Lymphocytic hypophysitis: non-invasive diagnosis and treatment by high dose methylprednisolone pulse therapy?

Rudolf A Kristof, Dirk Van Roost, Dietrich Klingmüller, Wolfram Springer, Johannes Schramm

Abstract
Criteria for the non-invasive diagnosis of lymphocytic hypophysitis (LyHy) and the results of the first prospective trial of high dose methylprednisolone pulse therapy (HDMPT) in nine patients are presented. In three patients, the diagnosis was established histologically, and in the others by clinical and endocrinological assessment, MRI, CSF examination, and measurement of thyroglobulin autoantibody concentration. After HDMPT, adenopituitary function improved in four in the nine patients and diabetes insipidus ceased or improved in all four concerned patients. The MRI findings improved in seven patients. LyHy has to be considered in the differential diagnosis of sellar lesions. The presumptive non-invasive diagnosis of LyHy seems possible in a high proportion of patients. HDMPT may result in the improvement of clinical, endocrinological, and MRI findings.

Keywords: lymphocytic hypophysitis; high dose methylprednisolone pulse therapy

Lymphocytic hypophysitis (LyHy) is a rare chronic inflammatory disease with little known natural history, usually diagnosed unexpectedly at surgery for presumptive pituitary adenoma. Experience in the treatment of LyHy is scarce. Non-invasive diagnostic criteria and results of standardised HDMPT are presented.

Patients and methods
All patients with LyHy (mean age 41 years, seven women) diagnosed at our institution are reported on. Adenohypophysal function was dynamically assessed as described by Thorner et al. Neurohypophysal function was assessed as described by Reeves and Andreoli. Evaluation of the sellar region by MRI was carried out as described by Elster. In six patients not operated on, CSF was evaluated by white cell count, cytology, global protein content, and neurotropic virus serology (herpes simplex, varicella zoster, mumps). The thyroglobulin autoantibody concentration was measured in four patients. In three patients, LyHy was diagnosed histologically. In the others, differential diagnosis was considered for tuberculosis, sarcoidosis, and syphilis by clinical, laboratory (tuberculosis test, angiotensin I converting enzyme measurement, treponema pallidum haemaglutination test), and chest radiography evaluation.

The high dose short lasting methylprednisolone administration aimed at minimising the side effects of chronic corticosteroid therapy and at differentiating therapeutic effects from longterm natural course of LyHy. HDMPT consisted of 120 mg methylprednisolone daily for 2 weeks, followed by a dose reduction to 80, 60, 40, and 20 mg daily for 1 week each. Each patient received one course of HDMPT.

Results were assessed by endocrinology and MRI as presented above, at 3, 6, and 12 month intervals thereafter. The average follow up amounted to 29 (19–38) months.

Literature research was done using the Medline program and the key word hypophysitis.

Results
The patient’s details and courses of disease are listed in the table.

Two of the three patients operated on were only biopsied because the intraoperative findings were inconsistent with an adenoma. The third was mimicking an adenoma and was completely resected. LyHy represented 1.1% of all sellar pathologies sampled by a transsphenoidal approach.

Disease onset was sudden in five (four diabetes insipidus, one local mass effect) and insidious in four (adenopituitary impairment) patients.

The amount of daily urinary excretion in the patients with diabetes insipidus varied between 6 and 12 litres. All patients presented with adenopituitary impairment.

Evaluation of CSF in six patients disclosed a raised cell count of 72 (SD 64) cells/mm³. The global protein content of CSF (47 (SD 18) mg/dl), cytology (lymphomonomocytic cells), and neurotropic virus serology were normal.
Findings and courses of nine patients with lymphocytic hypophysitis treated by high dose methylprednisolone pulse therapy

