

Utility of lumbar puncture in diagnosis of Vogt–Koyanagi–Harada disease

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Received: 5 April 2006 / Accepted: 13 January 2007 / Published online: 6 March 2007
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Abstract

Purpose To determine the significance of lumbar puncture in diagnosis of Vogt–Koyanagi–Harada disease (VKH).

Method A retrospective analysis was conducted on 116 consecutive patients diagnosed with VKH. Two additional patients who presented with acute VKH were included in the analysis. Demographic characteristics, including gender, age, and ethnicity, were extracted from the medical record. The stage of disease at presentation was documented. Pertinent laboratory results and diagnostic procedures such as lumbar puncture, fluorescein angiography, and echography that contributed to the diagnosis of VKH were collected.

Results Lumbar puncture results for 10 patients were available. Eight of these patients presented with pleocytosis consistent with a diagnosis of VKH. Clinical features and fluorescein angiography confirmed the diagnosis in these patients. Both of the patients who did not exhibit cerebrospinal fluid (CSF) pleocytosis presented with headache, vision loss, and bilateral uveitis. Fluorescein angiography disclosed multiple foci of leakage at the

retinal pigment epithelium level with accumulation of dye under the retina and disc leakage, confirming diagnosis of VKH.

Conclusion The utility of lumbar puncture as a diagnostic criterion for VKH should be re-evaluated given that clinical features and fluorescein angiography alone often support the diagnosis. The inherent risks and complications associated with the procedure must prompt the clinician to reserve this evaluation for atypical presentations.

Keywords Pleocytosis · Cerebrospinal fluid · Vogt–Koyanagi–Harada disease · Uveomeningitic syndrome · Lumbar puncture · Fluorescein angiography

Vogt–Koyanagi–Harada disease (VKH) is a bilateral, granulomatous uveitis often associated with exudative retinal detachments and extraocular manifestations involving the auditory organs, meninges and skin. Patients often present with severe signs of bilateral panuveitis with multifocal serous retinal detachments and hyperemia of the optic disc. Meningeal irritation, often noted in the initial stages of the disease, can result in headache, meningismus, and focal neurologic signs. Auditory manifestations include tinnitus and hearing loss, as well as vertigo. Cutaneous findings, which usually develop during the chronic phase of the disease, include vitiligo, alopecia, and poliosis of the lashes, eyebrows, and scalp hair [1, 2].

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The diagnosis of VKH is often made clinically when the patient presents with the above ocular and extraocular symptoms. However, in the absence of some of the ocular or extraocular findings, ancillary tests such as fluorescein angiography (FA), echography, and lumbar puncture (LP) have been used to aid in diagnosis. Prior diagnostic criteria described by Sugiura and the American Uveitis Society (AUS) have included the results of the lumbar puncture as a major requirement for diagnosis of VKH [3, 4]. A set of revised criteria [5] was published in 2001 as a result of the first international workshop on VKH. These criteria expanded on the traditional symptoms described by the Sugiura and AUS classification schemes but did not include cerebrospinal fluid (CSF) pleocytosis as a requirement for diagnosis. Of note, the revised criteria describe three different presentations: complete, incomplete and probable.

The majority of patients present acutely without the characteristic extraocular manifestations [6], and the clinician is often faced with the choice of which diagnostic evaluation to obtain in order to aid in diagnosis. The inherent risks and benefits of each test must be weighed, especially when patients present with contraindications for invasive procedures.

Although current recommendations include CSF evaluation as an integral part of the diagnostic work up for VKH, the percentage of patients with positive findings of pleocytosis ranges from 71.6% to 100% [6, 7]. It is the authors' experience that clinical features, along with fluorescein angiography, are all that are required to make the diagnosis of VKH in the vast majority of cases. The purpose of this study is to determine the utility of CSF evaluation in the diagnosis of VKH, and the extent to which those patients who underwent lumbar puncture could be diagnosed with VKH based on clinical features and fluorescein angiography alone.

Methods

A retrospective review was conducted on the charts of 116 consecutive patients seen at the uveitis clinic at the University of Southern

California/Doheny Eye Institute with a diagnosis of Vogt–Koyanagi–Harada disease from 1987 to 2005. Two additional patients who recently presented with acute VKH were incorporated in the analysis, bringing the total number to 118 subjects. Patients were classified into complete, incomplete, and probable cases of VKH based on the revised diagnostic criteria. Demographic factors, as well as clinical history, were extracted from the medical record. Clinical features, including visual acuity, intraocular pressure, degree of inflammation, posterior segment findings, and extraocular manifestations, were tabulated and analyzed. The stage at which each patient presented was also noted. The results of laboratory evaluations were collected, and ocular imaging studies such as fluorescein angiography and echography were reviewed if performed. Results from CSF analysis were also noted if available.

