be microscopic germ cells undetectable by current imaging methods(4)(28)(11) or perhaps reabsorption of a tumour leaving little evidence and resulting in poor detection.(27)

3. HERPES SIMPLEX VIRUS EXPOSURE

Herpes simplex virus (HSV) infection of the CNS may trigger auto immunity. Alexopoulos *et al.* (2017) describe 5 patients who developed autoimmune encephalitis (anti-NMDAR and anti-GABAR antibodies) post HSV infection and treatment.(15) This study postulates the development of autoimmune antibodies as molecular mimicry or as a result of the release of neuronal antigens from virus-induced damaged cells. Another report states that 26% of patients with newly diagnosed Herpes simplex encephalitis go on to develop antibodies to neuronal antigens, most commonly, anti-NMDAR antibodies.(13)

4. SYSTEMIC AUTOIMMUNE DISORDERS

In a review written by Gagnon and Savard (2016) systemic autoimmune disorders appeared frequently in patients with GAD65 antibodies.(14) Forty-eight percent of patients studied had autoimmune disease, with diabetes appearing in 50% of those cases studied (94% were type 1).(14) Also, psoriasis, celiac disease, and thyroiditis were reported in those cases at rates of 9%, 18%, and 73%, respectively.(14) This study demonstrates that patients with systemic autoimmune disease are at an increased propensity to develop other autoimmune disorders compared to those without evidence of previous autoimmunity.

5. BIPOLAR DISORDER

A report written by Leon-Caballero *et al.* (2015) hypothesizes an association between autoimmune encephalitis and Bipolar disorder (BD).(29) Studies have shown increased levels of autoantibodies in BD patients compared to the general population.(30)(31) Precise pathophysiological mechanisms of this association are yet to be elucidated and further research on the possible link between BD and autoimmune encephalitis need to be investigated.

6. INFECTIOUS TRIGGERS

A report written by Poulet *et al.* (2018) describe a 34-year-old man who tested positive for anti-Voltage-Gate potassium channel (VGKC) antibodies after having been recently cured from severe falciparum malaria.(32) This patient responded to high dose intravenous steroids. Another 4 patients from this study also developed encephalitis after having been exposed to malaria.(32) This report signifies yet another potential trigger of autoimmune encephalitis.

Various other infectious agents, including *Mycoplasma pneumoniae*, measles virus, group A hemolytic streptococcus, *Toxoplasma gondii*, and mumps have been implicated in anti-NMDAR.(33)(34)(35)

Despite the severity of the disease, prompt surgical and/or immunosuppressive therapy can lead to complete recovery from autoimmune encephalitis, specifically the extracellular targets. This study was designed to explore the demographics, potential comorbidities and triggers associated with autoimmune encephalitis in patients in Manitoba and to compare/contrast these cases to those in the current literature to further help our understanding of the disease.

III. PATIENTS AND METHODS

Records were acquired through the Health Information Services (HIS) at the Health Sciences Centre (HSC) in Winnipeg, MB. It was speculated that due to the rapid progression and severity of the disease, most patients in Manitoba (MB) would be directed to the HSC in Winnipeg for appropriate care and, hence, most autoimmune encephalitis cases would be captured at this location. Charts were collected through the International Classification of Diseases (ICD) – 10 (G04.9), non-infectious encephalitis, from January 2004-January 2019.

Data collected from the charts included details such as sex, symptoms, comorbidities, length of hospital stay, ICU admission, diagnostic auto immune antibodies, and miscellaneous information of interest. This information was collected to compare/contrast potential risk factors and comorbidities associated with autoimmune encephalitis.

IV. RESULTS

One hundred and four charts fell under this category. Thirty-one of these charts were categorized as “Iron Mountain” and were not accessible. Seventy-three charts were evaluated under the “non-infectious encephalitis” category for autoimmune encephalitis. Seven in total were diagnosed as autoimmune encephalitis (Figure 2).

Patients included 5 females and 2 males with autoimmune encephalitis. One patient was anti-DPPX positive, two were anti-NMDA positive (with one of these also showing a weak GAD65 positive result), and one was anti-GAD65 positive. One patient was negative for NMDAR, GAD65, GABAR, AMPA, and VGKC autoantibodies. Results for anti-DPPX were not included, therefore, it is possible this patient may have been anti-DPPX positive. Two other patients were presumed anti-NMDA positive. The three patients with no definitive autoimmune laboratory results all showed classic signs and symptoms of the disease and responded to the appropriate recommended therapy for autoimmune encephalitis.

