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Case Report

Infantile Herpes Simplex Virus Meningitis: A Case Report

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ABSTRACT

***Background*:** Herpes simplex virus (HSV) is one of the main causes of neonatal meningitis; nonetheless, it usually goes unreported. A lumbar puncture is needed to accurately differentiate between viral and bacterial meningitis. The cerebrospinal fluid can be analyzed to exclude bacterial meningitis; nevertheless, the identification of the specific viral cause may be beneficial. Viral diagnosis determines prognosis, improves the care of the patient, decreases hospitalization duration, and reduces unnecessary use of antibiotics. In young infants, the herpes simplex virus infection is responsible for serious complications leading to morbidity, mortality, and permanent sequelae in survivors. The clinical findings of this infection usually include tremors, seizures, lethargy, irritability, poor feeding, temperature instability, and a bulging anterior fontanel, which are common in almost all forms of meningitis. These similarities make the differential diagnosis rather difficult.

Case report: We report and discuss the case of an an11-day-old neonate girl who presented with fever and negative test results, as well as our challenges that finally led to the diagnosis of HSV-related meningitis and its management.

Conclusion: It could be managed to reach a firm diagnosis confirming the initial differential diagnosis through additional and repetitive testing. Therefore, it is concluded that clinical judgments may be more reliable than paraclinical results in the individual approach for each patient. Furthermore, HSV infection should also be considered for patients with a persistent fever of unknown origin. It is also recommended to adopt separate procedures for the suspicion of HSV type 1 and HSV type 2.

Keywords: Herpes simplex virus, Infantile fever, Meningitis

Introduction

Fever as one of the most common characteristic signs of underlying diseases affects about 1.4% of neonates under three months old (1). In newborns, herpes simplex virus (HSV) infection is responsible for serious complications leading to morbidity, mortality, and permanent sequelae in survivors. It occurs in 1 out of 3,200-10,000 live births (1-4). The fetus can be infected via the hematogenous (through the placenta) or ascending mechanisms (through fetal membranes) (2).

Neonatal HSV falls into three main categories, including localized, central nervous system (CNS) involvement, and disseminated disease (2-5). Approximately, 45% of cases manifest as the localized disease category, 30% as CNS involvement, and 25% as the disseminated disease (6). The rates of neonatal mortality in the disseminated and CNS involvement categories have reportedly decreased from 85% to 9% and 50% to 4%, respectively (2). Morbidity has also been improved but more modestly. In the disseminated disease category, the proportion of neonates who grow normally during the first year of life year has increased from 50% to 83% (2).

Infantile HSV meningoencephalitis is common in the second or third weeks of life but may present by the sixth week (6). The associated clinical syndrome is characterized by tremors, seizure, lethargy, irritability, poor feeding, temperature instability, and a full anterior fontanel (5, 7, 8).

Viral meningitis is the most common type

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of neonatal meningitis in neonates, and it can be fatal if left untreated (7). Herpes simplex virus type 2 (HSV-2) is the most common herpes virus causing meningitis; nonetheless, other viruses, such as HIV and Zika, may also cause viral meningitis (7). The clinical signs of viral meningitis are usually similar to those of bacterial meningitis but are less severe. The incidence rate of bacterial meningitis has significantly decreased; on the contrary, the rate of viral meningitis has demonstrated a marked increase. For instance, only 0.3-0.4% of American neonates presenting with fever may be diagnosed with bacterial meningitis (1); however, in the UK, the incidence rate of viral meningitis has been reported to be 312.5 per 100,000 neonates under three months old (7).

In this case report, we present the case of an 11-day-old newborn girl presented with fever and negative test results with the final diagnosis of HSV-related meningitis.

Case report

The case was an 11-day-old neonate girl presented with fever. She could not feed properly, was irritable since two days earlier, and got lethargic before being admitted to the emergency department. She was the first child of the family born after 40 weeks of pregnancy following a normal vaginal delivery without any complications during birth. Her birth weight was 3900 grams. She looked ill on examination, and her vital signs were as follows: pulse rate:150 per min, respiratory rate: 45 per min, axillary body temperature: 38.5°C, and oxygen saturation (SpO2): 100%. Her anterior fontanel was open with a size of 2.5×2 centimeters. There was a papule on her upper lip just at the site of her right naris since the fourth day of life and multiple red papules and pustules on her lower jaw since the sixth day of life that grew larger and became ulcerated (Figure 1). Her infantile reflexes, including sucking, Moro, and rooting reflexes, had diminished. She weighed 4,550 grams, and her height was 52 centimeters. Three days after admission, she had generalized tonic-colonic seizures with an upward gaze that lasted for a minute and was repeated three times in total. During those three days, her fever did not respond to conventional therapies.

