

Review

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COMPLICATIONS AND FACTORS OF REACTIVATION OF VZV- INFECTION IN CHILDREN AND ADULTS

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Data of our country and foreign data concerning complications of VZV-infection in children and adults are summarized in this article. The presented data confirm the urgency of VZV-infection complications in adults regarding its prevalence within able-bodied population and high possibility of lingering disability.

KEY WORDS: VZV-infection, varicella (chickenpox), herpes zoster (shingles), complications of VZV-infection

ХАРАКТЕР УСКЛАДНЕНЬ ТА ФАКТОРИ РЕАКТИВАЦІЇ VZV-ІНФЕКЦІЇ У ДІТЕЙ ТА ДОРОСЛИХ

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В статті підсумовані дані вітчизняної та закордонної літератури щодо характеру ускладнень у дітей та дорослих при VZV-інфекції. Наведені данні, підтверджуючі актуальність проблеми ускладнень VZV-інфекції у дорослих в зв'язку з високою частотою їх виникнення у працездатного населення та вірогідністю тривалої втрати працездатності та інвалідизації.

КЛЮЧОВІ СЛОВА: VZV-інфекція, вітряна віспа, оперізуючий лишай, ускладнення VZV-інфекції

ХАРАКТЕР ОСЛОЖНЕНИЙ И ФАКТОРЫ РЕАКТИВАЦИИ VZV-ИНФЕКЦИИ У ДЕТЕЙ И ВЗРОСЛЫХ

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В статье суммированы данные отечественной и зарубежной литературы о характере осложнений у детей и взрослых при VZV-инфекции. Приведены данные, подтверждающие актуальность проблемы осложнений VZV-инфекции у взрослых в связи с высокой частотой их возникновения у трудоспособного населения и вероятностью длительной утраты трудоспособности и инвалидизации.

КЛЮЧЕВЫЕ СЛОВА: VZV-инфекция, ветряная оспа, опоясывающий лишай, осложнения VZV-инфекции

The significant frequency of severe and complicated forms of varicella (chickenpox) is associated with high rate of disability among adults, especially within young ones, tells about the urgency of VZV-infection [1–3]. Nearly 150 000 cases of varicella within children population are registered annually in Ukraine [4]. The mortality rate of VZV-infection in children aged 1-14 years is 2 cases out of 100 000; at the same time its morbidity rate is less than common cold rate only [5, 6]. The

morbidity rate among Ukrainian soldiers significantly exceeds the same rate in civil population [1]. The amount of patients with acute forms of VZV-infection that need specific therapy, have doubled during the last two decades; nearly 70 % out of them are older 60 years with appreciable prevalence of women [7, 8]. Annually 80–90 million cases are registered worldwide in accordance to the WHO information; 90–98 % of Earth population is infected by VZV [9]. The final conclusion says

that virus carrying may be met in 90 % of population, but the frequency of its clinical manifestation is significantly less and makes up 10–25 % [11].

More than 3 million cases of varicella are registered annually in the USA, 90 % out of them are children aged from 1 to 14 years; and more than 300 000 cases of herpes zoster are registered mainly within elderly [10, 14, 15]. Specific antibodies against VZV (varicella-zoster virus) can be found in 95 % of adults. These people are under the high risk of herpes zoster development [14]. The annual rate of mortality because of different varicella complications is 105 cases in the USA [16].

The typical biological features of all human herpesviruses, including VZV, are tissue tropism, lifelong persistence and latency in an infected human body [17, 20].

VZV is the type III herpesvirus of human Herpesvirus family. It is neuro- and dermatotropic and affects cells of central and peripheral neurological system. The virion is oval-shaped and 120–200 nm in size. The virus invades intravertebral ganglions and posterior spinal roots, and stays there for a long time in the latent stage of its lifecycle. In the contemporary classification 5 principal taxons of VZV are marked out [104]. Genotyping, epidemiologic evidence and mathematical simulation showed all-round distribution of different VZV genotypes [105–111].

VZV is a unique virus, it is able to develop two different human diseases: varicella (a.k.a. chickenpox) and herpes zoster (a.k.a. shingles).

The source of VZV-infection is a person that suffers from varicella, who is dangerous for others from 10th day of incubation till 5th day after the last rash elements appearance [21]. Sometimes people with herpes zoster can be the source of infection (until the vesicles drying up). The transmission of infection realizes through droplet pathway. It could not be excluded the intrauterine infection [21]. The susceptibility to the infection is total.

The source of herpes zoster is the person with herpes zoster or varicella. The disease is transmitted through droplet pathway and contagion. The placental transmission may not be denied [21]. There is no seasonal prevalence. The disease is mainly sporadic.

Complications of VZV-infection. The main problem of VZV-infection concerning able-bodied population is its complications followed by disability and lethal cases. From the eco-

nomical point of view the cost of treatment of patients with postherpetic neuralgia (PHN) per se is a significant financial problem. For instance, in the UK the cost of PHN treatment reaches 18 million pounds per year. In the USA the only antiviral therapy costs nearly 1200 dollars for one patient [14]. In Germany the financial loss caused by varicella morbidity is 188 million euro, 82 % out of them (154 million) are payments for parents' disability, and remained 34 million are medical care costs, mainly for children older 12 years [22]. In Ukraine the cost of antiviral therapy has not been estimated yet.

