# Prolonged VZV IgM Seropositivity in Multiple Sclerosis is Associated with New Sensory Symptoms, A Case Series

Dolly Roy MD PhD, Northridge Hospital Medical Center, Northridge, CA

## Abstract

Objectives: Do subclinical active VZV infections complicate RRMS?

Methods: RRMS patients with new sensory symptoms were examined and had their serum tested for VZV IgM to assess for subclinical VZV activity.

Results: Case Series of 5 patients.

60 yr old woman with RRMS for 7 yrs with brain and cervical cord lesions, started complaining of tingling on her left shoulder, no rash. She takes Copaxone and lab testing revealed elevated serum VZV IgM titers that remain positive 15 months later despite valtrex treatment and prophylaxis. She continues to have rare shoulder paresthesias.

35 yr old woman with RRMS for 9 yrs on Avonex and Solumedrol therapy with lesions throughout the brain and spinal cord, started having worsening leg weakness and received extra solumedrol which helped her leg weakness, but then resulted in left face buzzing. No rash, but testing shows high VZV IgM titers. Despite valtrex treatment, elevated VZV IgM titers persisted for 7 months, and recurs. She still occasionally feels buzzing there.

58 yr old man with RRMS for 6 years with lesions throughout the brain and spinal cord, on Betaseron and pulse steroids, started having worsening leg weakness and received extra steroids that seemed to help. A few months later however, he complained of new burning neuralgia in his feet. Concurrently had first onset genital herpes at this time. Blood tests revealed elevated VZV IgM titers that stayed positive over 3 years despite continuous valtrex treatment. He has complained 2-3 times per year of new onset intense burning neuralgia type sensations.

45 yr old man with RRMS for 1 year on Copaxone with lesion in brain and spinal cord, was in a MVA and had a relapse with limb weakness and strong right thoracic MS hug symptoms—as he had on his initial MS attack. Serum tests revealed elevated VZV IgM titers that were treated with valtrex and he also received IV solumedrol 3 grams with resolution of his symptoms. His abnormally elevated VZV IgM titers persisted over 7 months and he did suffer from a possible shingles outbreak in the gluteal region 4 months after his MS relapse.

55 yr old woman with RRMS with secondary progression for 3 years with multiple sclerosis lesions throughout the brain and spinal cord on Avonex, had an outbreak of left upper thoracic possible shingles treated about 1.5 years into her diagnosis. Months later, she started having a tightness hug feeling in her upper thoracic area and serum lab tests revealed elevated VZV IgM titers. Her "hug" symptoms persist over 14 months later as do her abnormal VZV IgM titers.

Conclusions: This case series suggests that sustained high VZV IgM serum titers may not be uncommon in patients with RRMS experiencing sensory symptoms and that further prospective investigation for the role of VZV in sensory MS relapses should be considered.

## Introduction

The possibility that relapsing remitting multiple sclerosis could represent a distorted immune response in the central nervous system in response to the presence of a preexisting viral infection has been entertained but not proven for over the past 50 years (1). Varicella Zoster Virus, VZV is an attractive candidate for possibly triggering relapses in MS since it becomes latent in the dorsal root ganglion after primary infection and can recur as Shingles or Herpes Zoster as a painful skin eruption over 1-3 dermatomes; it is also known to sometimes cause a global infection of the CNS with meningitis or encephalitis, generally in an immune compromised host. The development of shingles seems to increase the risk of developing RRMS (2), while the FDA recognizes an increased risk of shingles with several approved disease modifying drugs. However a systematic review of available published studies failed to support an etiological role of VZV infection in the development of RRMS in the first place (3). The role of VZV reactivation as a trigger for MS relapses has been studied, but with conflicting results by different groups looking for increased VZV gene transcription in peripheral blood mononuclear cells and within the CSF within one week of an acute relapse (reviewed in 4). Limited research into the presence of VZV IgM serum antibody elevations in the setting of acute relapse have been negative (5). The possibility of prolonged abnormally elevated VZV IgM titers in the setting of acute sensory symptoms in Relapsing Remitting Multiple Sclerosis has not previously been reported or studied.

## Methods and Materials

Patients chosen to be highlighted here were purely identified by having prolonged elevated VZV IgM titers by blood work after having an investigation into why they may be having new or worsening sensory symptoms. Patients in general described intense sensory symptoms such as burning, tingling, buzzing, or pressure that appeared to follow a dermatome pattern of distribution. In all cases, patients in routine clinical practice complained or mentioned a new sensory symptom on their own initiative in the past five years. This case series is not an exhaustive list of all patients who may have had abnormal VZV IgM titers and sensory complaints in my practice. No patient felt that they were having a shingles outbreak simultaneously though 3/5 patients did have preceding or subsequent clinical shingles outbreaks; those who did have a shingles outbreak, did so in a dermatome distinct from the one in which they were experiencing symptoms. No clinical rash was evident in the dermatome in which the patient was complaining of sensory symptoms at any time point. Patients had initial and variably timed subsequent lab tests at different laboratories. Patients had variable timings for MRIs of the brain, cervical, and thoracic spinal cord performed at different imaging facilities. Four patients had EMG/NCV tests that were performed by other neurologists to aide in the understanding of their complaints. One of the patients sought the opinion of two Infectious Disease physicians to help guide the valtrex treatment decisions for that patient. Patient names and personal identifiers are omitted to ensure anonymity.