Results

Ten patients diagnosed with VKH who underwent lumbar puncture were identified. The clinical features for each at the time of presentation are noted in Table 1. Analysis of CSF revealed abnormal results in eight of the 10 patients in this population (Table 2). Two patients presented without pleocytosis upon CSF evaluation during the early (acute uveitic) stage of the disease. Of the 10 patients who underwent lumbar puncture, nine were initially examined by neurologists for symptoms of headache and decreased vision or hearing loss. One patient underwent lumbar puncture for CSF analysis after initiation of therapy due to the lack of response to systemic prednisone and was found to have pleocytosis on CSF analysis.

Analysis of the clinical features present in each patient included in this case series shows that eight (80%) presented with neurologic symptoms, including headache, nausea, neck stiffness and weakness. Anterior and/or posterior uveitis was noted in eight patients. Two patients presented with disc swelling, and subsequent examination during follow-up revealed cells in the vitreous cavity. Seven patients underwent fluorescein angiography and were noted to have typical findings of pinpoint leakage of dye at the level

Table 1 Initial clinical features documented in patients who underwent lumbar puncture for CSF analysis

| PT # | Sex | Neurologic symptoms | Auditory symptoms | Decreased VA | Ant uveitis | Post-uveitis | RD | Optic nerve |
|------|-----|---------------------|-------------------|--------------|-------------|--------------|-----|-------------|
| 117 | M | HA | | Yes | Yes | Yes | No | DE |
| 118 | F | HA | | Yes | Yes | Yes | Yes | DE |
| 15 | F | HA, V, N, weakness | | Yes | Yes | Yes | Yes | DE |
| 30 | F | HA, stiff neck | | Yes | Yes | Yes | Yes | DH |
| 34 | F | HA | | Yes | Yes | Yes | Yes | |
| 82 | F | | | Yes | Yes | Yes | Yes | DH |
| 55 | F | HA | Tin, HL | No | | | | DE |
| 71 | F | HA, stiff neck | Tin | Yes | | | | DE |
| 78 | F | HA, stiff neck | | Yes | Yes | Yes | Yes | DH |
| 113 | M | HA, N | | Yes | Yes | Yes | Yes | DH |

Abbreviations: Ant, anterior; DE, disc edema; DH, disc hyperemia; HA, headache; HL, hearing loss; N, nausea; Post, posterior; RD, retinal detachment; Tin, tinnitus; V, vertigo; VA, visual acuity

Note: All 10 patients were Hispanic

Table 2 Initial diagnostic evaluations for patients who underwent lumbar puncture for CSF analysis

| PT # | Sex | FA | B-scan | Positive laboratory tests | LP results |
|------|-----|---------|-----------|---------------------------|-----------------------|
| 117 | M | PPH, DL | Chor, ERD | | Normal |
| 118 | F | PPH, DL | | Lyme, ANA | Abnormal, pleocytosis |
| 15 | F | DL | | | Abnormal, Few WBC |
| 30 | F | PPH | | | Abnormal |
| 34 | F | | | | Normal |
| 82 | F | | | | Abnormal, pleocytosis |
| 55 | F | | | | Abnormal, pleocytosis |
| 71 | F | PPH, DL | | | Abnormal, pleocytosis |
| 78 | F | PPH, DL | Chor | | Abnormal, pleocytosis |
| 113 | M | PPH, DL | | | Abnormal, pleocytosis |

Abbreviations: ANA, antinuclear antibody; Chor, choroidal thickening; DL, disc leakage; PPH: pinpoint hyperfluorescence; ERD, exudative retinal detachment; WBC, white blood cells

Note: All 10 patients were Hispanic

of the retinal pigment epithelium, accumulation of dye under the retina and leakage of dye at the disc in late phases.

The findings for the two patients who did not present with pleocytosis (cases 34 and 118) are summarized in the following case reports.

Case 34

A 62-year-old Hispanic woman presented with complaints of blurry vision, flashing lights, and “a dark spot” in her central vision for two weeks’ duration. She also complained of headache and mild weakness but denied any hearing difficulty or skin problems. Visual acuity on examination was 20/80 OD and count fingers at 5 feet OS. Clinical examination revealed a low lying serous

detachment associated with retinal folds in the macula of the left eye. Examination of the right eye revealed no retinal detachment. A magnetic resonance image (MRI) of the brain showed no evidence of demyelination. A lumbar puncture was performed and CSF analysis was normal. Laboratory testing, including a complete blood count, metabolic panel, and sedimentation rate, revealed no abnormalities. Upon treatment with oral prednisone, the area of serous retinal detachment resolved.

