SHINGLES: EFFECTIVE SUPPRESSION

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Shingles, also known as herpes zoster (HZ), is an infective process caused by varicella zoster virus (VZV). Primary infection is manifested as chicken pox (varicella), which has a distinctive vesicular rash and is accompanied by constitutional symptoms, thereby, allowing for clinical diagnosis.

During this initial infection, most of the virus is eliminated. Remaining virions travel along sensory nerve fibres in the skin to the dorsal root ganglia of the spine as well as cerebral ganglia. The most commonly involved ganglia are lumbar, thoracic and sacral dorsal root ganglia, followed by the geniculate ganglion of the 7th cranial nerve and the trigeminal ganglion of the 5th cranial nerve.

Once the virus reaches the spinal ganglia, it becomes latent or dormant. This latent infection is life long and asymptomatic. The virus only 'reactivates' or awakens during a state of impaired cell mediated immune response. This may be a result of old age, stress, steroid use, malignancy, diabetes mellitus, or, commonly, HIV infection. Shingles may occur in the second half of pregnancy and usually has a mild course. VZV then travels along the sensory nerves to the skin. This secondary infection manifests as shingles.

Herpes zoster is characterised by maculo-papular and vesicular lesions with or without crusting typically in a dermatomal distribution and is commonly preceded by dermatomal neuralgia. History and examination of the affected patient, therefore, facilitates accurate clinical diagnosis. Atypical presentations may occur in immunocompromised individuals, which then necessitates laboratory confirmation.

Zoster sine herpete refers to dermatomal distribution of pain in the absence of rash. Diagnosis is via CSF PCR providing definitive confirmation of viral presence. VZV DNA is not found in the CSF of uninfected individuals.

IV acyclovir is necessary to treat the radicular pain. VZV reactivation without rash may cause all neurological complications known to be associated with herpes zoster.

COMPLICATED SHINGLES

- Post herpetic neuralgia (PHN) is the most common complication of shingles. This prolonged pain is difficult to manage and may remain for weeks, months or years. Patients with PHN have abnormal function of unmyelinated pain and sensory receptors. Pain and temperature receptors are hypersensitive to light mechanical stimulation, leading to severe pain. Acute neuritis and PHN require administration of various analgesics, including tramadol or amitriptyline hydrochloride. A short course of oral corticosteroids may improve PHN.
- Secondary bacterial infection of vesicles is usually caused by group A Streptococci or *Staphylococcus aureus*. It is a clinical diagnosis and is to be treated with an oral antibiotic. IV antibiotics and inpatient care are needed only in the case of bacteraemia.
- The risk of cutaneous and visceral dissemination of varicella zoster virus is significantly higher in severely immunocompromised persons, particularly those infected with HIV. VZV can initially cause atypical cutaneous lesions in patients with low CD4 lymphocyte counts, in the form of multiple hyperkeratotic papules that follow no dermatomal pattern. These lesions may be chronic and are sometimes associated with acyclovir-resistant strains of VZV. Ecthymatous VZV lesions may also occur, which present with multiple large punched-out ulcerations with a central black eschar and a peripheral rim of vesicles. VZV isolates from any of these atypical lesions should routinely be submitted for antiviral susceptibility testing.
- Herpes zoster also displays a much higher frequency of shingles recurrence in HIV-infected and AIDS-afflicted patients. One third of HIV-infected patients will develop one or more subsequent episodes of herpes zoster, which may involve the same or different dermatomes. HIV-infected patients may also experience zoster simultaneously in more than one dermatome, an event almost never seen in the immunocompetent patient. HIV-infected patients with herpes zoster usually respond well to oral antiviral therapy. However, in the case of dissemination, admission and IV anti-virals are essential to management.
- Neurological complications following HZ include various motor neuropathies, Guillain-Barre syndrome and aseptic meningitis. HZ encephalitis occurs with increased frequency in patients afflicted with AIDS.
- Pneumonia post-VZV infection in adults is also possible and has potentially devastating effects when complicating pregnancy. Pregnant women, developing fetuses and neonates are at risk of mortality and serious morbidity from varicella. Perinatal transmission of VZV can occur either during delivery or during pregnancy via the blood. Vaccinating VZV-susceptible women prior to pregnancy could prevent all of these scenarios. Aggressive IV antiviral therapy is recommended for pregnant women with varicella-related pulmonary involvement (including cough, shortness of breath, haemoptysis or abnormal chest x-ray). Although acyclovir is not recommended for use during pregnancy, fetal toxicity due to acyclovir has not been documented (FDA Category B) and the risk-benefit ratio supports use of acyclovir in the setting of maternal varicella pneumonia.
- Varicella vaccination of pregnant women is not currently recommended because of the theoretical risk of the live virus to both fetus and mother. Prophylactic acyclovir in the case of a VZV-exposed pregnancy is an unproven approach. Administration of Varicella Zoster IgG to the pregnant patient who has been exposed to varicella has been recommended and should be administered within 96 hours of exposure.
- Administration is via deep intramuscular injection at a dose or 12.5mg/kg with a maximum dose of 625 units.
- Herpes ophthalmicus (HO) is a form of shingles affecting the first branch of the trigeminal nerve; the ophthalmic nerve. It involves painful unilateral forehead rash, ocular pain, marked eyelid and corneal oedema, conjunctival hyperaemia and photophobia. Severe keratitis and uveitis may occur and may be followed by scarring and permanent vision loss. HO may be preceded by vesicles on the tip of the nose due to involvement of the nasociliary