Five out of seven patients were female (71%). The median age was 46 years and the mean age was 42.6 years (Table 1).

The range in length of hospitalization varied from 7 days to 53 days. The mean length of stay (LOS) was 25 days, the median LOS was 21 days. Case 1 had the shortest length of stay at 7 days. It is likely this patient had decreased LOS because her autoimmune encephalitis history was known, and appropriate therapeutics were administered promptly. The longest LOS was Case 7 at 53 days. This case was a diagnostic challenge and likely contributed to the increased LOS. The

2 male patients had the longest hospitalizations at 50 and 53 days compared to the female patients who ranged from 7-27 days.

Two of the 7 patients (one male aged 23 years and one female aged 18 years) in this study had been previously healthy prior to the autoimmune encephalitis diagnosis. Interestingly, one of these patients, however, was HSV, Hepatitis A, CMV, and toxoplasma gondii IgG positive. DNA was negative for these antigens indicating previous exposure as opposed to acute infection.

Three out of the 7 patients were admitted to the ICU during their illness. Both male patients had been admitted to the ICU. Again, it is likely that case 1 avoided an ICU admission due to prompt treatment.

Three of the seven patients had a past medical history of depression and anxiety. One patient had a recent diagnosis of anxiety alone before his autoimmune encephalitis diagnosis. Three patients in total had a history of diabetes mellitus, two had Type 2 diabetes mellitus and one had Type 1 diabetes mellitus prior to their diagnosis of autoimmune encephalitis. The same two patients with Type 2 diabetes mellitus also had a past medical history of hypertension and hypercholesterolemia.

One patient had a past medical history of Crohn's disease, primary sclerosing cholangitis (PSC), alopecia, vitiligo, and hypothyroidism prior to his diagnosis of anti-NMDAR encephalitis. This patient was also found to be positive for ParvoB19 virus. Adalimumab, a widely used biologic anti-TNF agent, was included in his at home medications. These agents are immune modulatory and have many adverse side effects, including autoimmune manifestations.(36)

All patients had negative imaging results for potential neoplasms. One, however, reveal ed an ovarian cyst by ultrasound.

V. DISCUSSION

In the sample size studied here at HSC in Winnipeg, the female to male ratio was 2.5:1. This is consistent with previous literature stating the incidence of autoimmune encephalitis is higher in females compared to males.(16)(4)

The mean age of onset in autoimmune encephalitis in this population was 43 years with a range from 18-65 years. In a review article written by Dalmau and Graus (2018), different autoimmune antibodies had varying means and ranges in age.(7) For example, the mean age of anti-NMDAR encephalitis was 21 years with a range from 2 months old to 85 years. Anti-DPPX encephalitis had a mean age of 52 years with a range from 13-76 years of age.(7)

Anti-NMDAR was previously documented to be the most prevalent autoimmune antibody causing encephalitis likely because the NMDAR is more prevalent in the body compared to other targets studied.(15) In this study, 2 of the 7 patients had positive anti-NMDAR antibodies detected through laboratory diagnosis. Cases 2 and 5 were presumed to be anti-NMDAR (case 2 based on MRI and clinical findings) however, no definitive CSF or blood test results were obtained. One patient was anti-DPPX positive and one was GAD65 positive. Patient 7 was negative for anti-NMDAR antibody as well as many other known autoimmune antibodies, however, based on his clinical findings and response to therapy, it is likely he, indeed, did suffer from autoimmune encephalitis, perhaps from a novel antibody aimed at a target yet to be identified.

Three out of 7 patients had anxiety and depression and one patient had anxiety alone. It has been postulated that the NMDAR plays a significant role in BD (mania and depression)(29), therefore, it is not surprising that these manifestations may be present in our autoimmune encephalitis patients. It is unclear whether anxiety and depression predisposes one to autoimmune encephalitis or whether these mood disorders are an early sign of the manifestation of autoimmune encephalitis. Accurate timing of anxiety and depression onset needs further investigation to evaluate an association versus the manifestation of autoimmune disease, itself.

