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ORIGINAL ARTICLE

FDG-PET assessment and metabolic patterns in Lafora disease

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Abstract

Purpose To describe cerebral glucose metabolism pattern as assessed by ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET) in Lafora disease (LD), a rare, lethal form of progressive myoclonus epilepsy caused by biallelic mutations in *EPM2A* or *NHLRC1*.

Methods We retrospectively included patients with genetically confirmed LD who underwent FDG-PET scan referred to three Italian epilepsy centers. FDG-PET images were evaluated both visually and using SPM12 software. Subgroup analysis was performed on the basis of genetic and clinical features employing SPM. Moreover, we performed a systematic literature review of LD cases that underwent FDG-PET assessment.

Results Eight Italian patients (3M/5F, 3 *EPM2A*/5 *NHLRC1*) underwent FDG-PET examination after a mean of 6 years from disease onset (range 1–12 years). All patients showed bilateral hypometabolic areas, more diffuse and pronounced in advanced disease stages. Most frequently, the hypometabolic regions were the temporal (8/8), parietal (7/8), and frontal lobes (7/8), as well as the thalamus (6/8). In three cases, the FDG-PET repeated after a mean of 17 months (range 7–36 months) showed a metabolic worsening compared with the baseline examination. The SPM subgroup analysis found no significant differences based on genetics, whereas it showed a more significant temporoparietal hypometabolism in patients with visual symptoms compared with those without. In nine additional cases identified from eight publications, FDG-PET showed heterogeneous findings, ranging from diffusely decreased cerebral glucose metabolism to unremarkable examinations in two cases.

Conclusions FDG-PET seems highly sensitive to evaluate LD at any stage and may correlate with disease progression. Areas of decreased glucose metabolism in LD are extensive, often involving multiple cortical and subcortical regions, with thalamus, temporal, frontal, and parietal lobes being the most severely affected. Prospective longitudinal collaborative studies are needed to validate our findings.

Keywords PET/CT · Disease progression · Progressive myoclonus epilepsy · PME · EPM2A · NHLRC1

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Introduction

Lafora disease (LD) is a rare fatal autosomal recessive disorder, belonging to the group of progressive myoclonic epilepsies [1]. LD typically begins with seizures and myoclonus in previously healthy children/adolescents, making it difficult to distinguish from idiopathic generalized epilepsies at early disease stages. Disease course is characterized by progressive cognitive decline, development of disabling myoclonus, and intractable seizures, inexorably leading to death, usually within 10 years from onset. Other associated symptoms may include ataxia, visual manifestations, and behavioral changes. More than one hundred causative mutations involving two genes, *EPM2A* and *NHLRC1*, have been described thus far [2]. Loss of function of either gene products, laforin and malin, respectively, results in structurally abnormal glycogen, which becomes insoluble and accumulates as Lafora bodies (LBs), found in the neurons as well as other tissues (muscle, liver, skin). LD diagnosis can be confirmed by skin biopsy or genetic testing, being the latter the procedure of choice [1, 3, 4]. To date, no specific therapy for LD is available in humans [1]. Structural neuroimaging techniques, such as computed tomography (CT) and magnetic resonance imaging (MRI), are often unremarkable or show variable degrees of cerebral/cerebellar atrophy, possibly related to LD progression and the intrinsic neurodegenerative process. Even MRI volumetry showed no statistically significant differences in patients compared with healthy controls [5]. A few case reports of ^{18}F-FDG positron emission tomography associated with CT (FDG-PET) assessment in LD showed heterogeneous findings [6–13]. Here, we describe the FDG-PET findings in a case series of LD patients and review previously published reports, discussing patterns of altered cerebral glucose metabolism in LD and their relation with clinical and genetic variables.