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branch of the trigeminal nerve. Shingles on the tip of the nose is referred to as Hutchinsons sign. Urgent ophthalmology referral is recommended in these patients. Early treatment with either acyclovir 800mg orally five times a day, famciclovir 500mg or valacyclovir 1g three times a day for seven days reduces ocular complications. Patients with uveitis or keratitis require topical corticosteroids. The pupil should be dilated with atropine 1%, one drop three times daily. Intra-ocular pressure should be monitored and treated if above normal.

- Reactivation of VZV along sensory nerves from the geniculate ganglion of the 7th cranial nerve results in facial nerve palsy. HZ affecting the 7th cranial nerve is more severe than a Bell's palsy and has a worse prognosis. Two thirds of patients will have incomplete recovery of paralysis. Alteration of taste may also affect the patient. Transmission of the virus from the 7th cranial nerve to the 8th cranial nerve is possible at the cerebello-pontine angle. This can result in hearing loss and vertigo. Infection of the inner, middle and/or external ear with VZV is referred to as Herpes Zoster Oticus. It manifests with severe otalgia and associated cutaneous vesicular eruptions of the external auditory canal and pinna. The condition of HZ Oticus in combination with HZ affecting the facial nerve is referred to as Ramsay Hunt Syndrome.
- Genital herpes zoster initially presents with severe unilateral pain and itching in the perineal area. Fever and dysuria may be present. A unilateral vesicular rash then develops in the region of the affected nerve. Over the following few weeks, the vesicles dry and crust before healing. PHN in this region is also possible. Treatment includes antiviral therapy and wet dressings with 5% aluminium acetate. Analgesia for pain is essential.

INVESTIGATION

Investigation is usually not essential. However, in the case of atypical forms of shingles, virus isolation and serological tests must be used. The simplest test that suggests the diagnosis of shingles is the Tzank smear. This involves deroofing a vesicle and scraping the base with a sterile scalpel blade. The epithelial cells and fluid obtained are then smeared onto a glass slide and allowed to air dry. This is then sent to the laboratory, where it is stained with Giemsa, Methylene blue or Wrights stain. Microscopic examination reveals tzank cells, which are multinucleate giant cells. In the setting of limited resources, this is the most cost effective and rapid method of diagnosis affirmation. Tzank cells, however, are also found in herpes simplex virus infection, pemphigus vulgaris and CMV infection.

Immunohistochemical staining of viral antigens, in the form of direct fluorescent antigen (DFA) staining, is far more specific for VZV. A sample is taken in the same manner as a Tzank smear but must be fixed with cold acetone and is stained with fluoroescein-conjugated monoclonal antibodies which are virus specific. It is then examined using a fluorescence microscope. VZV can then be distinguished from other viruses, making DFA staining a much more powerful technique then a simple Tzank preparation. DFA is also more sensitive than virus culture, especially in the later stages of VZV infection when virus isolation becomes more difficult.

PCR has been used successfully to detect viral DNA in cerebrospinal fluid (CSF) from patients with VZV encephalitis and in ocular fluids and tissues in VZV retinitis. Examination of CSF usually reveals a moderate lymphocytic picture, normal to moderately elevated protein, and normal glucose. The PCR for VZV DNA in CSF is positive in more than 75% of cases.

Serum IgG becomes detectable several days after the onset of varicella and titres peak after 2-3 weeks, so serologic testing provides only a retrospective diagnosis.

ELISA is capable of detecting IgG or IgM antibodies to VZV antigens and is a reliable indicator of immune status following natural infection. ELISA may not be sufficiently sensitive to detect vaccine-induced immunity.

Differential diagnoses for Shingles include Impetigo, erysipelas, enteroviral infections and herpes simplex infection. These diseases are excluded by using detailed history

taking, physical examination and laboratory findings.

Morbidity and mortality of Herpes Zoster have dramatically improved since the availability of anti-viral drugs. The vast majority of immunocompetent persons with shingles should be treated only symptomatically. Predominantly, management is directed toward reduction of fever and avoiding secondary bacterial skin infection.

The anti-viral used to treat shingles is acyclovir, an acyclic analogue of guanosine, which selectively inhibits VZV and HSV replication. In the case of HZ, it may be administered orally or parenterally. (Acyclovir eye drops can be used as part of HZ ophthalmicus management). Intravenous acyclovir should be reserved for those with unusually severe or complicated infections. The anti-viral penetrates well into most tissues, including the CNS. The approved dose of acyclovir for shingles is 800 mg five times daily for seven days. The drug is extremely safe and well-tolerated. Renal dysfunction, resulting from accumulation of acyclovir crystals in the kidney, has been observed following rapid intravenous infusion of large doses of acyclovir, but is uncommon and usually reversible. Dosage reduction is required in patients with renal insufficiency. Acyclovir-related neurotoxicity has been reported and presents with agitation, hallucinations, disorientation, tremors, and mild clonus. This may occur in elderly patients with underlying CNS abnormalities and renal insufficiency.