One patient in our study had numerous autoimmune diseases prior to his anti-NMDAR encephalitis diagnosis. These included Crohn's disease, PSC, alopecia, vitiligo, and hypothyroidism. In a patient with multiple autoimmune dysregulations, it is important to consider the possibility of autoimmune encephalitis when faced with signs and symptoms classic for the disease as it has been established that autoimmune dysregulation puts one at an increased risk of acquiring other autoimmune diseases.(14) Similarly, one patient had Type 1 diabetes. Type 1 diabetes is caused by auto-antibodies that target the Beta cells of the pancreas. In this patient, previous history of autoimmunity may have predisposed her to acquiring subsequent autoimmune encephalitis. The acquisition of one autoimmune disease increases risk of other autoimmune diseases and, therefore, the risk of autoimmune encephalitis increases.(14)

Interestingly, case 3 was positive for parvovirus B19. Previous reports describe the association of parvovirus B19 and encephalitis.(37) It has been postulated that exposure to HSV may be a trigger for autoimmune antibody development.(33) It may be possible that exposure to parvovirus B19 could also be a trigger for autoimmune development in a similar manner of that

hypothesized by HSV. Further studies are needed to explore the association between potential triggers such as HSV and parvovirus B19 and the development of autoimmune encephalitis.

The symptoms associated with different types of autoimmune encephalitis have some similarities and some distinct differences according to literature. Most types of autoimmune encephalitides are associated with clinical symptoms such as seizures, memory loss, confusion, dystonia, behavioural changes, and psychiatric symptoms.(7) In our study, 4 out of 7 patients were documented to have bizarre behaviour. Three patients were documented to have had memory loss, two as decreased LOC, and one documented as cognitive decline. In total, six out of the 7 patients had severe neurological issues involving memory/cognition. Two patients had seizures and one had dystonia/rigidity. Three patients were documented to have nystagmus. Previous literature reports GI symptoms associated with anti-DPPX encephalitis.(7) In this study, there was no documentation of the patient with anti-DPPX encephalitis experiencing GI symptoms. A larger sample size is needed to evaluate this association in our MB population.

In this study, both male patients had the longest hospitalizations, and both had ICU admissions. This suggests the possibility that although males are less likely to be diagnosed with anti-NMDAR encephalitis, perhaps they have a greater risk of increased morbidity compared to females. Further studies are needed to examine whether there is a significant difference in morbidity between females and males.

Adalimumab (sold under the brand name, Humira) is a human anti-TNF inhibitor which blocks TNF-alpha interaction with p55 and p75 surface receptors thereby decreasing inflammation. Adalimumab lyses surface TNF-alpha expressing cells and modulates leukocyte

migration.(38) One patient in our study had been administering Adalimumab via subcutaneous injections prior to his encephalitis diagnosis. The alteration of the immune system in response to this medication may be associated with the development of immune dysregulation and subsequent autoimmune encephalitis. Previous literature has suggested a correlation between Adalimumab and the development of autoimmune disorders such as Lupus.(36) Further studies on anti-TNF-alpha therapy are needed to determine if an association exists between the use of this antibody and the development of autoimmune encephalitis.

Previous literature reports an association between neoplasms and autoimmune encephalitis.(7)(10)(3) The literature describes up to 58% of patients with anti-NMDAR encephalitis were also found to have neoplasms, mostly ovarian teratomas.(7) Autoimmune encephalitis caused by anti-DPPX were less likely associated with cancer (<10%).(7) In this study, none of the cases had associated neoplasms at the time of diagnosis. It is possible that our current imaging modalities are unable to detect very small neoplasms. A report by Mann *et al.* (2014) documents the discovery of neoplasms years after autoimmune encephalitis diagnosis.(4) It may be possible that more cases are, indeed, associated with neoplasms, however, at an undetectable level at the time of autoimmune encephalitis diagnosis.

VI. LIMITATIONS

There were some limitations to this study that necessitate future investigations. One limitation was sample size. Patient numbers were too small to create statistically significant data in this study. This is, partly, due to the rarity of the disease. Due to sample size limitations, it was not feasible to separate the different types of autoimmune encephalitides. A larger study

population may have revealed a significant difference in mean age between different autoimmune antibodies. This study investigated 7 cases discovered in the MB patient population to explore manifestations, comorbidities, and potential triggers and to compare these cases to the current literature. No other study or reports have investigated autoimmune encephalitis in the MB patient population.