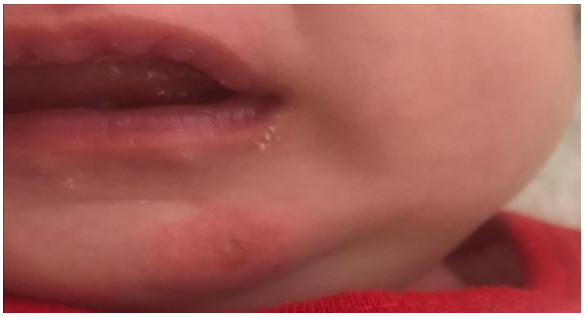

Figure 1. A papule on the upper lip, and multiple red papules and pustules on the lower jaw of the case

Her first laboratory results are summarized in Table 1. As illustrated in this table, the lymphomononuclear leukocytosis was the first abnormal finding.

Cardiomegaly was suspected upon evaluating her chest X-ray (CXR) result. Taking into account her tachycardia, a cardiologic consultation was

Table 1. The laboratory results

Test	Value	Normal range
Hematology-CBC		
RBC	9×10³*	4.4-11.3 (×10³)*
Hb	15.7 g/dL	12.3-15.3 g/dL
Hct	46.0 %	36-45 %
MCV	102.4 **	80-100 **
MCH	35.0 pg	-
MCHC	34.1 g/dL	-
RDW-CV	15.6 %	11.5-15 %
Platelet	440×10³*	150-450 (×10³)*
PDW	11.4 **	9.8-17 **
MPV	10.0 **	8.6-12.7 **
WBC	9×10³*	4.4-11.3 (×10³)*
Neutrophils	35 %	45.5-73.1 %
Lymph	51.2 %	20-45 %
Mixed (mono + Eos + baso)	13.8 %	6-15 %
CRP	3.3 mg/L	<6 mg/L
VBG		
PH	7.350	
PO2	50.9 ***	
PCO2	35.8 ***	
HCO3	19.8 mEq/L	
BE	-4.7 ****	
BB	42.7 ****	
O2 sat	83.5 %	
SBE	-4.8 ****	
TCO2	20.9 ****	
a-ADO2		
ESR 1h	6 mm/h	<18 mm/h
BS	79*****	
Urea	17*****	17-45*****
Creatinine	0.5*****	0.5-1.3*****
Sodium	136*****	135-145*****
Potassium	5.2*****	3.5-5.3*****
UA	NL	

* : microL, ** : fL, *** : mmHg, **** : Mmol/L, ***** : mg/dL

RBC: red blood cell, Hb: Hemoglobin, Hct: hematocrit, MCV: Mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW-CV: Red blood cell distribution width, PDW: platelet distribution width, MPV: Mean platelet volume, WBC: white blood cell, CRP: C-reactive protein, VBG: Venous blood gas, P2o: partial pressure of oxygen, pCO2: Partial Pressure of Carbon Dioxide, HCO3: Bicarbonate, O2 sat: Oxygen saturation, SBE: Subacute bacterial endocarditis, TCO2: total carbon dioxide, A-aDO2: Alveolar-arterial Oxygen Gradient, erythrocyte sedimentation edimentation rate: ESR, UA: urine analysis

requested, and electrocardiogram and echocardiography were performed accordingly. A small patent foramen ovale (PFO) and closing patent ductus arteriosus (PDA) were found with no abnormality relevant to her condition.

After one unsuccessful lumbar puncture (LP), the procedure was tried again 12 h later. The obtained specimen was bloody with a semi-clear appearance. The following cerebrospinal fluid (CSF) analysis showed a polymorphonuclear dominant white blood cell (WBC) count of 1940/mm^3. The red blood cell (RBC) count was high, and a high protein level and a normal glucose level were detected. The CSF culture did not demonstrate any growth after 48 h. Considering the new-found results and the clinical picture, the first suspicion was the HSV infection. The CSF analysis results are presented in Table 2.