For the current moment there are no exact recommendations regarding early diagnostic and treatment of VZV-infection, that is the one of cause of increased number of patients with PHN and other complications and gives a reason for detailed investigation of this not only «children's» infection [14].

Within the complications of VZV-infections the followed prevail over the rest: CNS alteration, pyoderma and pneumonia [4, 23]. Encephalitis after varicella makes up 90 % of all neural system injuries.

The literature data overview reveals 0,1–0,2 % frequency rate of neural system injuries; accounting this the frequency of acute cerebral ataxy is 1 per 4 000 cases [25]. In rare cases the ataxy develops before exanthema appearance, but more often from 5th till 10th days from the onset of rash.

The VZV-mediated injuries of neural system develop as encephalitis or encephalomyelitis mainly in children aged less 2 years [23, 28, 29]. The frequency of encephalitis is 1 case per 4 000. VZV-mediated encephalitis in immunocompromised patients has been described in plenty publications in recent years. Authors point that the number of VZV-mediated encephalitis cases meaningly rose in era of HIV/AIDS and other immunodeficiency states [31, 34].

The literature data of author's country says that activation of VZV-infection is followed by viral ganglionitis development with damage of spinal ganglia (including posterior roots) or ganglia of cranial nerves [14, 17, 39]. In severe cases the anterior and middle horns, white substance, and cerebrum are involved into pathological process, causing meningoencephalitis [13, 32, 33, 35, 36]. It was established that there is no dependence between the severity of varicella course, onset and course of neuro-

logical complications; the last ones may arise in the time of very severe as well as in the time of mild cases of infection [25].

The one of the widely-distributed complications of VZV-infection, mainly herpes zoster, is PHN that follows hemorrhagic necrosis and fibrosis of sensory spinal ganglia and is characterized by hard pain along nerves and leads to temporary or permanent disability [12, 13, 18, 19, 24, 26, 27].

The Ukrainian literature data point that 10–20 % patients with VZV become ill with PHN immediately after acute manifestation of herpes zoster. PHN develops in 60 % patients, 80 % out of them are people older 65 years [41]. The risk of PHN development in old patients may reach 50 % [43]. In typical cases the pain in the injured nerve region becomes extinct during 2–3 months in 50 % of patients; during 1 year in 80 % of patients and it may last for years in 10–20 % of patients [8, 17, 25, 44].

The less frequent, but mentioned in the literature neurological complications in adults are ganglionitis of Gasser's ganglion, osteonecrosis and spontaneous falling out of teeth in the case of middle and inferior trigeminal nerve branches involvement into VZV-infection course; oculomotor nerve injury (III, VI and IV cranial nerves in accordance to the frequency of their alteration), Hunt's syndrome (in the case of geniculate ganglion and tympanichord injury followed by vestibular, trifacial, facial and sublingual nerves involvement), affection of jugular sympathetic ganglia, herpetic ganglionitis of bottom part of jugular and top part of thoracic and lumbosacral vertebral regions, myelitis with pyramidal paraparesis with sensory and sphincter disorders, granulomatous arteritis (encephalitis with great and minute vessels affection) (lethality rate is about 25 %), ventriculitis and meningitis, meningoencephalitis [14, 25, 26, 28, 37, 38, 40, 42, 46–48, 51, 53–56, 59, 93–95, 100]. The majority of neurological states during VZV reactivation are connected to single or multiple infarctions due to vasculopathy development because of virus replication in the walls of great and minute cerebral arteries [60]. From 7 to 31 % of ischemic strokes in children were evoked by acute form of VZV-vasculopathy, and 44 % of children suffered from periodic ischemic attacks following varicella [45, 49, 61–63]. In childhood 1 out of 15 000 cases of varicella are complicated by stroke.

Shingles is rarely complicated by acute inflammatory demyelinating radiculoneuropathy — Guillain-Barre syndrome [23, 25, 28, 51, 64]. This heterogenic immunologically mediated disease includes primary demyelinating and primary axonal variants. Autoantibodies against membrane components gangliosides GM2 play the main role in the disease development. VZV infection is associated with disseminated sclerosis development [98, 99].

It is known that VZV is able to affect autonomic ganglia causing visceral disfunction [7, 14, 17, 21, 48, 65]. Affection of urino-genital system caused by varicella is presented usually as cystitis and characterizes by vesicle rash on mucus, followed by hematuria and leucocyteuria as well as neurogenic urinary bladder with urinary retention. The urinary retention and constipation arise against the background of viral alteration of sacral nerves [66, 96].

Another complication VZV-infection is eye involvement which occurs provided a 1st branch of trigeminus involvement [13, 26, 30]. Without antiviral therapy 50 % of patients with VZV-infection develop ophthalmological complications (episcleritis, iridocyclitis, keratitis). In some cases glaucoma may emerge. Such lesions were registered in about 45 % of patients with shingles as reported E. P. Dekonenko et al. (1999).