Several months later, the patient presented with iridocyclitis. Best-corrected visual acuity was 20/70 OD and 20/60 OS. The patient denied headache or tinnitus. Physical examination revealed no evidence of poliosis or vitiligo. Ocular examination revealed anterior segment inflammation, as well as trace cells in the

vitreous cavity. Fundusoscopic examination revealed characteristic sunset glow fundus with retinal pigmentary changes noted in the macula and nummular scars in the peripheral retina. A diagnosis of chronic VKH was made, and topical corticosteroids were prescribed.

Case 117

A previously healthy, 25-year-old Hispanic man presented to an outside hospital with a three-week history of headaches and acute painful loss of vision in the right eye of seven days' duration. Best-corrected visual acuity was 20/60 OD and 20/25 OS. Examination revealed bilateral optic disc edema. The remainder of his initial workup was unremarkable, including a negative computerized tomography (CT) of the head and orbits, lumbar puncture with normal CSF analysis, complete blood count, and chemistry profile. He was referred for further evaluation five days later. At that time, visual acuity had dropped to 6 feet/200 OD and 8 ft/200 OS. Anterior and posterior uveitis was noted upon clinical examination. Optic disc edema, retinal striae, and mild serous retinal detachments were noted in both eyes. Fluorescein angiography demonstrated leakage around the optic nerve head along with multiple foci of hyperfluorescence with adjacent areas of leakage (Fig. 1a, b). Echography revealed diffuse, medium-reflective thickening of the choroid with shallow retinal detachments in both eyes. The patient was diagnosed with acute VKH.

Discussion

The use of lumbar puncture as an adjunct in the diagnosis of VKH has been considered a standard of care and has been cited as a major symptom/criterion in both Sugiura's diagnostic criteria and those outlined by the AUS. It is also incorporated in the revised criteria and is used to differentiate complete from incomplete forms of VKH. However, CSF analysis does not always reveal abnormalities. In our select population of 10 patients who presented with neurologic manifestations, eight (80%) were found to have abnormalities,

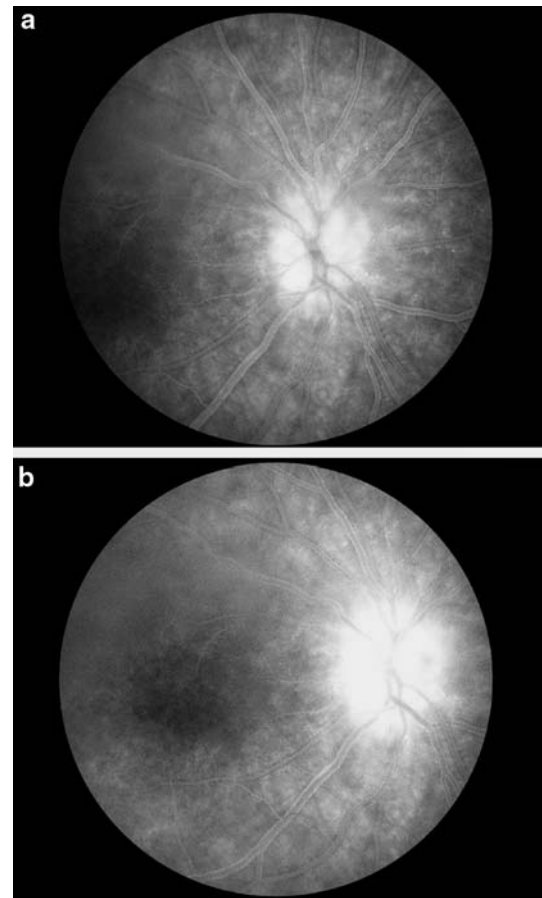


Fig. 1 Fluorescein angiogram findings in a patient (case 117) who presented with acute Vogt-Koyanagi-Harada disease without CSF pleocytosis. **(a)** Angiogram of the right eye, arterio-venous phase. Leakage of dye is noted at the optic disc. Moreover, there are multifocal foci of hyperfluorescence with adjacent areas of leakage in the peripapillary region. **(b)** Angiogram of the right eye, late venous phase. Persistent leakage of dye is noted at the optic disk. There is evidence of early filling of a serous retinal detachment along the supero-temporal arcade

including lymphocytic pleocytosis, on CSF evaluation. This is very similar to the percentage obtained by Kitamura et al. in their recent publication [6].