Materials and methods

Study population

We included patients with genetically confirmed LD referred to three Italian epilepsy centers who underwent FDG-PET scan between April 2014 and January 2019. Anonymized FDG-PET data were centrally collected at the Nuclear Medicine Unit of the University of Bologna, Italy. All individuals underwent a comprehensive clinical assessment, including medical history, physical examination, and instrumental investigations at the time of PET examination. The stage of disease progression was assessed using a disability scale based on the residual motor and mental functions, daily living, and social abilities, ranging from 1 (mild cognitive and motor impairment, preserved daily living activities, and social interaction) to 4 (patient wheelchair-bound or bedridden, and no significant daily living activities or social interaction) [14]. This retrospective analysis was approved by the local ethics committee (reference number: 18076). Written informed consent was obtained from all participants or their legal representatives.

Image acquisition and PET scanning protocol

Patients were scanned in three different Italian Nuclear Medicine Centers (S. Orsola Hospital, Bologna; Fondazione IRCCS Ca′ Granda Ospedale Maggiore Policlinico, Milan; and Ospedali Riuniti, Foggia) with two different dedicated 3D PET/CT systems: a Siemens Biograph PET/CT scanner (Siemens Healthineers) and a GE Discovery STE PET/CT scanner (GE Healthcare). Following the European Guidelines [15], about 200 MBq of ^{18}F-FDG were administered to each patient and acquisition was performed 45–60 min after the radiotracer injection. Images were corrected for scatter and attenuation and reconstructed using a 3D OSEM algorithm (2 iterations and 18–20 subsets). When available, we also collected data on FDG-PET examinations repeated during the follow-up assessment of the included cases.

Visual image interpretation

Anonymized imaging datasets were evaluated independently by two experienced nuclear medicine physicians with at least 3 years of experience in neuroimaging and unaware of clinical history, using an Advantage Workstation 4.6 (GE Healthcare). FDG-PET images were axially reoriented parallel to the anterior commissure-posterior commissure line, according to the method described by Friston et al. [16]. FDG-PET and MRI coregistration was performed to provide anatomical reference. Using a graduated scale ranging from preserved metabolism to severe hypometabolism, the following regions (right and left) were systematically analyzed: frontal, temporal, parietal, and occipital lobes, and thalamus, cerebellum, and basal ganglia. In case of disagreements between readers, the final diagnosis was reached by consensus and by the opinion of a third reader.

SPM image analysis

All patients were individually analyzed using the statistical parametric mapping (SPM12) software (Wellcome Department of Imaging Neuroscience, Institute of Neurology, London) [17]. In addition, a SPM group analysis was performed dividing the patients into 6 groups, namely, *EPM2A* positive, *NHLRC1* positive, patients with visual symptoms, patients without visual symptoms, patients with disease scale progression 1–2, and patients with disease scale progression 3–4. Parametric analysis of FDG uptake in SPM

was obtained using voxel-level statistical parametric mapping at the whole-brain level, in the framework of the general linear model by means of a two-sample *t* test, comparing each subject/group against images pertaining to a reference control group, made of 40 subjects with a mean age of 61 years (range 27–84 years). Increased or decreased metabolism was regarded as statistically significant if the uncorrected *p* value was under 0.001, with a cluster level above 100 voxels.

Literature review

A systematic literature search was performed focusing on the terms "Lafora disease" and "^{18}F-FDG-PET" on the PubMed/MEDLINE database. We reviewed all genetically and/or histopathologically confirmed LD published cases in order to find those who underwent FDG-PET assessment. When available, clinical and genetic features of the subjects, clinical assessment at the time of FDG-PET examination, and MRI and FDG-PET findings were entered in an ad hoc database. The last search was performed on 10 November 2018.

Results

Study population

Eight patients (3M/5F) with genetically confirmed LD (mean age 19 years; range 12–25 years) underwent FDG-PET examination after a mean of 6.6 years from disease onset (range 1–12 years), including both patients at early- and middle-late stages of disease. Clinical and genetic features as well as MRI findings are summarized in Table 1. Patient 7 showed only seizures as disease manifestation, while the other cases also had myoclonus, gait ataxia, and cognitive impairment, ranging from mild to severe in various combinations. Five patients carried pathogenic variants in *EPM2A*. Patients 6 and 7, harboring the same homozygous mutation in *EPM2A* (c.323G>T, p.Arg108Leu), are sisters from non-consanguineous parents. At the time of the first FDG-PET scan, three patients had a LD progression scale ≤ 2. Half of the patients complained of visual hallucinations. All subjects but patient 7, who refused medications, were treated with multiple AEDs. MRI scan results were available for 7/8 patients and included a standard morphological MRI diagnostic protocol inclusive of diffusion-weighted sequence. Abnormal neuroradiological findings were found in 2 patients, and only 1 presented diffuse cerebral atrophy.