Visceral complications of VZV-infection regarding some authors' data are the followed: pericarditis, myocarditis, endocarditis, fulminant hepatitis, splenic infarction, acute appendicitis [50, 52, 57, 58]. In addition to that hematological and vascular complications may occur: sickle-cell disease, purpura fulminans, disseminated intravascular clotting [67, 72, 74, 79, 85, 91, 92].

Along with neurological complications there were registered bacterial complications of VZV-infection, causative agent of which in most cases was *S. pyogenes* [4, 48, 97]. In accordance to examining of 119 patients in 1996 authors revealed the followed bacterial complications caused by *S. pyogenes*: pyoderma (26,0 %), pyoarthrosis (4,2 %), osteomyelitis (3,3 %), necrotizing fasciitis (2,5 %), orbital cellulitis (1,6 %), pneumonia (0,8 %).

Necrotic phlegmon caused by *S. aureus* was reported as VZV-infection complication [68]. Mikaeloff Y. et al. consider that nonsteroidal anti-inflammatory drugs and paracetamol increase a risk of skin bacterial infection development in patients with chickenpox, espe-

cially in children [103]. Retrospective assessment of 680 case reports of children (56,3 % out of them were boys and 43,7 % were girls) aged from 3 weeks till 19 years old (average age $6,2 \pm 4,6$ years) with varicella was led. The population involved into the study was treated since 2001 till 2011 in the hospital of children's infectious diseases department of O. Bogomoltsa National medical university [39]. The first place among complications of varicella took bacterial infection (12,1 % out of all patients and 49,1 % out of all complications). Among bacterial complications in all age groups till 15 years were found out the listed below diseases: pyoderma (25,7 %), pneumonia (23,2 %), stomatitis (23,2 %), skin abscess (12,2 %), acute gastroenteritis (7,3 %), bronchitis (2,4 %), purulent otitis media (2,4 %), mucousopurulent conjunctivitis (2,4 %), infection of urinary tracts (1,2 %).

Rarely the varicella is complicated by viral pneumonia, lethality of which may reach 10–30 % especially among adults with immunodeficiency and pregnant women [69, 70].

Factors of VZV reactivation. The state-of-the-art of infectious diseases and their complications development lies mainly in their immunopathogenesis, notably in relationship between macro- and microorganism, immunoreactivity decrease, features of microorganism, including their ability to hide from immune control by antigenic mimicry as well as modify human immune response [71].

Latent infection activates because of reduced immunological resistance connected to concomitant diseases, organ function impairment, immunosuppressive medications administration, old age [7, 14, 17]. In an age group 60–69 years morbidity of zoster makes up 6,9 out of 1 000; in an age group of people older 80 years it is already 10,9 out of 1 000 [73]. Other not less important risk factors are: belonging to the white race, psychological stress and physical trauma. In accordance to the assessment of patients from risk groups which were stressed (during the space flight) it is possible to develop inapparent infection followed by virus distribution with saliva [75]. Family predisposition is accounted as a risk factor of VZV reactivation too [76].

VZV reactivation followed by zoster development may be explained by cell-mediated immunity malfunction [77, 78].

VZV reactivation against the background of immunosuppression may lead to virus dissemi-

nation that can end lethally [10, 13, 17, 43, 80–84, 86, 87]. The most severe forms of zoster are observed in patients with leukemia, lymphogranulomatosis, malignant tumors, HIV infection and in people treated by corticosteroids and X-ray therapy [7, 14, 17, 21, 28, 43, 88].

VZV-infection reactivation can be observed in 25 % of patients with AIDS and may arise during any stage of this infection. It was established that HIV-positive people are 10 times more inclined to zoster development than seronegative patients independently from their social and financial status and sexual behavior [14, 43]. Some authors reported that people who suffered from varicella during 1st year of life are more susceptible to zoster development at the age after 60 years.

Prevention of VZV-infection. Vaccination is called to reduce the severity of complications and VZV-reactivation frequency. Cohort immunization against varicella was included into vaccination calendar in 1997 in the USA. Children are vaccinated at the age of 12–18 months with followed booster dose at 12 years of age. Administration of attenuated vaccine against VZV in the USA favoured decrease of morbidity rate 76–87 % down in the period from 1995 till 2000 years and led to lethality rate reduction from 50–100 to 10 cases annually [89, 90].

The European branch of WHO recommends by all means vaccinating selectively patients with leukaemia during remission and patients from transplantation waiting list which do not have varicella in their history.

The Ukrainian national calendar of vaccination is regulated by Ukrainian Health Department instruction of prophylactic vaccination (Instruction № 48 from 03.02.2006). The vaccination against VZV was included as recommended manipulation for healthy children older than 15 months old; for children before entrance the school and for health workers which are under the high risk to be infected and which do not have varicella in their history. The data exist which show the absence of efficacy of human immunoglobulin administration for varicella prevention without previous assessment of specific antibodies rate [89].

Hereby the urgency of immune reactivity problem during VZV-infection is obvious that is confirmed by worldwide tendency of active immunization against VZV infection and consequently its complications development prevention in adults and children.

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