

Clinical Research

Cases of Clinically Proven Hantavirus Infection with a Pulmonary Syndrome among Pregnant Women in Tashkent, Uzbekistan

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Abstract

Background: For nearly a decade, a disease likely to have been misdiagnosed was observed in pregnant women in Tashkent, Uzbekistan. It caused the rapid decline and death of patients, with about 45% mortality rate. The disease was suspected to be caused by a virus of the HVP (Hantavirus) family, and clinical studies were conducted to ascertain. **Methods:** As no system for registration of such cases had been maintained, researchers developed a questionnaire with indicators chiefly based on relevant literature. All the women admitted exhibiting the symptoms listed were covered by the study. **Results:** Among the 16 cases identified from September to December 2008, ten survived; 80% belonged to the indigenous ethnic group; 80% were housewives. Most (90%) were between 16 and 34 weeks' pregnancy, 24.5 weeks on average. Almost all of them experienced labored breathing and abnormally high body temperature. About 75% of the women lived in the vicinity of rodents' habitats, and about half of them could have been in direct contact with the aerosolized rodent excreta. **Conclusions:** Researchers believe that those women exposed to the excreta were cases of HPS. In practice, the surgical removal of the fetus proved to be the most efficient treatment. However, the medical community has a growing concern about patients with HPV being misdiagnosed and the related difficulties in diagnosing and treating them.

Key words: HPV; diagnosing; treating; pregnancy.

Introduction

For about ten years, an unknown disease was observed to attack pregnant women in the city of Tashkent, Republic of Uzbekistan. Characterized by an acute beginning, rapid development with severe complications, high mortality level and pronounced seasonal character (autumn and winter) the major clinical symptoms included respiratory problems (bronchopneumonia) with associated hypotension (arterial blood pressure under 90/60 mmHg). Conservative treatment was observed in less severe cases; however, surgical removal of the fetus was found to be more efficient.

In the 1st Perinatal Center in Tashkent alone up to 60 severe

cases of this disease were observed annually. In ten of these 60 cases (the research results between September and December 2008) surgical interventions were conducted. Across the city of Tashkent, among pregnant women with similar symptoms, the following outcomes were observed: 10 deaths out of 20 cases in 2003; 16 deaths out of 36 cases in 2004, and 8 deaths out of 21 cases in 2005.

This disease is new and virtually unknown to the health care practice in Uzbekistan. After referring to the international publications [1-5] and comparing the clinical symptoms of the cases observed in Tashkent and those described in the literature, we concluded that the closest match was the disease caused by virus *Sin Nombre (SNV)*, a member of the *Hantavirus* genus in the *Bunyaviridae* family, which manifests itself in pronounced pulmonary syndrome.

Hantaviruses have genomes comprising three negative-sense, single-stranded RNA segments. The name Hantavirus is derived from the Hantan River, where the prototype of the Hantaan virus strain was isolated for the first time, from the striped field mouse (*Apodemus agrarius*) in 1976 [4]. Other

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strains, such as *Seoul*, *Dobrava* and *Puumala*, were also isolated. These viruses together with the Hantaan virus are responsible for a number of diseases causing hemorrhagic fever with a renal syndrome [5]. All hantaviruses were noted to have a common reservoir, namely rodents, and were transmitted to humans through infected aerosolized rodent excreta (urine and feces).

The new disease caused by hantaviruses which was recognized as an important problem of the public health system was identified in the Southwestern USA in 1993 [1,2]. The first identified cases of this disease were referred to as Hantavirus pulmonary syndrome (HPS) and the etiologic agent which had not been described before was called *Sin Nombre virus* (SNV) [6]. For HPS attacks, it is typical to develop severe non-cardiogenic pulmonary edema which leads to lung insufficiency, similar to the symptoms of Acute Respiratory Distress Syndrome (ARDS).

According to some sources, the mortality in the case of this disease exceeds 45% [2,7]. Thus, of the 229 cases of HPS registered and verified in the US in October 1993, only 5 of them were pregnant women. The issue is complicated because most such cases are registered as ARDS [2, 8-10], and the Hantavirus effects are not recognized as there is relatively little information about them [11-14]. Therefore, the number of pregnant women who developed HPS could be much greater. In any case, these 5 verified cases permitted the investigation to ascertain whether the vertical transmission of the virus is possible, which was important, as evidence revealed that other members of this family possess the same ability [15-17]. However, in the case of SNV these assumptions were not proven [3].