Visual analysis and interobserver agreement

All patients showed bilateral hypometabolic areas with a 100% agreement between two readers. Patient 7 had a bilateral and mild reduced metabolism in the lateral temporal lobe, whereas 7/8 patients (88%) showed a diffuse and symmetric cortical and subcortical hypometabolism involving more than 3 different areas (Table 2). Most frequently, hypometabolic areas were respectively the temporal lobe (8/8, 100%), the parietal and frontal lobes (7/8, 88%), and the thalamus (6/8, 75%). Mild cerebellar hypometabolism was observed in two patients who had mild gait ataxia. Overall, region interpretation among two readers had substantial agreement (Cohen' κ 0.63) applying the graduated scale (preserved metabolism; mild, moderate, and severe hypometabolism). Most frequently, disagreement was seen between regions with mild and moderate hypometabolism.

SPM individual analysis

All patients showed at least one hypometabolic area. Patients 4 and 7 had, respectively, right frontal lobe and bilateral temporal lobe hypometabolism, whereas 6/8 patients (75%) showed a bilateral reduced metabolism involving two or more different areas. Frontal and temporal lobes were hypometabolic in 5/8 patients (63%), parietal lobe in 4/8 (50%), and occipital lobe and thalamus in 2/8 (25%). A patient example is given in Fig. 1.

SPM group analysis

The paired *t* test, comparing patients with LD and the reference database, showed a bilateral hypometabolism in the parietal and frontal lobes and within the thalamus. Moreover, a lower diffuse and reduced metabolism in the parietal and frontal lobes and within the thalamus was seen in patients with higher LD progression scale ($p < 0.001$). Conversely, the group of patients with LD progression scale = 1–2 showed no significant differences in cortical activity. In both groups of patients harboring *EPM2A* and *NHLRC1* mutations, paired *t* test found hypometabolism in the thalamus and parietal lobe bilaterally ($p < 0.001$). There was an isolated hypometabolism within the thalamus in the group of patients without visual symptoms ($p < 0.001$), while the group of patients with visual symptoms showed bilateral lower metabolism within the parietal and temporal lobes and within the thalamus ($p < 0.001$) (Fig. 2).

Longitudinal FDG-PET examinations

In three patients (2, 6, and 8), FDG-PET examination has been repeated during disease progression, respectively, after 7, 36, and 8 months. A significant global clinical worsening was seen in patient 6, while the others were clinically stable. In patient 2, FDG-PET showed a mild hypometabolism in the cerebellum, not present in the first examination. Patient 6 had a metabolic progression with moderate to severe hypometabolism in the bilateral frontal, parietal, and temporal lobes, and thalamus, without new areas of hypometabolism

Table 1 Clinical, genetic, and neuroradiological findings at FDG-PET examination

Pt.	Age at onset (years), sex	Genetic findings[a]	Disease duration (y)	Visual symptoms	Myoclonus[b]	Gait ataxia[c]	Intellectual disability[c]	LD progression scale[d]	Antiepileptic drugs	MRI findings
1	16, M	*NHLRC1*: c.436G>A (p.Asp146Asn), c.1133T>C (p.Leu378Pro)	5	Yes	+	Mild	Moderate	2	VPA, LEV, PER, CNZ, CLB	Unremarkable
2	13, F	*EPM2A*: c.243_246del (p.Asp82Argfs*7)	12	Yes	+++	Not evaluable	Severe	3	VPA, LEV, ZNS, PB, CNZ	Non-specific white matter signal abnormalities
3	14, M	*EPM2A*: c.721C>T (p.Arg241*)	6	No	++	Mild	Moderate	3	TPM, LEV	Unremarkable
4	10, M	*EPM2A*: c.721C>T (p.Arg241*)	9	No	++	Severe	Moderate	4	VPA, PB, CNZ	Unremarkable
5	13, F	*NHLRC1*: c.992delG (p.Gly331Glufs*3)	8	No	+++	Severe	Moderate	4	VPA, ZNS, PER, CNZ	Unremarkable
6	11, F	*EPM2A:* c.323G>T (p.Arg108Leu)	8	Yes	+++	Severe	Moderate	3	VPA, PER, PB, CNZ	Diffuse cerebral atrophy
7	11, F	*EPM2A*: c.323G>T (p.Arg108Leu)	1	No	None	None	None	1	None	Not performed
8	10, F	*NHLRC1*: c.205C>G (p.Pro69Ala), c.826_829dup (p.Ala277Aspfs*23)	7	Yes	++	None	Moderate	3	VPA, LEV, ZNS, CNZ	Unremarkable