<table>
<thead>
<tr>
<th>Case</th>
<th>Age, sex</th>
<th>Clinical presentation</th>
<th>Laboratory findings</th>
<th>MRI</th>
<th>Biopsy</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>44 y, F</td>
<td>Sudden onset of diabetes insipidus (DI) 1 month previously</td>
<td>Impaired pituitary functions: S, DI, CSF: 78 lympho-monocytic cells/mm², 28 mg/dl global protein content; virus serology negative.</td>
<td>Global symmetric enlargement of anterior pituitary lobe with suprasellar extension, ring-like enhancement of pituitary. Thickened and markedly enhancing pituitary stalk.</td>
<td>Not done</td>
<td>36 months. Normalisation of G and improvement of T impairement, C and L impairement unchanged.</td>
</tr>
<tr>
<td>5</td>
<td>40 y, F</td>
<td>Progressive hypopituitarism over 6 months</td>
<td>Impaired pituitary functions: C, T, G, L, CSF: 48 lymphomonocytic cells/mm², 38 mg/dl global protein content; virus serology negative.</td>
<td>Sellar content of normal extent, posterior lobe not delineable. Homogeneous marked contrast enhancement of the sellar content.</td>
<td>Not done</td>
<td>Shrinkage of sellar content 27 months. Normalisation of C function. Improvement of DI and S impairment. Shrinkage of the thickened pituitary stalk</td>
</tr>
<tr>
<td>6</td>
<td>42 y, F</td>
<td>Sudden onset of DI 1.5 years previously</td>
<td>Impaired pituitary functions: C, S, DI, CSF: 50 lymphomonocytic cells/mm², 31 mg/dl global protein content; virus serology negative.</td>
<td>Thyroglobulin autoantibody concentration not risen.</td>
<td>Thyroglobulin autoantibody concentration not risen.</td>
<td>Slight shrinkage of sellar content with prominence of the posterior lobe. Marked and homogeneous contrast enhancement of the sellar content. Pituitary stalk of normal appearance.</td>
</tr>
<tr>
<td>7</td>
<td>30 y, M</td>
<td>Sudden onset of DI 2 months previously</td>
<td>Impaired pituitary functions: C, DI, CSF: 33 lymphomonocytic cells/mm², 54 mg/dl global protein content; virus serology negative. Thyroglobulin autoantibody concentration not risen.</td>
<td>Slight symmetric enlargement of sellar content with prominence of the posterior lobe. Marked and homogeneous contrast enhancement of the sellar content. Pituitary stalk of normal appearance.</td>
<td>Not done</td>
<td>19 months. DI ceased, G normalised, S improved, persistent impairment of C function. Shrinkage of pituitary stalk.</td>
</tr>
<tr>
<td>9</td>
<td>62 y, F</td>
<td>Progredient decrease of performance over 1.5 years</td>
<td>Impaired pituitary functions: S, CSF: 45 lympho-monocytic cells/mm², 75 mg/dl global protein content; virus serology negative. Thyroglobulin autoantibody concentration markedly risen (1935.6 U/ml).</td>
<td>Global symmetric enlargement of the anterior pituitary lobe with suprasellar extension and marked homogeneous contrast enhancement.</td>
<td>Not done</td>
<td>19 months. Persistent impairment of S function. Thyroglobulin autoantibody concentration normalised (&lt;40 U/ml). Slight shrinkage of sellar content and of pituitary stalk.</td>
</tr>
</tbody>
</table>

C= Corticotroph; T= thyreotroph; G= gonadotroph; S= somatotroph; L= lactotroph.

On plain T1 weighted MRI, the sellar content was slightly to moderately and roughly symmetrically enlarged with suprasellar expansion in seven patients. The posterior lobe was not discernible in two patients. On postcontrast T1 weighted images, the sellar content enhanced strongly and homogeneously in eight patients, and showed a hypointense area in one case. The pituitary stalk was thickened and strongly enhancing in five patients. The presence of a thickened pituitary stalk and the occurrence of diabetes insipidus were not invariably linked.

HDMPT was well tolerated by all patients (a transient rash and an oral mycosis occurred once each). Diabetes insipidus resolved in three patients and improved to the degree of a lesser need of desmopressin in one. In patient 3, diabetes insipidus developed after surgery and was not influenced by HDMPT. Adenopituitary function improved in four out of nine patients and remained unchanged in the others (including patient 3). Hormone replacement could be reduced or stopped in four of seven patients.

Shrinkage of the sellar mass or pituitary stalk was seen on MRI in seven patients (patient 3 not assessable), varying from a slight degree of shrinkage to nearly an empty sella (figure).

Discussion
The histological characteristics of LyHy are well established. Its aetiology is unclear, with some evidence for an autoimmuneological, possibly virus induced origin. 11

DIAGNOSIS
Up to 1990 43, and up to 1995 72 additional patients were reported on (authors' review). Probably due to a higher awareness, modern
endocrinology, and neuroimaging, LyHy is diagnosed with increasing frequency, and there is an apparent change in its presentation. The preponderance of females (98%-79%), often with a peripartum onset (62%-47%) and the sudden onset of diabetes insipidus (“exceptional”-31%) are clinical hallmarks of LyHy. However, the present series suggests that the involvement of the neuropituitary on MRI and diabetes insipidus are not invariably linked. Other manifestations such as headache, chiasm compression, and diplopia (44%, 26%, and 6% respectively) lack specificity.

The adenopituitary impairment was disproportionate to the often small extent of the pituitary mass on MRI in the present series. The impairment (77%-47%) seems to develop earlier in LyHy and more often concerns corticotrophic and thyrotrophic functions (56% and 40%) than in pituitary adenoma, in which the somatotrophic and gonadotrophic functions are usually the first to be impaired.16 20

The association with other autoimmune diseases in 30% of the patients, usually a thyroiditis, may be a diagnostic hint for LyHy. White cell count in the CSF showed a significantly ($\alpha=0.05$) higher lymphomonocytic pleocytosis in LyHy (72 (SD 64) cells/mm$^3$), compared with seven patients with
Lymphocytic hypophysitis

histologically confirmed pituitary adenoma (14
(SD 11) cells/mm³). Together with the absence
of antiviral antibodies and of clinical meningitis,
this slight pleocytosis in LyHy is likely to be
an aseptic meningeal reaction to pituitary
inflammation.