Another limitation was the use of the ICD-10 (G04.9) code (non-infectious encephalitis) as the method to capture patients diagnosed with autoimmune encephalitis. This method may not have captured all the autoimmune encephalitides in the MB patient population as some patients may have been miscoded or misdiagnosed due to the novelty and rarity of the disease. Also, the chart review included only those patients that presented to HSC. It is possible that some patients may have been missed if they presented to other hospitals and were managed elsewhere. This, however, is unlikely given the severity of the disease and the expertise at HSC in managing the disease. It was presumed that most patients that presented elsewhere would have eventually been transferred to HSC for management.

It is possible that new, unknown autoimmune antibodies may cause encephalitis, preventing accurate laboratory diagnosis and forcing the diagnosis based on clinical manifestations and response to therapy. This could explain, in part, why despite extensive investigations and expanding discoveries of novel antibodies and targets, 60% of patients with encephalitis continue to have unknown etiology.(13) It is likely that autoimmune encephalitis is underdiagnosed and unknown antibodies are yet to be discovered.

This study had some logistic challenges with regards to access to charts. There was limited access to full patient charts. Charts that included the discharge diagnosis of “non-infectious encephalitis” from the time of admission to discharge were available for investigation. Follow-up and previous hospitalizations were not accessible which may have revealed more information with regards to associated comorbidities, signs and symptoms, diagnosis, hospitalization, and treatment. As well, some cases may have been missed in the “Iron Mountain” category.

In many cases, an autoimmune antibody panel was sent out for testing, however, the patient responded to empiric therapy and was discharged prior to diagnostic completion of results and, therefore, the results did not make it into the current chart. This likely erroneously decreased sample size as laboratory diagnosis was unavailable. In the future, to capture a more definitive population of autoimmune encephalitis one could acquire patient identifiers and charts through laboratory results (i.e. Mitogen, Mayo Clinic) as opposed to ICD codes.

VII. CONCLUSION

Autoimmune encephalitis remains a challenging diagnosis. Triggers and/or risk factors predisposing one to this disease may help to expedite diagnosis, thereby, allowing prompt treatment leading to improved prognosis and decreased hospital stays. Thus far, many potential triggers have been hypothesized to be associated with autoimmune encephalitis and further studies on these patients, their demographics, and their comorbidities needs to be investigated to further advance our knowledge of the disease. In patients with unexplained seizures, acute change in behaviour, and decreased memory, it is important to consider the diagnosis of autoimmune encephalitis as untreated cases may lead to severe debilitation or mortality and

increased burden on the health care system whereas prompt, appropriate therapy can lead to full recovery.

VIII. REFERENCES

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Figure 1: Crosslinking and internalization of NMDA receptors with subsequent reduction in NMDAR density