CLB, clobazam; *CNZ*, clonazepam; *LEV*, levetiracetam; *PB*, phenobarbital; *PER*, perampanel; *PHT*, phenytoin; *TPM*, topiramate; *VPA*, valproate; *ZNS*, zonisamide

[a] When only one variant is indicated, this is intended as homozygous. *EPM2A* RefSeq ID: NM_005670.4; *NHLRC1* RefSeq: NM_198586.2

[b] Myoclonus severity: +, mild myoclonus, i.e., does not interfere with activities of daily living; ++, moderate myoclonus, i.e., interferes with activities of daily living but not with deambulation; +++, severe myoclonus, i.e., interferes with deambulation

[c] Classified as "none," "mild," "moderate," or "severe"

[d] Disability scale developed by Franceschetti et al. [18]: 1, mild cognitive and motor impairment, preserved daily living activities, and social interaction; 2, moderate mental decline, limitations in motor activities, and limited social interaction; 3, severe mental and motor impairment, needing help in walking and regular assistance in daily activity, and poor social interaction; 4, patient wheelchair-bound or bedridden, and no significant daily living activities or social interaction

(Fig. 3). Patient 8 presented a progression from moderate to severe hypometabolism in the bilateral frontal, parietal, and temporal lobes, and the appearance of mild hypometabolism in the occipital lobes, cerebellum, and right thalamus.

Literature review

A total of 9 LD cases who performed FDG-PET at least one-time during the disease course were identified from 8 reports, published from 1995 to 2017 [6–13]. Clinical features and imaging findings are summarized in Table 3. Diagnosis was made by genetic testing in 4/9 patients; however, in one patient atypical for the early age of onset [13], the variants were not specified. MRI scans were available in 7/9 (78%) patients and showed mild enlargement of the subarachnoid spaces in two patients. Two out of 9 (22%) patients had an unremarkable FDG-PET scan and 1/9 (11%) showed focal and unilateral temporal hypermetabolism. Six out of 9 (67%) presented diffuse hypometabolism. Two cases at early stages of disease which showed prominent visual symptoms had occipital posterior localized hypometabolism. SPM analysis is not reported in any study included in the literature review.

Discussion

We described FDG-PET findings in 8 LD patients, analyzed with homogeneous, standardized, and rigorous methods, and reviewed the metabolic features of 9 previously published case reports, providing an exhaustive and updated knowledge base of FDG-PET assessment in LD. In our cohort, all patients disclosed hypometabolic cortical areas, most frequently in the parietal, temporal, and frontal lobes. In addition, severe thalamic hypometabolism was a recurrent finding. MRI investigation disclosed significant cerebral atrophy in only one subject, suggesting that a large number of LD patients have cortical and

Table 2 FDG-PET visual assessment findings

Pt.	Frontal lobes	Parietal lobes	Temporal lobes	Occipital lobes	Basal ganglia	Thalami	Cerebellum
1	+	+++	+++	++	–	+	+
2	+	+++	++	++	–	+	–
3	+	+++	+++	–	–	+++	+
4	++	++	++	–	–	++	–
5	++	+++	++	+	–	+++	–
6	++	++	+++	+	–	+++	–
7	–	–	+	–	–	–	–
8	++	++	++	–	–	–	–

–, preserved metabolism; +, mild hypometabolism; ++, moderate hypometabolism; +++, severe hypometabolism

subcortical abnormalities at the functional level, not detectable by conventional neuroimaging. The findings of the literature review were more inhomogeneous, ranging from diffusely decreased cerebral glucose metabolism to even totally normal results in two subjects [11, 12]. These data have to be considered in the context of methodological limitations, i.e., different acquisition and post-processing techniques among the various case reports, lack of quantitative analysis, absence of longitudinal evaluations, scarce clinical information available.