A polymerase chain reaction (PCR) test was ordered to assess the presence of HSV types 1 and 2 in the blood; moreover, liver enzyme levels were evaluated. The blood PCR was negative, and the levels of ALT and AST were 40 and 42 IU/L, respectively.

In addition to fever, the seizure was observed as a new sign; therefore, a battery of tests was requested, including brain magnetic resonance imaging (MRI), electroencephalogram (EEG), calcium, and ammonia blood level. The brain MRI without contrast showed high signal intensity on the right temporal lobe, especially in T1 and T2 views. Calcium and ammonia levels were normal, and EEG demonstrated no abnormality. A new laboratory test was performed at that stage, and the test results are summarized in Table 3.

A lumbar puncture was performed again, and a PCR was conducted on the CSF sample to look for HSV types 1 and 2. The results were rather conclusive for our suspected diagnosis, and HSV particles were found; therefore, the patient was diagnosed with HSV-related meningoencephalitis.

Table 2. Cerebrospinal fluid (CSF) analysis results

Metric	Observation
Macroscopic	
Color before centrifuge	Bloody
Appearance	Semi-clear
Microscopic	
WBC	1940 mm^3
RBC	9400 mm^3
Polynuclear	70%
Mononuclear	30%
Sugar	49 mg/dL (Normal: 45-85)
T.protein	125 mg/dL (Normal: 15-45)

WBC: white blood cell, RBC: red blood cell

Table 3. Laboratory findings of additional laboratory tests performed after observing seizure

Test	Value	Normal range
Urea	6*	17-45*
Creatinine	0.5*	0.6-1.3*
Calcium	10.5*	8.5-10.5*
Phosphorus	7.1*	4-7*
Magnesium	1.85*	1.7-2.7*
Sodium	140 **	135-145**
Potassium	5.9**	3.5-5.5**
CRP	0.5	<6
Hematology-CBC		
RBC	8 ×10^3***	4.4-11.3 (×10^3)***
Hb	15.4 g/dL	12.3-15.3 g/dL
Hct	47.5 %	36-45%
MCV	106 ****	80 - 100 ****
MCH	34.4 pg	-
MCHC	32.4 g/dL	-
RDW-CV	15.4 %	11.5 - 15%
Platelet	165×10^3***	150-450 (×10^3)***
PDW	14.2 ****	9.8-17****
MPV	11 ****	8.6-12.7 ****
WBC	8×10^3***	4.4-11.3 (×10^3)***

* : mg/dL, ** :mEq/dL, *** : microL, **** :fL

RBC: red blood cell, Hb: Hemoglobin, Hct: hematocrit, MCV: Mean corpuscular volume, MCH: mean corpuscular hemoglobin, MCHC: mean corpuscular hemoglobin concentration, RDW-CV: Red blood cell distribution width, PDW: platelet distribution width, MPV: Mean platelet volume, WBC: white blood cell, CRP: C-reactive protein,

In ill-appearing patients presented with fever, the logical course of empiric therapy includes ampicillin and cefotaxime; however, in our case, the fever was not resolved after two days of therapy. Suspecting the HSV infection, we administered ampicillin, in addition to acyclovir 80 mg IV stat and 20 mg/kg q8h. On the third day, the patient began to contract tonic-clonic seizure attacks which were managed by phenobarbital. According to biochemical testing, the empirical therapy was modified, ampicillin was discontinued, and the patient received vancomycin. The antibiotics and acyclovir were continued for two weeks. An LP was performed again after this period, and due to the positive PCR test for HSV particles, the intravenous anti-HSV treatment was continued until the 21st day and switched to oral therapy afterward.

Discussion

An ill febrile neonate with poor feeding and irritability presented to the emergency room. Sepsis workup was performed, and the patient was initiated on antimicrobial empiric therapy. Her blood test results showed leukocytosis, and her lumbar puncture analysis demonstrated elevated protein levels, the glucose level was normal, and polymorphonuclear dominant WBC was detected. During her admission, she had

seizures multiple times; accordingly, a CSF PCR was ordered for the detection of HSV particles, and acyclovir was added as part of the empiric therapy. The PCR result was positive for HSV, confirming our diagnosis.