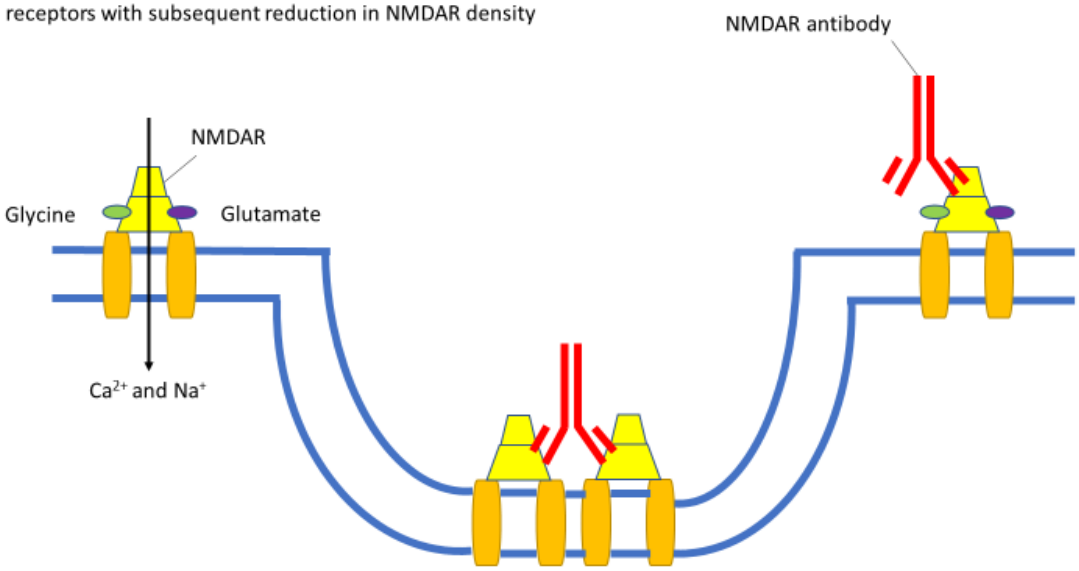
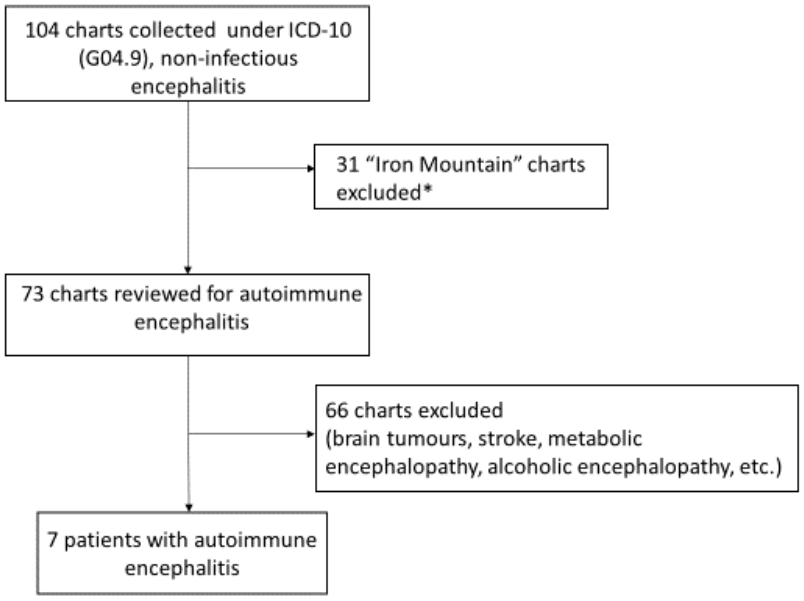


Figure 2: Study profile



*these patients may or may not have fulfilled the inclusion criteria

Table 1: Clinical, immunologic features, and comorbidities of antibody-mediated encephalitis in seven Manitoba cases

Case No.	Age	Gender	Symptoms	Antibody[1]	Length of Stay (days)	Comorbidities[2]	ICU	Misc.
1	18	F	headache, dizziness, decreased memory, hallucinations, left leg weakness, foot drop, right eye nystagmus	DPPX	7	none	No	
2	56	F	memory loss, bizarre behaviour	MRI suggestive of AIE	21	OA	No	
						Depression		
						Anxiety		
3	35	M	memory loss, bizarre behaviour, seizure	NMDAR	50	Crohn's	Yes	ParvoB19 positive
				GAD65		Hypothyroidism		Medications: Adalimumab
						PSC		
						Alopecia		
						Vitiligo		
						Anxiety		
4	65	F	headache, ataxia, vertigo, nystagmus, weakness, oscillopsia	NMDAR	10	DM2	No	U/S revealed left ovarian cyst
						Hypertension		
						Hyperlipidemia		
5	46	F	decreased LOC, bizarre behaviour, seizures	AIE	27	DM2	Yes	influenza positive
						Depression		
						Anxiety		
						HTN		
						ESRD		
						Hyperlipidemia		
						Hep A		
6	55	F	Ataxia, nystagmus, nausea, vomiting, right-sided tremor, dysequilibrium, Parkinsonism	GAD65	8	DM1	No	Meds: chlorpromazine
						Depression		
						Anxiety		
						OA		
7	23	M	bizarre behaviour, hyperkinetic movements, dystonia, rigidity, cognitive decline	AIE	53	none	Yes	[3]ANA+, HSV+, HepA IgG+, CMV+, Toxoplasma gondii IgG+

[1]AIE Autoimmune Encephalitis; DPPX dipeptidyl-peptidase-like protein 6; NMDAR N-methyl-D-aspartate receptor; GAD65 glutamic acid decarboxylase

[2]OA osteoarthritis; HTN hypertension; DM1 diabetes mellitus Type 1; DM2 diabetes mellitus Type 2; PSC primary sclerosing cholangitis; ESRD end stage renal disease

[3]ANA anti nuclear antibody; HSV herpes simplex virus; HepA hepatitis A; CMV cytomegalovirus