Several mechanisms might explain the decreased glucose cerebral metabolism in LD. First, it could reflect the destruction of neurons rather than an enzymatic deficit in glucose metabolism, since a reduction in both glucose and oxygen metabolism has been documented [8]. Glucose hypometabolism may also reflect cell damage due to LB accumulation process [7], which in human post-mortem histopathologic studies was found in the dentate nucleus, substantia nigra, thalamus, and the entire cerebral cortex [18–20]. Finally, metabolic defect in LD could be related to the impairment of synaptic function, as documented in other neurodegenerative disorders such as Alzheimer's disease [21, 22].

Moderate-severe bilateral thalamic hypometabolism was present in half of the patients presented in the current study and might be related to the underlying neurodegeneration, as histopathologic examinations have shown a prominent thalamic involvement [18, 23]. However, thalamic metabolic impairment may also be related to the abundant epileptiform activity typical of LD, as already reported in other severe forms of epilepsy [24–28]. Conversely, in juvenile myoclonic epilepsy, a type of idiopathic generalized epilepsy which can mimic progressive myoclonic epilepsies at early disease stages, FDG-PET has shown increased glucose metabolism in bilateral thalami [29].

We did not find a clear relation between cerebellar glucose hypometabolism and ataxia, as our cohort included both patients with severe ataxia and normal cerebellar metabolism and, vice

