Diagnosis of CNS Histoplasmosis by Cerebrospinal Fluid EIA Antibody Detection

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BACKGROUND

Central Nervous System (CNS) histoplasmosis represents a diagnostic and therapeutic challenge. Cerebrospinal fluid (CSF) culture is the gold standard, but is insensitive and slow, resulting in potentially life-threatening treatment delay.

We performed a nested case-control study to evaluate the use of CSF enzyme immunoassay (EIA) antibody (Ab) testing to expedite and improve the diagnosis of CNS histoplasmosis

METHODS

Subjects were patients with CSF samples submitted to MiraVista Diagnostics for histoplasma antigen testing as part of clinical care. Categorization as a case of CNS histoplasmosis was determined by chart review. Data abstracted included epidemiologic, clinical, radiographic and laboratory characteristics.

Cases:
- CSF WBC≥5mm³/ml PLUS
- Laboratory confirmation of *H. capsulatum* in CSF samples OR
- Laboratory confirmation of *H. capsulatum* from extra-CNS sites with no alternative etiology for CSF pleocytosis

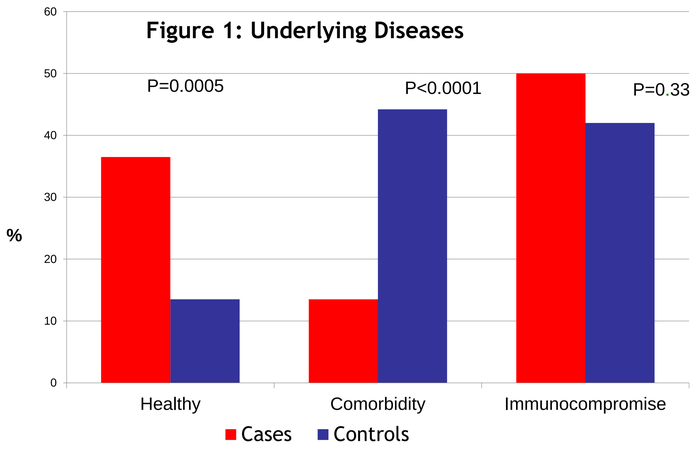
Controls:
- Alternative diagnosis
- Extra-CNS histoplasmosis with no neurologic involvement

Histoplasmosis EIA IgG and IgM antibody testing was performed on CSF as previously described. CSF samples were diluted to 1:25. Results of ≥10 units were considered positive.

RESULTS

A total of 208 patients met eligibility criteria, with 51 (25%) having evidence of CNS histoplasmosis. Among the 157 controls, 25 (16%) had an alternative fungal infection. There was no significant difference between cases and controls with respect to age (median 43.5 vs 49.0 years, p=0.12) or gender (57.7% vs 58.3% male, p=0.92). CNS histoplasmosis cases were more likely to have no underlying medical conditions (Figure 1).

Figure 1: Underlying Diseases

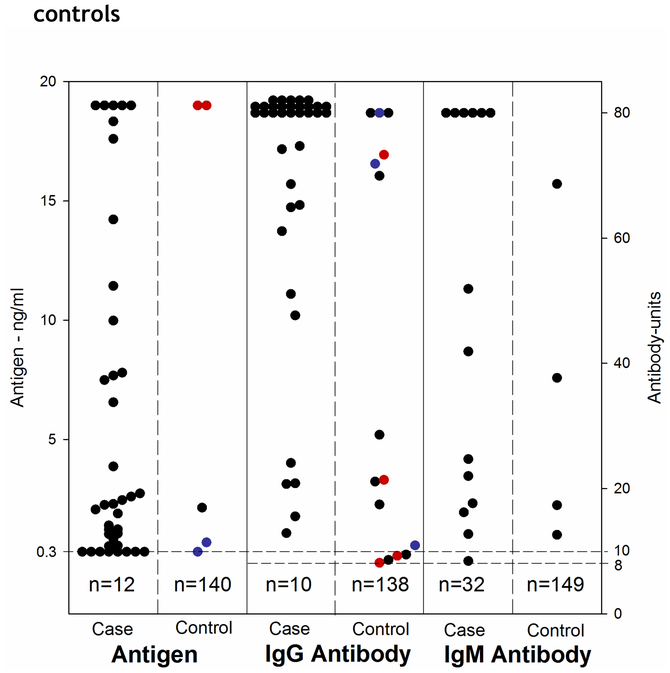


Results of CSF testing for *H. capsulatum* are listed in Table 1 and Figure 2.

Table 1: *Histoplasma* CSF Testing Results

Test Type	Cases (n = 51)	Controls (n = 157)	p-value
CSF culture growing *H. capsulatum*	9/51 (17.6%)	0/119 (0%)	<0.0001
Histoplasma antigen (AG)	39/51 (76.5%)	5/134 (3.7%)	<0.0001
Histoplasma EIA Ab CSF (IgM or IgG)	37/46 (80.4%)	11/153 (7.2%)	<0.0001
EIA IgM Ab	13/46 (28.3%)	4/153 (2.6%)	<0.0001
EIA IgG Ab	37/46 (78.7%)	11/153 (7.2%)	<0.0001
Histoplasma ID or CF Ab CSF	19/45 (42.2%)	0/22 (0%)	0.0003
Beta d-glucan (BDG)	26/45 (57.8%)	20/153 (13.1%)	<0.0001

Figure 2. CSF levels of Antigen (panel 1&2), EIA IgG Ab (panel 3&4) and EIA IgM Ab (panel 5&6) for cases and controls



Red circles represent control patients with other CNS fungal infections. Blue circles represent control patients with extra-CNS histoplasmosis.

Table 2: Frequency of False Positive *Histoplasma* CSF Test Result by Population

	Non-CNS Histoplasmosis N=12	Other Fungal Infection N=13	No Fungal Diagnosis N=132
EIA IgG	4 (33%)	3 (23%)	5 (4%)
EIA IgM	2 (17%)	1 (8%)	3 (2%)
Ag	1 (8%)	2 (15%)	1 (0.8%)
Any positive CSF test	5 (42%)	4 (31%)	7 (5%)

Other fungal infections included *Aspergillus* meningitis (0/2 positive), CNS blastomycosis (2/3 positive), candidiasis (1/2 positive), coccidioidomycosis (0/1 positive) and cryptococcal meningitis (1/5 positive).

Non-fungal diagnoses with false positive test results included melanoma, TB meningitis, bacterial meningitis (n=2), medication reaction, neurosarcoid, and migraine.

Performance characteristics are provided in Table 3.

Table 3. Sensitivity and Specificity of Selected *Histoplasma* Testing on CSF

CSF test	Sensitivity	Specificity
Histoplasma EIA (IgM or IgG)	80.4%	92.8%
Histoplasma Ag (CSF)	76.5%	96.6%
Histoplasma EIA and Ag testing	94.1%	90.8%
Beta-d-glucan	57.8%	86.9%

CONCLUSIONS

- Detection of anti-*Histoplasma* antibodies in CSF using an EIA assay was the single most sensitive diagnostic test for CNS histoplasmosis.
- Combination testing of CSF with *Histoplasma* antigen and EIA antibody had a sensitivity of 94.1%, and a specificity of 90.8% for the diagnosis of CNS histoplasmosis.
- The *Histoplasma* antibody EIA test is a potentially powerful adjunct test in the diagnosis of CNS histoplasmosis.

REFERENCES

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