Numerous factors need to be considered while choosing the best possible management of an infant presenting with fever. The appearance of the patient is the first factor. For instance, the risk of a bacterial infection is higher in an ill-appearing patient. Moreover, in patients younger than six weeks of age, the HSV infection should be taken into account as a possible diagnosis (9, 10).

Empiric antimicrobial therapy in ill infants may be started regardless of the laboratory results, while the choice of empiric therapy depends on the patient's age. Neonates under 28 days old are administered ampicillin, cefotaxime/gentamicin, and acyclovir as the antimicrobial agents of choice (11-13). Before the initiation of acyclovir therapy, samples should be obtained for the detection of HSV infection, and the treatment plan should be modified based on the results (6, 14). Experts recommend acyclovir as an empiric therapy candidate after obtaining CSF samples for PCR and analysis in ill-appearing newborns with aseptic meningitis or clinical findings of meningoencephalitis without a bacterial cause (15, 16). Our patient was started on empiric antibiotics without acyclovir. The absence of acyclovir in her regimen was due to her parents' disagreement with a lumbar puncture at the beginning. Furthermore, the administration of acyclovir may be left optional.

An ill appearance with or without fever would be enough to have a full sepsis workup panel: Complete blood count (CBC) with differential, blood glucose and culture, inflammatory markers (e.g., C-reactive protein (CRP) and procalcitonin (PCT)), urine analysis and culture, CXR, CSF analysis and culture, and CSF PCR (indicated in HSV or enterovirus studies) (9, 11, 17). Among the aforementioned tests, all of them were normal in our patient, except the CSF analysis which showed an underlying CNS-related disease.

The chance of a successful LP in neonates in the first attempt to obtain CSF with <10,000 RBC varies from 45-74% (29, 30), and the age of <90 days is one of the major risk factors of failure to obtain CSF, despite several attempts (18). In our case, after instructing the patient's family on the aspects and involved risks and obtaining informed consent, LP was performed which failed in the first attempt, followed by a successful try.

After suspecting meningitis based on the LP results and the occurrence of seizures, the identification of the main cause was essential for choosing the course of action. The clinical manifestations of infantile viral meningitis are similar to those of bacterial meningitis but are usually less severe (19). Common features may be fever followed by nonspecific symptoms, such as poor feeding, diarrhea, rash, and vomiting (20). It is not possible to differentiate between viral and bacterial meningitis solely based on clinical features, and the CSF profile tends to overlap, especially in the early stages of the disease (21-23). Although pleocytosis with a predominance of mononuclear cells in CSF analysis is not always suggestive of viral meningitis and can be observed in non-viral infections, the glucose CSF level can help make the differential diagnosis more narrow and specific (24). The features of CSF analysis in the background of viral meningitis include WBC< 500 cells/microL with a mononuclear predominance, a normal glucose level, CSF protein < 100 mg/dL, and a negative gram stain (25, 26).

CSF analysis may yield a normal or moderately elevated glucose concentration, mildly elevated protein, and mononuclear cell pleocytosis in the setting of HSV CNS infection (27). Normal CSF findings do not rule out the possibility of HSV infection due to the probable lag in the early stages of the disease. The presence of RBC in HSV infected CSF is not common and is usually due to a "bloody tap" (27). Vesicles are useful findings that may lead the clinicians to the diagnosis of HSV CNS disease, which is otherwise quite challenging to be distinguished from other types of meningitis (14, 28).

In our patient, a series of findings raised suspicion of HSV CNS disease. These findings included high total protein and normal glucose level in the CSF analysis, a herpetic-like lesion on the jaws, and persistent fever despite administering an antibacterial regimen. Therefore, the patient was initiated on IV acyclovir. The signs of HSV infection in infants, such as seizures, mucocutaneous vesicles, and focal neurological findings should prompt the physicians to perform a blood PCR for HSV, serum alanine transaminase and aspartate transaminase for evaluating HSV-associated hepatitis, swab or scraping samples from skin vesicles for culture, and immunological assay (9, 11, 17).