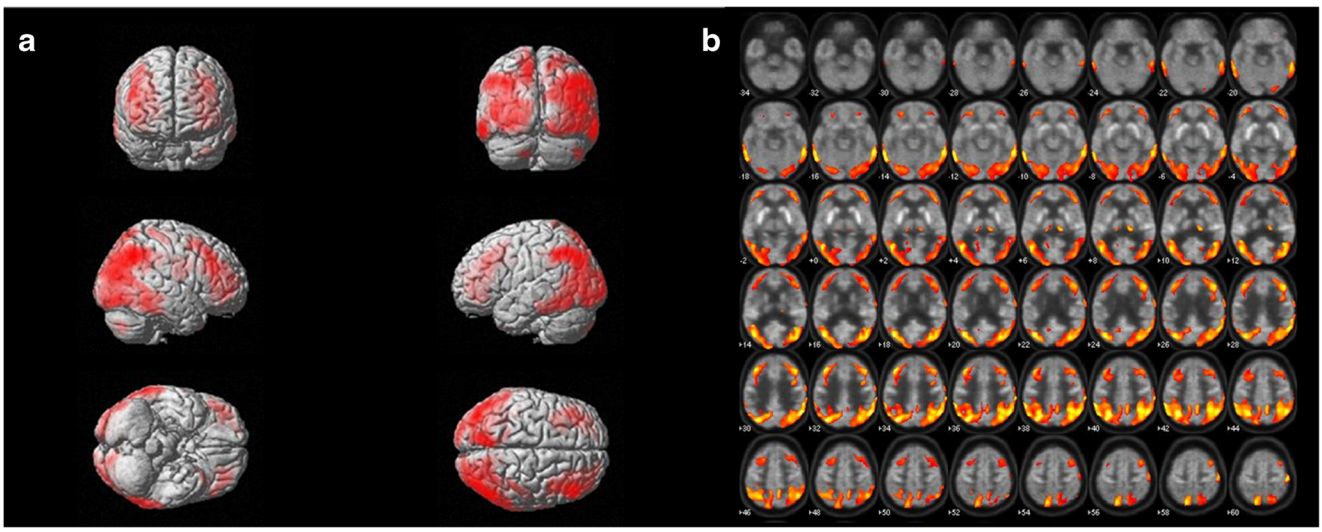

Fig. 1 SPM patient analysis. Patient 1: a 21-year-old male patient with slow disease progression, who had myoclonus limited to the eyelids, mild ataxia and dysmetria, moderate cognitive impairment, and visual hallucinations elicited by eye closure. Brain FDG-PET showed severe bilateral hypometabolism in the parietal and temporal lobes and a mild to moderate bilateral hypometabolism in the occipital and frontal lobes, thalamus, and cerebellum. SPM analysis confirmed the visual assessment result. **a** FDG-PET hypometabolism SPM-t-map on 3D MRI rendering. **b** FDG-PET hypometabolism SPM-t-map on axial view

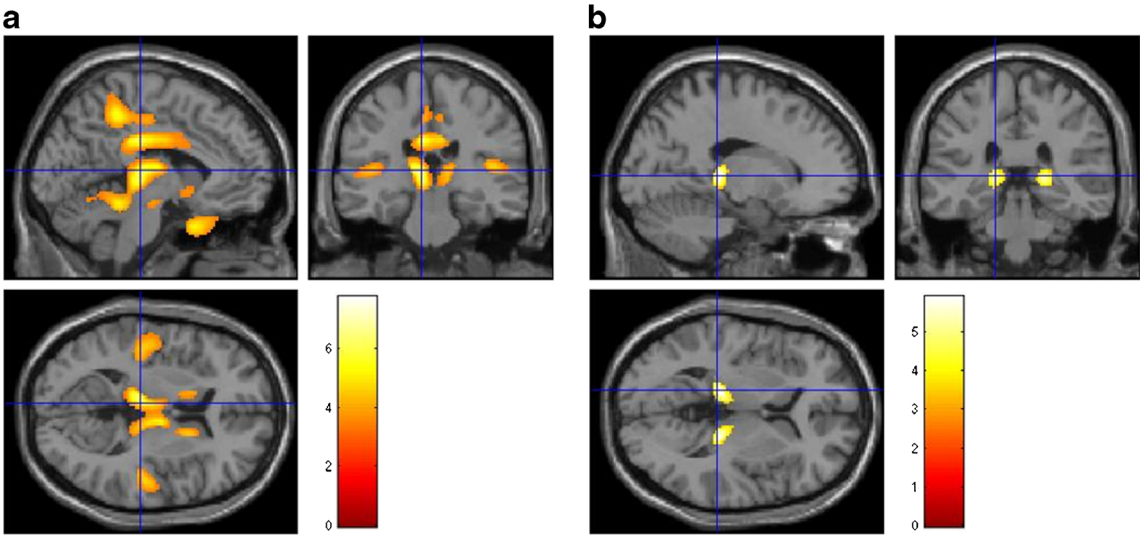

Fig. 2 SPM results in patients with and without visual symptoms. SPM paired *t* test comparing patients with visual symptoms and reference database (**a**) showed lower bilateral metabolism in the parietal and temporal lobes and within the thalamus, as well as the cingulate gyrus and the cerebellum ($p < 0.001$). The group of patients without visual symptoms (**b**) showed hypometabolism within the thalamus bilaterally ($p < 0.001$)

versa, individuals with mild ataxia and cerebellar hypometabolism in the context of a diffuse hypometabolic pattern. Among literature reports, only one patient with prominent ataxia showed FDG-PET hypometabolism prevalent in the cerebellum [7]. Therefore, cerebellar hypometabolism does not seem a specific or sensitive finding in patients with LD, whereas it could be associated with ataxia only when predominant in comparison with the hypometabolism of other brain regions.

