Servizio Sanitario della Toscana

www.regione.toscana.it/sst

Azienda Ospedaliero-Universitaria

Le Mucopolisaccaridosi: la terapia

Maria Alice Donati, Elena Procopio

Sezione di Malattie Metaboliche e Muscolari Ereditarie

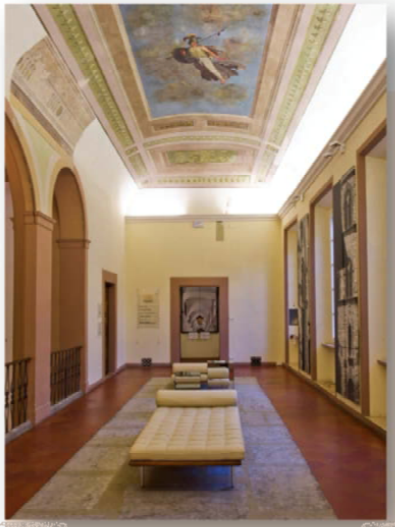
Azienda Ospedaliera Universitaria A. Meyer Firenze

XVII Corso residenziale

REGISTRO TOSCANO DIFETTI CONGENITI

Malformazioni Congenite dalla Diagnosi Prenatale alla Terapia Postnatale

Le Mucopolisaccaridosi
La Trisomia 21



18-19 ottobre 2018

Palazzo delle Professioni
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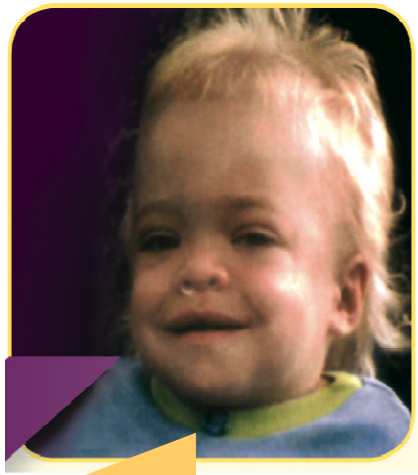


GRAVE INTERMEDIO LIEVE

HURLER
MPS I H

HURLER-SCHEIE
MPS I H/S

SCHEIE
MPS I S

Attività enzimatica

0% 10% 100%

Infantile Juvenile Adult

Severità del difetto

JIMD Reports
DOI 10.1007/8904_2011_90

CASE REPORT

Report of a Large Brazilian Family With a Very Attenuated Form of Hunter Syndrome (MPS II)

C.R.D.C. Quaio · H. Grinberg · M.L.C. Vieira · A.C. Paula · G.N. Leal · I. Gomy · S. Leistner-Segal · R. Giugliani · D.R. Bertola · C.A. Kim

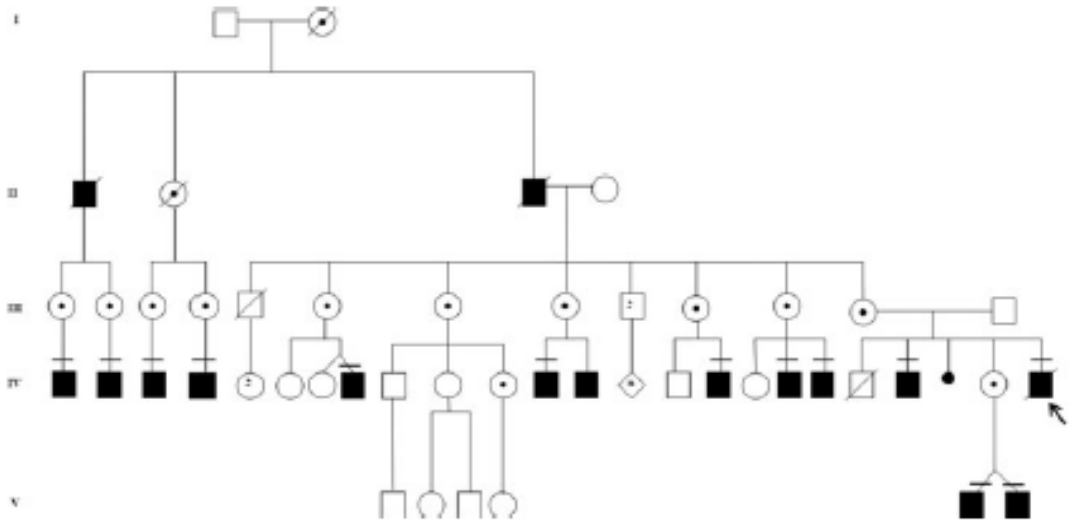


Fig. 1 Family pedigree

Fig. 2 Affected relatives: (**a**) proband; (**b**) proband's brother; (**c**) proband's cousin; (**d**) proband's twin nephews