Nevertheless, acyclovir neurotoxicity and nephrotoxicity are rare occurrences. Studies of patients receiving long-term acyclovir for chronic suppression of genital herpes have revealed no cumulative toxicity.

Acyclovir sodium for intravenous infusion is supplied as a sterile water-soluble powder that must be reconstituted and diluted to a concentration of 50 mg/ml. The recommended dose of intravenous acyclovir for VZV infections is 10mg/kg eight hourly, although higher doses (12-15mg/kg) are sometimes used for life-threatening infections, especially in immunocompromised patients.

Valacyclovir is an orally administered prodrug of acyclovir that overcomes the problem of poor oral bioavailability of acyclovir and exhibits improved pharmacokinetic properties. Valacyclovir is administered at a dose 1g three times daily for seven days. Following administration of valacyclovir at a dose of 2g orally four times daily, efficacy mimics that of acyclovir given intravenously at a dose of 10mg/kg every eight hours. Clinical experience with this drug is limited. At standard doses, valacyclovir is also a very safe and well-tolerated drug. There is no contraindication to using the anti-viral at approved doses in HIV-infected patients. Clinically significant interactions between acyclovir or valacyclovir and other drugs are extremely uncommon.

Famciclovir may be used for uncomplicated herpes zoster. The recommended dose is 500mg three times daily for seven days. Doses of 250 mg three times daily and 750mg once daily are approved for treatment of shingles in some countries and appear to be comparable with respect to cutaneous healing of herpes zoster. Dosage adjustment is required in patients with creatinine clearance of <60 ml/min. The adverse effects most frequently reported by patients participating in clinical trials of famciclovir were headache and nausea.

VZV isolates that are resistant to acyclovir and related drugs remain susceptible to foscarnet. Foscarnet is administered only by the intravenous route. Doses ranging from 40 mg/kg every eight hours to 100mg/kg every 12 hours have been used successfully. The most important adverse effect associated is nephrotoxicity as 80%-90% of the administrated dose is excreted unchanged in the urine. Loading the patient with intravenous saline prior to foscarnet infusion aids in reducing the risk of nephrotoxicity. Foscarnet may also induce a variety of electrolyte and metabolic abnormalities when administered via bolus infusion. Most notably, hypocalcemia. This predisposes patients to cardiac arrhythmias, tetany, altered mental status and seizures. To avoid such adverse effects, foscarnet must be administered with an infusion pump over a duration of at least one hour. Serum creatinine levels should be checked at least three times weekly and the dosage adjusted accordingly.

Administration of alpha-interferon to immunocompromised patients with herpes zoster reduces the risk of viral dissemination, but has little impact on dermatomal rash healing or pain. Interferon therapy has been shown to be associated with signifi cant adverse events and has been supplanted by more specifi c antiviral drugs. MC

References available on request.

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CHOOSE EITHER A, B OR C

1. Herpes zoster is characterised by:
   a) Maculo-papular and vesicular lesions with crusting, typically in a dermatomal distribution
   b) Maculo-papular and vesicular lesions without crusting, commonly preceded by dermatomal neuralgia.
   c) Maculo-papular and vesicular lesions with or without crusting, typically in a dermatomal distribution, commonly preceded by dermatomal neuralgia.

2. The aetiological agent in Shingles pathogenesis is
   a) Herpes simplex virus
   b) Varicella Zoster Virus
   c) Cytomegalovirus.

3. VZV travels along
   a) Motor neurons
   b) Sensory neurons
   c) Motor and sensory neurons.

4. Where VZV affects the 7th and 8th Cranial nerve, the resulting syndrome is referred to as
   a) Zoster sine herpete
   b) Huchinsons syndrome
   c) Ramsay Hunt syndrome.

5. A DFA assay identifies:
   a) VZV antibodies
   b) VZV antigens
   c) VZV antibodies and antigens.

6. The most cost effective test for shingles is:
   a) Direct fluorescence antigen assay
   b) PCR (Polymerase Chain Reaction)
   c) Tzank smear.

7. Multinucleate giant cells are:
   a) Specific to VZV
   b) Non specific
   c) Specific to HSV.

8. Acyclovir may be:
   a) Hepatotoxic
   b) Nephrotoxic
   c) Ototoxic.

9. HIV affected individuals may have atypical lesions including:
   a) Verrucous lesions
   b) large punched out ulcers
   c) salmon pink lesions with silvery scales.

10. In pregnancy, acyclovir is:
    a) FDA category D drug
    b) FDA category X drug
    c) FDA category B drug.

This is to state that I have participated in the CPD-approved programme and that these are my own answers.

Signature Date

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