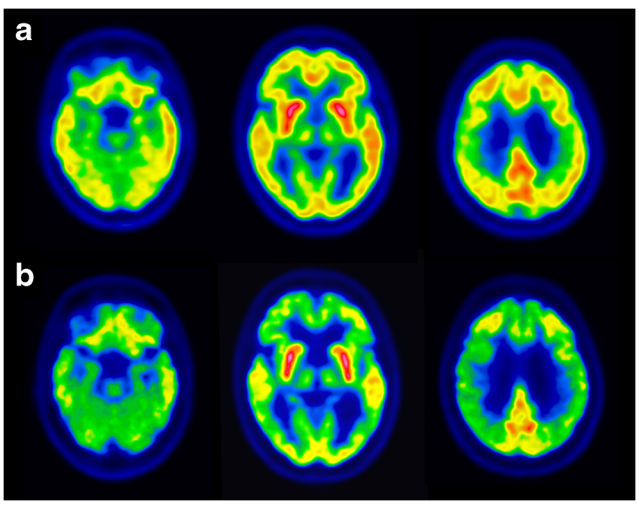

Fig. 3 FDG-PET longitudinal evaluation. Patient 6: This 19-year-old female patient had a significant clinical worsening between the two FDG-PET examinations, from mild cognitive and motor disabilities in (**a**) to end-stage disease in (**b**). **a** Axial FDG-PET images showing mild to moderate bilateral hypometabolism in the mesial temporal, parietal, frontal, and occipital lobes, and a moderate bilateral hypometabolism in the thalamus. **b** Axial FDG-PET images 3 years later showing progression of hypometabolism: moderate to severe bilateral hypometabolism in the temporal, parietal, frontal, and occipital lobes and within the thalamus

In our cohort, we found that frontal lobes were more severely affected than the occipital ones, according to [^{1}H]MR spectroscopy studies [4, 30], confirming the predominant frontal cortical metabolic involvement in LD. This correlates with the ideomotor slowing and severe impairment of executive functions described in these patients [30].

The SPM subgroup analysis in patients with visual symptoms, compared with those without, revealed a more severe hypometabolism in parietal and temporal lobes. Of the four patients who reported visual symptoms in our cohort, only 2 had significant abnormalities in occipital lobe glucose metabolism. Previously, occipital hypometabolism was described in two patients with prominent visual symptoms [6]. Visual manifestations in LD were classically considered to be of epileptic origin, i.e., related to occipital-onset seizures. However, it has been hypothesized that these could coexist with non-epileptic visual manifestations, which may arise as part of the degenerative process underlying the progressive dementia [31], as it happens in other neurodegenerative disorders [32, 33]. The disclosed hypometabolism in temporal and parietal regions in LD patients with visual symptoms might be related to a dysfunction of visual processing areas, i.e., of both the ventral (occipitotemporal) and the dorsal (occipitoparietal) visual pathways, thus causing an impairment in perceptual processes, necessary for hallucinations to occur [32, 33]. Therefore, both occipital and temporoparietal hypometabolic patterns may be associated with visual symptoms in LD, possibly depending on different pathophysiological mechanisms.

In the SPM subgroup analysis, there was no significant difference between patients with *EPM2A* and *NHLRC1* mutations. This is consistent with the fact that both laforin and malin have a crucial role in a single functional complex and

Table 3 Clinical and neuroimaging findings from the literature review

Ref.	Age at onset (years), sex	Diagnostic technique	Age at FDG-PET (y)	Visual symptoms	Myoclonus	Gait ataxia	Intellectual disability	MRI findings	FDG-PET findings
6	Childhood, F	Genetics (*NHLRC1*)	14	Yes	Yes	Yes	Yes	Unremarkable	Bilateral OL hypometabolism
6	11, F	Genetics (*EPM2A*)	13	Yes	Yes	NA	Yes	Unremarkable	Bilateral OL hypometabolism
7	8, M	Histopathology	16	No	Yes	Yes	Yes, severe	Moderate dilatation of the cisterna magna	Diffuse hypometabolism, accentuated in the cerebellum
8	NA, M	Histopathology	18	NA	Yes	NA	Yes	NA	Diffuse hypometabolism
9	16, F	Histopathology	16.75	NA	Yes	No	Yes, severe	Unremarkable	Diffuse hypometabolism
10	16, M	Genetics (*NHLRC1*)	16	Yes	Yes	Yes	Yes	Unremarkable	Slight right temporal hypermetabolism
11	NA, M	Histopathology	NA[a]	Yes	Yes	NA	Yes	Mildly enlarged ventricles	Unremarkable
12	13, M	Histopathology	NA[b]	NA	Yes	NA	NA	Unremarkable	Unremarkable
13	NA, M	Genetics (*EPM2A*)	6	NA	NA	NA	NA	NA	FL, PL, TL hypometabolism

FU, follow-up; *NA*, not available; *FL*, frontal lobe; *OL*, occipital lobe; *PL*, parietal lobe; *TL*, temporal lobe;

[a] In this case, the authors reported that the FDG-PET was performed 4 years after disease onset

[b] This patient deceased at 18 years of age

with the similar clinical progression showed by patients harboring *EPM2A* and *NHLRC1* mutations [1, 34].

