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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

Elena Sieni[1☯*], Carmen Barba[2☯], Marzia Mortilla[3], Sara Savelli[3,4], Laura Grisotto[5], Gianpiero Di Giacomo[2], Katiuscia Romano[2], Claudio Fonda[3], Annibale Biggeri[5,6], Renzo Guerrini[2], Maurizio Aricò[1,7]

- 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 -1$^{st}$ 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.