Methods

The objective was to study the clinical and epidemiological aspects of this disease among the pregnant women in the city of Tashkent in order to be able to clinically prove the diagnosis of the Hantavirus pulmonary syndrome. If the diagnosis is proven, then relevant observations can be made of the virus' behaviour.

As the disease is new and quite unknown for Uzbekistan, no system of registration and documentation is available for such cases. Also, as laboratory test systems did not exist earlier to detect such viruses, researchers had to rely on the analysis of the clinical picture as proof of the hypothesis.

Therefore, to determine the case selection criteria we used the methodology employed for HPS identification recommended by the US Centers for Disease Control and Prevention (CDCs). The methodology had to be tweaked and expanded because of the inability to conduct relevant laboratory tests. Any woman admitted to any maternity hospital of the city of Tashkent between September and December 2008 with the following symptoms: body temperature above 38°C or below 36°C, with an acute beginning, labored respiration with apnea (24 respiratory movements per minute and more), general weakness, indisposition and sluggishness was considered a suitable candidate, given that one or more of the following symptoms was present as well: arterial blood pressure below 90/60 mmHg, icterus, hemorrhagic petechiae on the sclerae and palms, and absence of rales in the lungs at the time of admission.

When suitable cases were identified, the data was collected through interviews with the patient and her relatives, as well as the patient's doctor using a questionnaire form.

Results

In all, 16 cases complying with the suitable case definitions were identified in the maternity hospitals of the city of Tashkent between September and December 2008. Ten of them survived. Of these 16 cases, 80% belonged to the indigenous ethnic group, and 80% were housewives (Table 1). All of them had a normal pregnancy before contracting the disease, and the only medications they were taking were vitamins. None of them drank alcohol or smoked. All women were receiving prenatal care at their respective local health facilities, twice a month on average. In all, 90% of the women were between 16 and 34 weeks of pregnancy, 24.5 weeks of pregnancy, on average.

Table 1
Description of Suspected HPS Cases Observed in Tashkent (n=16)

Indicator	Number/percentage
Occupation	
Housewife	13 (81%)
Nurse	2 (12%)
Accountant	1 (7%)
Average age (Spread)	24 (20-30)
Average gestation time, months (Spread)	24.5 (11-39)
Pregnancy number, median (Spread)	2 (1-5)

On average, the women were admitted to the hospital on the 5th day of falling ill. More than 60% of them noticed the ARI symptoms within 1.5 months prior to admission to the hospital, while 80% noticed such symptoms 4 days prior to admission. In all, 87.5% reported that their body temperature rose to 38°C prior to the admission (Table 2).

Table 2
The Characteristics of Disease Development before Admission to the Hospital (n=16)

Indicator	Value
Average time period from the beginning of the disease till hospital admission, days (Spread)	5 (1-17)
Presence of ARI symptoms in the case history within 3 months prior to the admission to the hospital (%)	10 (62.5%)
ARI symptoms within 4 days prior to the admission to the hospital (%)	13 (81%)
One- or two occurrences of fever with the body temperature up to 38°C (%)	14 (87.5%)
Use of anticoagulants (%)	5 (31%)

Of the many clinical symptoms, virtually all these women experienced labored breath (Table 3), nearly 90% expressed general weakness and indisposition, and three-fourths of all cases reported shivers, headaches and appetite loss. Only ten of them (63%) had fever at the time of admission; in their cases, the average body temperature at the time of admission or later was 38.7°C.

