Background

- Varicella zoster virus (VZV) is the causative agent of varicella (chickenpox) and zoster (shingles).
- The introduction of live-attenuated vaccine has drastically reduced VZV burden in the population, but the virus continues to be a significant public health issue.
- VZV commonly causes mild disease but can result in severe complications including CNS involvement with encephalitis.
- Circulation of clades 1-6 occur worldwide (Figure 1), with dominant clades representing each region.
- The clade 2-derived vaccine strain can cause adverse reactions and has been documented to establish latency and reactivate to cause zoster.
- Reported cases of vaccine-associated CNS disease are rare and the extent of vaccine-associated CNS involvement is unclear.
- We aimed to assess the frequency of vaccine-associated CNS disease and compare VZV clade distribution in CNS and non-CNS disease.

Methods

Wild-type/Vaccine Discrimination

- Cerebrospinal fluid (CSF) from patients with encephalitis or meningitis, collected from 2004-2017, and non-CSF specimens (lesion, rectal swabs), collected from 2013-2017, were reviewed for study.
- VZV-positive samples were selected for further characterization, including wild-type/vaccine discrimination and genotype analysis.
- VZV viruses were determined to be wild-type or vaccine using three separate bi-allelic TaqMan real-time PCR assays, each targeting a specific known SNP marker in ORF62 of VZV (Figure 2A).

Table 1: Detection of VZV vaccine strains in CSF and non-CSF samples

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Vaccine strain detected (%)</th>
<th>Age of patients with vaccine strain detected (%)</th>
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<tbody>
<tr>
<td>CSF</td>
<td>277 (1.36)</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Non-CSF</td>
<td>606 (12)</td>
<td>1 (70)</td>
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</table>

Clade Analysis and Distribution in CNS and Non-CNS Disease

- 158 CSF and 571 non-CSF samples were successfully genotyped.
- A diversity of clades were detected in both CNS and non-CNS disease. Clades 1-5 were detected in both sample sets.
- Three clade 6 viruses were detected in non-CSF specimens from three different patients in 2017.
- Clades 1 and 3 were most prominent in both CNS and non-CSN disease.
- Distribution of clades 1-5 were statistically similar between CNS and non-CSN disease.
- Gender proportions in CNS and non-CNS disease were statistically similar.
- VZV incidence between CNS and non-CNS disease was statistically similar in age groups 21-40, 41-60, and 61-100 years (p > 0.05, Pearson chi-squared test).
- Patients in the 0-20 year age group showed a higher incidence of non-CSN disease, as compared to CNS disease (p = 0.03, Pearson chi-squared test).

Conclusions/Discussion

- The vaccine strain of VZV can cause disease in all ages, but at a much lower rate than wild-type virus.
- Vaccine strain was detected in only one CSF sample from a patient with meningitis, suggesting that, while capable of causing CNS disease, this is a rare occurrence.
- A high diversity of VZV clades circulate and cause CNS and non-CNS disease, however, clades 1 and 3 represented the majority of VZV genotypes associated with both CNS and non-CSN disease.
- Interestingly, statistical analysis indicated that clade proportions are distributed similarly in mild and moderate VZV disease manifestations to those in more severe CNS disease.
- These findings highlight the pathogenic potential of VZV independent of clade.

Works Cited

- VZV global circulation paper
- Vaccine strain paper: VZV vaccine strain paper
- Genotyping paper: VZV

Acknowledgements

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Figure 1: Global distribution of VZV clades

Figure 2A: VZV wild-type/vaccine discrimination and genotyping schemes. A. Three separate real-time assays target known SNPs in ORF62 of the VZV genome. B. Clade-specific SNP combinations used for VZV genotyping.

Figure 2B: VZV wild-type/vaccine strain discrimination and genotyping schemes. A. Three separate real-time assays target known SNPs in ORF62 of the VZV genome. B. Clade-specific SNP combinations used for VZV genotyping.

Figure 3: Clade prevalence in CNS and non-CNS disease. A. For CSF samples, 277 CSF samples were VZV positive. One vaccine strain was detected. 158 samples were successfully genotyped. B. VZV in non-CSF samples. 571 non-CSF samples were VZV positive. 12 vaccine strains were detected. 571 wild-type viruses were successfully genotyped.

Figure 4: Yearly distribution of VZV clades in New York State. A. VZV in CSF samples. 277 CSF samples were VZV positive. One vaccine strain was detected. 158 samples were successfully genotyped. B. VZV in non-CSF samples. 571 non-CSF samples were VZV positive. 12 vaccine strains were detected. 571 wild-type viruses were successfully genotyped.

Figure 5: Distribution of VZV clades by gender. A. Male patients with VZV disease. B. Female patients with VZV disease.