Several different inflammatory and infectious conditions present with neurologic manifestations and CSF pleocytosis (Table 3) [8, 9]. Lyme borreliosis, for instance, can affect the neurologic system and can be found to cause a predominantly lymphocytic pleocytosis, similar to that seen in VKH disease [10]. Patients diagnosed with Lyme disease also present with uveitis although

Table 3 Differential diagnosis for cerebrospinal fluid pleocytosis

| |
|---|
| Viral encephalitis |
| Lupus erythematosus |
| Sarcoidosis |
| Behçet's disease |
| Vogt–Koyanagi–Harada disease (VKH) |
| Acute posterior multifocal placoid pigment epitheliopathy (APMPPE) |
| Syphilis |
| Multiple sclerosis |
| West Nile virus encephalitis |
| Headache with neurologic deficits and cerebrospinal fluid lymphocytosis (HaNDL) |
| Sjögren's syndrome |

the inflammatory changes are often nongranulomatous. Syphilis, another infectious condition, can also present with headache, visual complaints, uveitis, and lymphocytic pleocytosis on CSF evaluation [10], especially after the CNS becomes involved. Neurosarcoidosis, Behçet's disease, and multiple sclerosis also present with a similar picture [11]. This demonstrates that, although abnormalities are frequently found in chronic inflammatory diseases, it is difficult to use the results of CSF analysis as a major criterion for differentiating between VKH and these other conditions. The presence of clinical features suggestive of VKH, as well as the high index of suspicion for those populations commonly found to have VKH disease, should prompt ocular evaluation before the initiation of an invasive diagnostic procedure.

One may argue that symptoms such as meningismus, weakness, or headache warrant a complete neurologic evaluation, complete with CSF analysis for possible infectious or autoimmune encephalopathies. Previous studies have been conducted on macrophages in CSF and the immunological components of CSF in VKH patients when compared to peripheral blood and to other viral and bacterial infections of the central nervous system [12, 13]. Nakamura et al. note that the cells obtained in their CSF samples exhibit pleocytosis composed predominantly of lymphocytes; however, the use of silver impregnation and immunocytochemical studies identifies melanin-laden macrophages distinctly seen in VKH [12]. Although such investigation appears to be promising, the

number of clinical cases is limited, and there is currently a lack of retrospective or prospective data to support such findings.

Lumbar puncture is a relatively safe procedure. However, it is important to realize that the procedure is not without associated risk, including but not limited to post-dural puncture headache [14–17]. More-serious complications include infection, injury to the spinal cord, uncal and cerebellar tonsil herniation, intracranial or intrathecal bleeding, and seizures. Although most of these complications are uncommon, judicious use of this invasive diagnostic modality should be exercised [17].

In light of these issues, most cases of VKH can be diagnosed without performing the lumbar puncture to obtain CSF for laboratory testing. Analysis shows that the majority of patients included in this case series presented with clinical features suggestive of VKH. Eight of 10 patients presented with neurologic symptoms, as well as uveitis. Every patient presenting acutely in this series underwent fluorescein angiography, and echography was performed if the quality of the fluorescein angiography was compromised by a lack of media clarity. The fluorescein angiogram revealed characteristic dye leakage of dye at the retinal pigment epithelium level, as well as at the optic disc. For those patients who did not undergo fluorescein angiography (patients 34, 55, and 82), signs of chronic VKH disease were present and aided in diagnosis. These signs include sunset glow fundus and peripheral nummular chorioretinal scars.

One minimally invasive diagnostic modality that is often overlooked is standardized A-scan and contact B-scan echography. The characteristic findings of a thickened choroid with low to medium reflectivity are almost pathognomonic for VKH and sympathetic ophthalmia. The echographic findings, in addition to the clinical scenario, can also be a very useful aid in diagnosis. Specifically, these include the presence of: (1) diffuse, low- to medium-reflective thickening of the choroid posteriorly; (2) serous retinal detachment, located inferiorly or in the posterior pole; (3) mild vitreous opacities with no posterior vitreous detachment; and (4) thickening of the sclera and/or episclera posteriorly. Of note, it is

important to differentiate between other entities that mimic VKH disease clinically, as well as on fluorescein angiography and contact B-scan echography [18].

In reviewing the 118 charts, we found 48 patients who presented with features suggestive of early VKH disease but did not undergo lumbar puncture. In the absence of CSF findings, the diagnosis of VKH was considered on the basis of fundus changes, fluorescein angiography, and in select cases, ultrasonography. Three patients did not undergo fluorescein angiography as they presented in the chronic stage of the disease, with findings of peripheral nummular scarring and sunset glow fundus. These results indicate that the diagnosis of VKH can be made with certainty without CSF analysis, particularly in the presence of fluorescein angiographic findings.

The diagnosis of VKH is often difficult to make in the acute stage, in large part because of the lack of extraocular manifestations at the onset of disease. However, fluorescein angiography at this stage appears to be a sensitive test for diagnosis of VKH. The authors suggest that for those cases that occur in more common populations and present with characteristic clinical features and fluorescein/echography findings, lumbar puncture is unnecessary for diagnosis, and therefore, its use can be reserved for those cases that present in atypical fashion or in regions where VKH may be uncommon. Even in these regions, fluorescein angiography and ophthalmic examination will be highly useful in establishing the diagnosis of VKH.

Acknowledgements This work was supported in part by a grant from Research to Prevent Blindness, Inc., New York, NY.

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