Overall, a higher stage of the LD progression scale was positively associated with a more severe and diffuse hypometabolism. The 3 patients in whom the exam was repeated after a mean of 17 months showed a more pronounced hypometabolism compared with the baseline FDG-PET. Interestingly, two patients showed a metabolic worsening after just 7 and 8 months, thus suggesting that FDG-PET findings may be strictly related with disease progression. These preliminary data suggest that FDG-PET might be speculatively useful to evaluate responses to upcoming therapeutic strategies for LD, so far successfully experimented only in animal models. Indeed, the greatest factor preventing clinical trials of LD-targeted therapies to commence is the lack of markers of effectiveness, as no natural history study and no marker of disease progression exist for LD.

Limitations

The main limitations of the present analysis are the retrospective design and the limited number of patients included. These are, however, intrinsically related to the rarity of LD and the consequent difficulty in recruiting patients. Another limitation, common to all FDG-PET studies involving pediatric patients—including a subgroup of our study population—is that data on healthy children and adolescents are scarce, mainly due to ethical reasons. However, in the age groups included in our work, subjects without epilepsy or any other major neurological illness were found to have local cerebral metabolic rates for glucose substantially similar to those of adults [35]. A subsequent report on FDG-PET analyses in children with idiopathic epilepsy showed a relative thalamic hypometabolism in comparison with adults, possibly because corticothalamic connectivity intensifies during development [36]. We acknowledge this methodological limitation; however, it is unlikely that this may significantly influence the disclosed severe thalamic hypometabolism in our cohort of patients. The last point is the possible effect of AEDs on cerebral glucose metabolism, namely a reduction [37, 38]. Carbamazepine and phenytoin are among the drugs for which this was demonstrated, but none of our patients was taking either of these agents at the time of PET examination. Conversely, six out of eight subjects were taking valproate, in association with phenobarbital in one case. Both these drugs have a more pronounced effect on cerebral glucose metabolism [37, 38]. However, it would be unethical and not feasible to perform a study on FDG-PET metabolism in LD avoiding this possible bias, considering that valproate can be considered as the first-line drug in LD medical management [5].

Conclusions

FDG-PET seems highly sensitive to evaluate LD at any stage, consistent with a functional brain defect occurring early in the disease course, and may correlate with disease progression. The areas of decreased glucose metabolism in LD are extensive, often involving multiple cortical and subcortical regions,

with thalamus, parietal, frontal, and temporal regions being the most severely affected. To validate our results and to better relate FDG-PET findings with clinical symptoms and disease progression in LD, prospective longitudinal collaborative studies in larger cohorts of patients are needed.

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Author contributions Francesca Bisulli, Lorenzo Muccioli, Andrea Farolfi, and Federica Pondrelli contributed to the study conception and design. Material preparation, data collection, and analysis were performed by all authors. The first draft of the manuscript was written by Lorenzo Muccioli and Andrea Farolfi. Review and editing was performed by Francesca Bisulli, Paolo Tinuper, Andrea Farolfi, Federica Pondrelli, Laura Licchetta, Rachele Bonfiglioli, Simona Civollani, Cinzia Pettinato, Elisa Maietti and Francesco Toni. All authors read and approved the final manuscript. Study supervision: Francesca Bisulli, Paolo Tinuper, and Stefano Fanti.

Compliance with ethical standards This retrospective analysis was approved by the local ethics committee (reference number: 18076). Written informed consent was obtained from all participants or their legal representatives.

Conflict of interest The authors declare that they have no conflicts of interest.

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