The symmetric enlargement of sellar content
(66%) seen on MRI with thickening of the
pituitary stalk (56%), both homogeneously
enhancing, were confirmed in 51 patients
reviewed from the literature (published 1991 to
1997) in 51% of the patients. Asymmetry of the
enlarged sellar content (18%), signal altera-
tions on native T1 weighted (9%) or inho-
mogeneous contrast enhancement (12%), cavern-
ous sinus and hypothalamic involvement
(12%), empty sella (9%), and no pathological
findings (9%) have also been described.

Although no single above feature is pathog-
nomonic of LyHy, their simultaneous presence
will confer a higher amount of diagnostic
reliability. However, some uncertainty will
always persist without histological confirma-
tion of the diagnosis.

Differential diagnosis against common sellar
tumours, such as pituitary adenomas, crani-
opharyngiomas, and meningiomas, will focus
on the frequent peripartal occurrence, the
marked adenopituitary impairment, and fre-
quent presence of diabetes insipidus, the pre-

cence of other autoimmunological diseases, and
on the common MRI appearance of LyHy.

Differential diagnosis to common sellar infla-

mations, such as tuberculosis, sarcoido-

sis, and syphilis, will focus on medical history
(usually chronic and previously known dis-
eses), laboratory findings (tuberculin test and
antigene polymerase chain reaction in CSF for
tuberculosis, angiotensin-I-converting enzyme
in plasma for sarcoidosis, treponema pallidum
hemagglutination test for syphilis), chest radi-
ography (tuberculosis and sarcoidosis), and less
upon MRI. In very rare tumours such as histo-
cytosis X and inflammations such as primary
granulomatous hypophysitis, differential diag-
nosis is virtually impossible to establish except
by histology. It has been suggested that LyHy
and primary granulomatous hypophysitis may
be part of the same disease range.1-7

TREATMENT

LyHy may become worse due to progressive
pituitary insufficiency,4-7 but also may
improve spontaneously.5,12 26 Adequate hormone
replacement therapy is crucial.

Although LyHy is a chronic inflammatory
process, probably of autoimmune aetiology,
anti-inflammatory corticosteroid treatment has
not been systematically used so far. Thirteen
patients in the literature,5 6 8-12 16-18 23-25
nine of them preoperatively, were treated with a mean
daily dose of 27.5 mg methylprednisolone
equivalent (range 13 to 41 mg, not detailed in
three patients) for a mean time of 4.75 months
(range 5 days to 19 months). Lasting improve-
ments (endocrinological and neuroradiologi-
cal) occurred in 15% and transient improve-
ments (also neurological ones) in 62% of the
cases. Relapse of symptoms occurred days to a
few months after discontinuation of cortico-
steroid therapy.

The nine patients of this series were treated
in a standardised manner by HDMPT. Im-
provement of adenopituitary function was
found in 44% of the patients and was more
favourable in cases with short standing disease
(6 months or less). In three patients the
improvements occurred within 6 weeks and in
the fourth within 6 months after HDMPT.

Diabetes insipidus ceased in three and im-
proved in one of four patients during HDMPT.
Normalisation or improvement of MRI find-
ings occurred in 88% of the patients, in seven
within 6 weeks and in the eight within 6
months after HDMPT. Here, the duration of
the disease seemed to be of no importance.

Because of the close temporal relation, endo-
crinological and MRI improvements are most
likely attributed to HDMPT and not to a
favourable natural course of LyHy which even-
tually would be expected to occur over months
or years.1 2 12 16-22 26 Neither a relapse of the dis-
ease, nor further (spontaneous) improvement,
were found in this series.

It remains doubtful whether the results of
HDMPT are definitive because follow up is
relatively short. Nevertheless, they compare
favourably with those reported in the literature
and also with the natural course of the disease,
the most probable explanation being the
regimen of drug application used in this series.

On the other hand, complete recovery of the
pituitary was achieved in none of our patients.
This might be due to a suboptimal regimen of
drug application, but also to an already
irreversible destruction of the pituitary by
LyHy.11

Whereas surgery for mass effect in LyHy
invariably led to rapid relief of neurological
symptoms, endocrinological improvement was
seldom reported.5 In some patients, however,
surgery led to worsening of pituitary function
or was followed by recurrence of symptoms
(patient 3).5 12 17 26 Usually the intraoperative
findings differ from those of a pituitary
adenoma. Quick frozen sections will help to
clarify any doubts. In some patients, inflamma-
tion may intraoperatively mimic a pituitary
adenoma (patient 3).15 21 To avoid potential
worsening of the pituitary function, surgery
should be kept limited when LyHy is suspected
intraoperatively and HDMPT should be con-
sidered.

In view of recent experience, the presumpt-
ive diagnosis of LyHy may be established by
conservative evaluation in a high proportion of
patients. The presented results suggest a trial of
HDMPT under close monitoring of endo-
crinological, neuro-ophthalmological, and
MRI findings. Follow up has to be at short
intervals to identify a possible relapse in time.
Indications for surgery are the presence of
gross chiasm compression, ineffectiveness of
corticosteroid therapy, and the impossibility
of establishing the diagnosis of LyHy with suf-
cient certainty by conservative evaluation.