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A multidisciplinary approach to early detect Neurodegenerative Langerhans Cell Histiocytosis and monitor response to intravenous immunoglobulin treatment

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ND-LCH

- Rare, challenging and enigmatic permanent consequence of LCH.
- Patients may undergo progressive deterioration, refractory to LCH-directed therapies used in the past.
- **Unresolved questions**:
  - natural history
  - standardized diagnostic approach
  - effective therapy

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ORIGINAL ARTICLE

Follow-up of pediatric patients treated by IVIG for Langerhans cell histiocytosis (LCH)-related neurodegenerative CNS disease

Shinsaku Imashuku · Naoto Fujita · Yoko Shioda · Haruyoshi Noma · Shiro Seto · Toshinori Minato · Kazuo Sakashita · Nobuhiro Ito · Ryoji Kobayashi · Akira Morimoto · Japan LCH Study Group (JLSG)

- 8 patients followed-up for a median time of 11.6 years
- IVIG appeared to be most beneficial when it was administered soon after ND-CNS disease diagnosis when the Expanded Disability Status scores were low.
- The authors proposed that IVIG should be initiated early and continued for >3 years to prevent progression of disease.

PLOS | ONE

RESEARCH ARTICLE

Early Diagnosis and Monitoring of Neurodegenerative Langerhans Cell Histiocytosis

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- Proposal of a novel multidisciplinary protocol of evaluation for patients with LCH, with the main purpose to early identify and monitor patients with ND-LCH

- 27 patients with either ND-LCH verified by MRI or risk factors for ND-LCH (craniofacial bone lesions and/or DI)

- Patients with ND-LCH deserve a targeted structural MRI study for early identification of demyelination.

- SEPs has the highest capability to predict ND-LCH and discriminate its grading.

- SEPs and careful neurological evaluation may represent a valuable, low-cost methodology to monitor patients from pre-symptomatic to symptomatic ND-LCH.

- Wider use of multidisciplinary protocol might allow the selection of patients for early therapeutic intervention.

Sieni E et al. PlosOne 2015

Aim of the present study

To validate our multidisciplinary diagnostic protocol for:

- **yearly following-up ND-LCH patients**
- early selecting **IVIG-treatment candidates**
- **monitoring treatment response**

Methods: study population

- Since 2010, a **prospective diagnostic neuro-radiological study** for patients with/or at risk for ND-**LCH** is ongoing at Meyer Children's Hospital, as national referral centre for LCH.
- As part of the protocol, patients with MRI findings of ND-LCH underwent **yearly neurological, neurophysiological and MRI follow-up**.

- **ND-LCH patients with at least one abnormal neurological or neurophysiological evaluation received monthly IVIG 0.5 g/kg.**

- Treatment response to IVIG was evaluated yearly using our multidisciplinary protocol and compared to a control population.

- The lack of at least one complete follow-up evaluation was an exclusion criterion.

Diagnostic protocol

- Targeted MRI with Spectroscopy
  - Grading: score 1 (mild) to 4 (severe)
- Neurological evaluation:
  - Complete neurological examination
  - Scale for the assessment and rating of ataxia (*SARA)*
  - Barthel scale
- Neurophysiological evaluation:
  - Brainstem auditory evoked potentials (BAEPs)
  - Somatosensory evoked potentials (SEPs)

ND-LCH patients, n=20: Results at first multidisciplinary evaluation

Abnormal findings	N (%)
MRI grading = 1	9 (45)
MRI grading > 1	11 (55)
MRS abnormal	10 (50)
NE abnormal findings	8 (40)
Barthel Index: 100%	6/8
Barthel Index: 50-80 %	2/8
SEPs abnormal	9 (45)
BAEPs abnormal	6 (30)

ND-LCH
Abnormal NE and/or EP as indication to IVIG

13 patients were candidates because of abnormalities at 1° (n=11) or 2° evaluation

7/13 patients consented treatment

Features	Treated IVIG+ N=7	Controls no-IVIG N=6
Gender	4 M, 3 F	4 M, 2 F
Median age at study entry (range)	6.6 y (2.7y - 27.5 y)	4.1 y (15 m - 22.1 y)
Median Follow-Up since ND-LCH dx (range)	4.8 y (13 m - 6 y)	3 y (1.9 y – 5.2 y)
Median time since IVIG indication (range)	1.6 y (16 m – 4.4 y)	2 y (1 y – 5.2 y)
Median age at onset of ND-LCH (range)	5.7 y (2.4 y – 16 y)	4.5 y (1.2 y – 22 y)
Median time interval between onset of LCH -1st MRI ND finding (range)	3 y (6 m - 13 y)	2 y (3 m -14.5 y)
MS vs. SS	4 vs. 3	5 vs. 1
Reactivating or chronic active LCH	5 (71%)	4 (67%)
Risk lesions for ND-LCH: DI/ CFBL	4 / 7	3 / 5
Previous CT/ ongoing	7	6
Active disease	0	1

IVIG-treated patients (n=7)

T1, follow-up results

Median time of IVIG therapy: 1.6 y (16 m – 4.4 y)

PATIENT (#)	MRI findings	MRI grading	MRS	NE (SARA)	SEPs	BAEPs
1	Cerebellum	1-stable	stable	stable	stable	stable
2	Cerebellum sWM brainstem	2-stable	**worsened**	stable	stable	stable
4	Cerebellum sWM	2-stable	stable	**improved**	**improved**	stable
7	Cerebellum sWM, BG Brainstem	4-stable	stable	**worsened**	stable	stable
8	Cerebellum sWM Brainstem	4-stable	stable	stable	**improved**	stable
10	Cerebellum sWM	1-stable	stable	**improved**	stable	stable
15	Cerebellum BG Brainstem	4-stable	stable	**worsened**	stable	stable

IVIG vs not-IVIG *T1, follow-up results*

DIAGNOSTIC TOOL		IVIG +(n=7) N (%)	no-IVIG (n=6) N (%)
Median FUP time (since IVIG indication) (range)		1.6 y (1.3 y – 4.4 y)	2 y (1 y – 5.2 y)
MRI	stable	7 (100)	5 (83)
	worsened	0	**1 (17)**
	improved	0	0
MRS	worsened	1 (14)	2 (33)
NE	stable	3 (44)	3 (50)
	worsened	**2 (28)**	**3 (50)**
	improved	**2 (28)**	0
SEPs	stable	5 (72)	4 (66)
	worsened	0	**2 (33)**
	improved	**2 (28)**	0
BAEPs	stable	7 (100)	4 (66)
	worsened	0	**2 (33)**
	improved	0	0

Conclusions

- At a median time of 1.6 years after IVIG treatment start, the 5/7 patients who were pauci-symptomatic at baseline either improved or remained stable, while the two patients who were severely impaired worsened.

- In the control (untreated) population, at a median time of 2 years since the indication to IVIG, no patient improved, 3/6 worsened.

Conclusions (2)

- ✓ This multidisciplinary protocol **was effective, standardized, low-cost and reproducible as a diagnostic tool for selecting** patients with early-stage ND-LCH, eligible for IVIG treatment (or potentially other treatments)

- ✓ It is suitable for monitoring ND-LCH patients' **response** to IVIG treatment

- ✓ The potential of IVIG to alter the ND-LCH disease course remains to be fully documented with longer FUP and hopefully larger numbers in additional centers.