## Results

Five representative patient profiles are described from 2011 to the present. See the attached Table for a concise comparison of these patients, their symptoms, treatment and outcomes.

The first patient is a 60 yr old woman who had an episode of transverse myeltiis with thoracic numbness to her feet that spontaneously resolved 15 years prior to her diagnosis of RRMS that occurred with new onset left hand paresthesias and subsequent abnormal MRIs following a MVA. She has taken Copaxone +/- LDN for approximately four years prior to experiencing fleeting tingling paresthesias over her left shoulder and neck area. Two years later she occasionally still has symptoms and now has new onset right big toe numbness. From the onset of her tingling paresthesias, her lab work revealed elevated VZV IgM titers that remain elevated two years later.

The second patient is a 35 yr old woman who was diagnosed with RRMS at the age of 25 with left sided numbness. Over the years that has recurred, in addition to optic neuritis, vertigo, nausea, right leg weakness and spasticity. She was taking Avonex with pulse solumedrol when she suffered a relapse of increased right sided weakness; extra solumedrol improved her right sided strength but then she began feeling strong intermitted buzzing adjacent to her left eye in a linear isolated manner. Nearly 5 years later, she still occasionally has this sensory complaint. She was transitioned to Tecfidera, and then recently to Aubagio for lymphocytopenia concerns. Her VZV IgM titers remained abnormally elevated for 2.5 years from initial identification.

The third patient is a 58 yr old man who was diagnosed with RRMS vs PPMS in his early 50s with workup for subtle right sided weakness and right foot drop. He was maintained on Betaseron and pulse solumedrol to help his right sided weakness. He received extra steroids and then a short course of plasmapheresis from which his right sided weakness significantly improved; but was complicated by an apparent genital herpes outbreak for the first time. Within 3 months of this outbreak, he was found to have abnormal VZV IgM titers and nearly simultaneously the complaint of new burning/cold sensory symptoms on the bottoms and tops of his feet. Every 4-6 months since then, he complains of abrupt increases in sensory discomfort in his feet. Nearly 3.5 years after the initial identification of abnormally elevated VZV IgM titers, he experienced his first definitive shingles outbreak in his left T8 torso.

The fourth patient is a 45 yr man diagnosed with RRMS after a sudden onset Rt sided hug like chest pressure and weakness and numbness on his right side from the chest down. He received initially 5 grams of IV solumedrol and started Copaxone with a brief course of steroids 4 months later with ongoing numbness and weakness complaints. One year later after diagnosis and after a MVA, he had another relapse with nearly identical symptoms, with benefit from IV solumedrol and valtrex after labs revealed abnormally elevated VZV IgM titers. Four months later, he suffered a brief shingles attack in his left gluteal region. The patient went on to electively undergo a bone marrow transplant with ongoing valtrex prophylaxis 8 months later and is doing well 1 year later.

The fifth patient is a 55 yr old woman with RRMS with secondary progression for 3 years on Avonex had an outbreak of possible shingles in her left shoulder and clavicle area that was treated and resolved with valtrex by her PCP. Five months later and intermittently for the next 1.5 yrs, she has experienced banding/hug new symptoms in her left T6 torso with steadily elevated VZV IgM titers.