Table 3
Frequency of Symptoms at the Time of Admission (n=16)

Symptom/Indicator	Number	Percentage
Body temperature above 38°C	10	63
Average body temperature (Spread)	38.7	(37-41)
Body temperature below 36°C	1	6
Shivering	11	69
Laboured breath (respiratory distress)	15	94
Coughing	8	50
Headache	12	75
General weakness and indisposition	14	88
Loss of appetite	12	75
Inadequate perception	3	19
Mental dullness	5	31
Rhinitis	1	6
Pharyngitis or tonsillitis	5	31
Laryngitis or laryngotracheitis	4	25
Bronchitis	5	31
Myalgia (muscular pain)	8	50
Low arterial BP (below 90/60 mmHg)	7	44
Skin paleness	11	69
Sclerae icterus	8	50
Hemorrhagic petechiae on the sclerae and palms	3	19
Absence of rale in lungs at the moment of admission verified by auscultation	5	31

In terms of epidemiological factors (Table 4), it should be noted that only 20 of the patients interviewed mentioned the presence of rodents in their houses. Half of the women lived in private houses while 25% of them lived on the first floor of an apartment house, implying that 75% of the women lived at ground level, close to the rodents' habitat. It was possible that half of the women could have had direct contact with the aerosolized rodent excreta, during cleaning the area or looking after cattle. This strongly suggests that the disease was carried and spread by rodents.

Table 4
Presence of HPS Risk Factors

Indicator	Number	Percentage
Living in a one-storey house	8	50.0%
Living at the ground floor of an apartment house	4	25%
Presence of rodents or signs of their presence in the house	3	18.8%
Presence of a plot of land with cattle/sheep or a kitchen garden	8	50.0%
Cleaning house or yard on a regular basis	8	50.0%

During the observation period, the researchers concluded that disease spread vertically (from animal excreta to human beings) and not horizontally (from humans to humans by air). This disease affected the victim's liver, kidneys and lungs. Earlier, liver damage had been noted by some local professionals who

consequently described it as a type of liver disease (hepatosis). However, post mortem revealed that the changes that occurred within the liver were functional and not organic in nature. The cause of death was determined as Pulmonary Syndrome. This appears to contradict the liver disease theory. The research group also suggested a connection between the damaged organs in light of the most recent findings: the vital organs were damaged because parts of several internal systems were under pressure. This could explain why the women who were admitted developed a dangerously critical condition immediately after admission: they were admitted in the late stages of the disease and their bodies were highly stressed. These findings indicate that their condition had a viral cause.

Finally, among those women who successfully survived the disease, at least ten cases were known to have later given birth to perfectly normal healthy babies. The head of the research team, A.V. An [18] in one of several interviews confirmed that he had personally delivered healthy newborns: "I was very pleased to see them give birth. ... They all had perfectly normal and healthy babies. It made me very happy." This may also be considered strong evidence to prove that the changes were reversible and that they were caused by a virus.

Discussion

The clinical picture of this disease has been studied. A description of similar diseases has been studied from the international sources. Based on the results of this comparison, it has been found that the local medical society has been encountering cases of HPS. On comparing the data obtained with the data available from published sources [2,3,8,9,10,11,14], the following characteristics appeared very similar: the age of the patients in this study was between 20 and 30 years versus the average age of 20 to 34 documented in the literature; 38% mortality was recorded against 45%, respectively; gestation period of 11-39 weeks versus 13-29 weeks; frequency of occurrence of fever at the time of admission which constituted 63% versus 60% and average maximum temperature being 38.7°C versus 37.5°C; symptoms of labored breath; general condition at the time of admission and the presence of ARI-like symptoms. The involvement of factors predisposing a contact with rodents indicates that the cases described in this study bear even more similarity to the proven HPS cases. All these characteristics enabled us to arrive at the clinically proven conclusion that the cases described above were in reality cases of HPS. In terms of the observations of the behavior patterns of this HPS virus, the research group has made several observations. Due to the behavior of the virus, many cases were misdiagnosed as ARDS (severe ARI) and liver degenerative disease. Another important observation, thus far, is that the illness is not contagious and does not spread from person to person. This indicates the high improbability of the virus being SNV; on the contrary, all the evidence points to it as being a member of the Hantavirus family.

Also, this HPS virus is assumed to be responsible for the deaths of over half the pregnant women in the city's hospitals [18]. It was also noted to be seasonal in character, occurring mainly during the warmer periods of autumn and winter. Local clinicians are dealing with a serious disease that requires in-depth investigation to identify the best options for treatment and prevention.

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