Swabs/scrapings from skin lesions should be obtained when there is a solid suspicion against

HSV infection, and viral culture should be performed on the specimen. Although a direct immunofluorescence assay (DFA) on skin lesions is a rapid test, it does not offer sufficient sensitivity as culture does (6). The role of PCR in assessing skin lesions has not been studied and is not generally recommended (6). Nevertheless, PCR of blood or plasma samples should be performed to detect HSV DNA. A positive result confirms the diagnosis of HSV infection (2, 27, 29-31). On the contrary, these tests were normal in the case of our patient.

The inflammatory markers, such as CRP and PCT, are useful when accompanied by urine analysis, WBC count, or absolute band count (32, 33). In our patient, CRP was assessed and reported to be normal. An abnormal EEG is common in the very early stages of HSV CNS infection and manifests as focal or multifocal periodic epileptiform discharges which are characteristic of the disease; therefore, it should be performed in suspected cases (2, 34). The EEG performed on our patient did not point to any significant abnormality.

Neuroimaging should be conducted in all newborns with any type of HSV disease, and MRI, CT scan, and ultrasonography are all acceptable options (6). MRI and CT scan are the recommended techniques to determine the location and extension of brain involvement. Findings vary substantially and may include a normal scan in some cases, parenchymal brain edema, hemorrhage, destructive lesions, or an abnormal attenuation (2, 7). The MRI results in our case were suggestive of high signal intensity on the right temporal lobe, especially in T1 and T2 views with heterogeneous low signaling areas without significant restriction.

The best option for detecting CNS HSV infection is PCR with a sensitivity of 75-100% and specificity of 70-100%. Diagnosis of CNS disease is based on positive CSF HSV DNA in PCR testing or clinical evidence, as mentioned above, along with the isolation of HSV in swab/scraping of skin lesions or positive HSV DNA PCR in the blood or plasma (35). In our patient, the test was positive, confirming our diagnosis.

Acyclovir is recommended as the therapy of choice for all types of HSV infection (6, 17). It is used in both virologically proven and clinically suspected HSV disease and infection (6, 16, 28). On suspicion of HSV infection, the intravenous acyclovir should be administered without any delay to improve clinical outcomes (36-40). The appropriate dosing of acyclovir for all types of HSV disease in young infants is 60 mg/kg/day intravenously, divided into three doses administered every 8 h (37). In our case, the acyclovir administration was 80 mg IV q8h.

The literature search yielded a few comparable cases, especially two cases with noticeable similarities to our patient. One of them was presented by Whelan and Carpa (41). The only finding reported in the mentioned study was vesicular lesions on the chest. Their workup included similarly HSV PCR testing of CSF and blood which showed positive results. Their patient was managed by acyclovir for 21 days, followed by repeated CSF analyses (41). To respect the preference of the patient's family, the follow-up CSF testing was not performed in our case; therefore, we had to follow up with the patient just by clinical conditions.

Along the same lines, Kumasaka et al. reported the case of a 13-day febrile neonate born to a mother diagnosed with HSV during her pregnancy. Their patient did not have any skin lesions, and the laboratory results were normal, except for the CSF analysis that showed mild mononuclear cell-dominant pleocytosis, high protein level, and a normal glucose range. However, the HSV CSF PCR was positive. They also evaluated the level of specific IgG and IgM against HSV in serum multiple times. The patient was started on acyclovir at a dosage of 30 mg/kg/day and immunoglobulin at the commencement of the treatment, and the acyclovir dosage was doubled after confirming the diagnosis based on PCR results (42).

Conclusion

On suspicion of HSV infection in the setting of fever, further investigations may be vital to confirm the diagnosis; however, in some cases, the results may not be conclusive. Non-response to empiric therapy may also add to clinicians' confusion. In our case, we were presented with a suspected diagnosis and managed to reach a firm diagnosis confirming our initial differential diagnosis through additional and repetitive testing. In light of the obtained results, it can be concluded that clinical judgments should be more greatly relied upon, as compared to paraclinical results, in the individual approach for each patient. In addition, it is recommended to adopt separate procedures for the suspicion of HSV type 1 and HSV type 2.

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None.

Conflicts of interest

The authors declare that they have no conflict of interest regarding the publication of this article.

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