## Results

| Patient Profile | Sensory Complaint | Labs | MRI Findings | EMG/NCV results | Treatment | Outcomes |
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| 60 yr old woman, Copaxone +/- LDN | Intermittent tingling and "spiders crawling" on left neck and shoulder, Left C3-C4 dermatomes; recent right toe numbness | VZV IgM 2.81 H in 7/2014; 2.26 H in 4/2016; HSV IgM wnl | Scattered periventricular WM lesions, **C6-7 dorsal plaque**; T spine not involved., no contrast enhancement | No evidence for radiculopathy or sensorimotor neuropathy | Intermittent valtrex treatment over 2 years, no steroids given. | Rare left shoulder paresthesias, new right toe numbness, walks unassisted. |
| 35 yr old woman on Avonex and solumedrol with extra steroid for right leg weakness | After treatment for motor exacerbation, started having left V2 type intermittent buzzing | VZV IgM 1.25 H in 12/11; 1.05 and equivocal in 11/13; 0.77 wnl in 6/14 | Bilateral pericallosal and subcortical WM lesions, left posterior limb internal capsule**, left paramedian pons**, rt middle cerebellar peduncle, C1, C3, Rt C7, T1, T3, T4, T8; no contrast enht | No evidence for radiculopathy or sensorimotor neuropathy | Valtrex treatment dose and drug holiday at onset. | 40 months from symptom onset, occasionally has left V2 buzzing but generally only if very stressed or sick. Walks with cane rarely. |
| 58 yr old with Betaseron and pulse steroids with mild right sided weakness | Complaining of left>right abnormal heat/cold sensations over L4/L5 | VZV IgM 1.12 H in 9/12 with HSV IgM -; VZV IgM 1.54 H in 10/12; 1.39 H in 4/13; 6/13 1.62 H, 4/14 1.02; 11/14 HSV IGM +, VZV IgM 1.32 H; VZV IgM 1.77 H in 3/15 | Periventricular WM lesions, C2-3 central posterior cord, L C4, **T8-9**, L4-5 disk herniation and right foraminal stenosis; no contrast enht | No radiculopathy; moderate axonal sensory neuropathy | Numerous valtrex treatment doses and prophylactic doses, then no ongoing treatment until recent clinical outbreak of shingles. | Strength and stamina are relatively stable, but pt feels ongoing worsening sensation in his feet; clinical shingles outbreak 3.5 years on Rt torso after initial abnormal labs identified. |
| 45 yr old man with RRMS on Copaxone | Right thoracic MS hug symptoms in addition to right sided core and leg weakness, Right T7 | VZV IgM 2.46 H and HSV IgM 1:40 in 3/14; 2.62 H in 10/14; VZV IgM 3.27 H and HSV IgM 1:40 in 2/15; serum PCRs for VZV and HSV IgM negative in 2/15 | Scattered periventricular WM lesions and corpus callosal lesions, left cerebellar lesion, C2 posterior and right anterior, and anterior **T6-7**; no contrast enht | Not applicable | Valtrex treatment dose and 3 days 1 gram IV solumedrol for MS relapse | Weakness and right sided hug symptoms resolved over 1 month; four months later left gluteal shingles outbreak. |
| 55 yr old woman on Avonex with suspected shingles outbreak on left shoulder area. | Within 5-6 months, began noticing new MS hug symptoms intermittently in Left T6 distribution. | VZV IgM 0.98 H equivocal in 4/14; 1.31 H in 8/14; 1.58 H in 4/15; 1.52 H in 12/15 | Left centrum semiovale, L lateral ventricle, R parietal lobe, L corona radiata, C1-2, C3, **T5-6**, T8-9, T10-11; no contrast enht | Not applicable | Valtrex treatment dose | MS hug symptoms self-subside over 9 months, rarely recurs |

## Discussion

Through routine clinical practice and a deeper analysis of clinical symptoms and serology, the possibility of subclinical VZV activity itself or an immune response to VZV virions might help determine why sensory symptoms occur and in which location. Anecdotally, though several RRMS treatments carry a warning for an increased risk of shingles, none of the above highlighted patients were on these therapies, though several did have some type of concurrent steroid treatment. Abnormally elevated VZV IgM titers in the general population have not been comprehensively studied, but these patients carry abnormally elevated VZV titers for sometimes 3 years before a clinical shingles attack is apparent. Interestingly, when clinical shingles attacks did occur, they were distinct neuroanatomically from the patient's new sensory complaints. Interestingly, all of the above patients have visible preexisting MS plaques corresponding precisely or nearly to the patient's dermatomal sensory complaint, and to some extent to their shingles' dermatomal involvement. Despite aggravated sensory symptoms, short term followup suggests overall MS stability over the course of a few years. What role valtrex plays or can play in treating the abnormally elevated titers remains unclear.

## Conclusions

As a neurotrophic sensory virus that lives in the dorsal root ganglion cells adjacent to the spinal cord, it is tempting to speculate that subclinical VZV reactivation could predispose certain sensory symptoms if not sensory relapses in Relapsing Remitting Multiple Sclerosis. The natural history of VZV serologies in RRMS should be revisited in the context of baseline symptoms and new sensory symptoms/relapses. Whether or not antiviral treatment prophylactically, or with sensory relapses with elevated VZV IgM titers, changes clinical outcomes should also bear consideration. Lastly, this small case series suggests that VZV latency could help predict why certain neuroanatomic locations may be involved in sensory symptoms. Finally, on a reassuring note, despite intense new or old sensory symptoms, no significant longer term consequences were evident over the course of several years and no serious VZV neurological complications were identified.

## Contact

Dolly Roy MD PhD
Private Practice and Northridge Hospital Medical Center
Email:dollybroy@yahoo.com

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