Terapia e LSD: criticità

- **Malattie rare**
  - Paz. a diversi stadi di malattie
  - Malattie eterogenee, con progressione paziente-specifica
  - Fenotipi severi, moderati e mild
  - Sintomi e segni secondari potenzialmente irreversibili
  - In trial a breve termine possiamo non vedere gli effetti benefici

- **Popolazioni piccole**

più di 120 pubblicazioni nel 2016 sull'outcome terapeutico nell'uomo e nei modelli animali

- **Storia naturale della malattie**
  - La raccolta di dati retrospettivi è difficile
  - Difficile identificare gli endpoint clinici

MPS e terapia

- La maggior parte delle terapie non sono curative ma modificano l'espressione fenotipica della malattia

- L'efficacia varia tra le diverse malattie ma anche tra sottogruppi di paz.

- La eterogeneità fenotipica complica la predizione dei benefici della terapia, soprattutto in paz. con forme mild.

MPS IERI: IL TRATTAMENTO

Trattamento sintomatico

terapia di supporto

☞ trattamento delle complicanze

☞ migliorare la qualità di vita

- Antiepilettici
- Adenotonsillectomia
- Stabilizzazione cervico-occipitale
- Trapianto di cornea
- Fisioterapia
- Protesi acustiche
- cPAP, Bi PAP
- Farmaci cardiologici
- PEG
- …..

MPS I: Trapianto di midollo osseo per i pazienti più gravi con particolari caratteristiche (< 2 anni e Q.I. > 70)

TRATTAMENTO SINTOMATICO (ieri)

FARMACI

NSAIDs (dolore articolare)

ANTIBIOTICI (infezioni respiratorie)

N-CPAP, OSSIGENOTERAPIA (OSAS, IR)

INTERVENTI

RIPARAZIONE ERNIE OMBELICALI

ADENO-TONSILLECTOMIA

OSTEOTOMIE FEMORALI

CHIRURGIA CORRETTIVA DELLE FORME SEVERE DI GINOCCHIO VALGO

FUSIONE DEL RACHIDE CERVICALE/DECOMPRESSIONE

SOSTITUZIONE VALVOLARE.

…….

LSD (Malattie d'accumulo lisosomiale) e terapia oggi

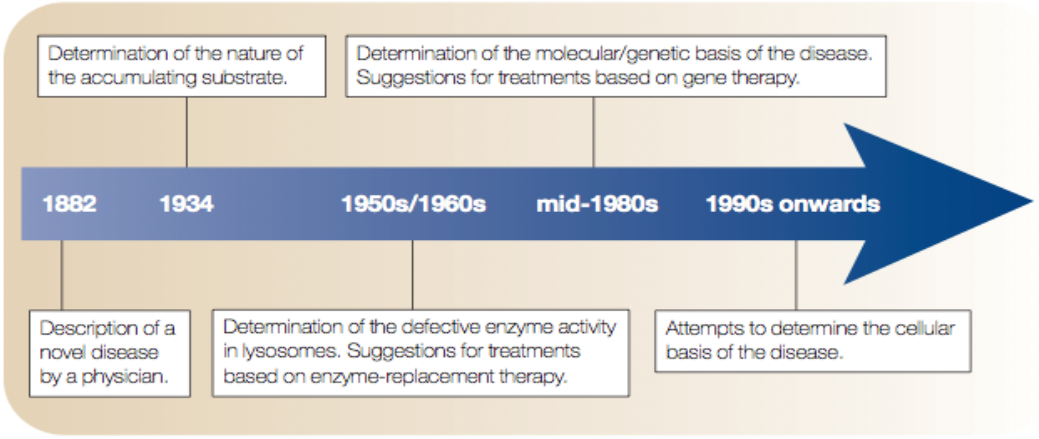
Terapia di supporto multidisciplinare nelle passate due decadi fino a circa 20 anni fa

Le conoscenze della biologia ha portato a terapie specifiche:

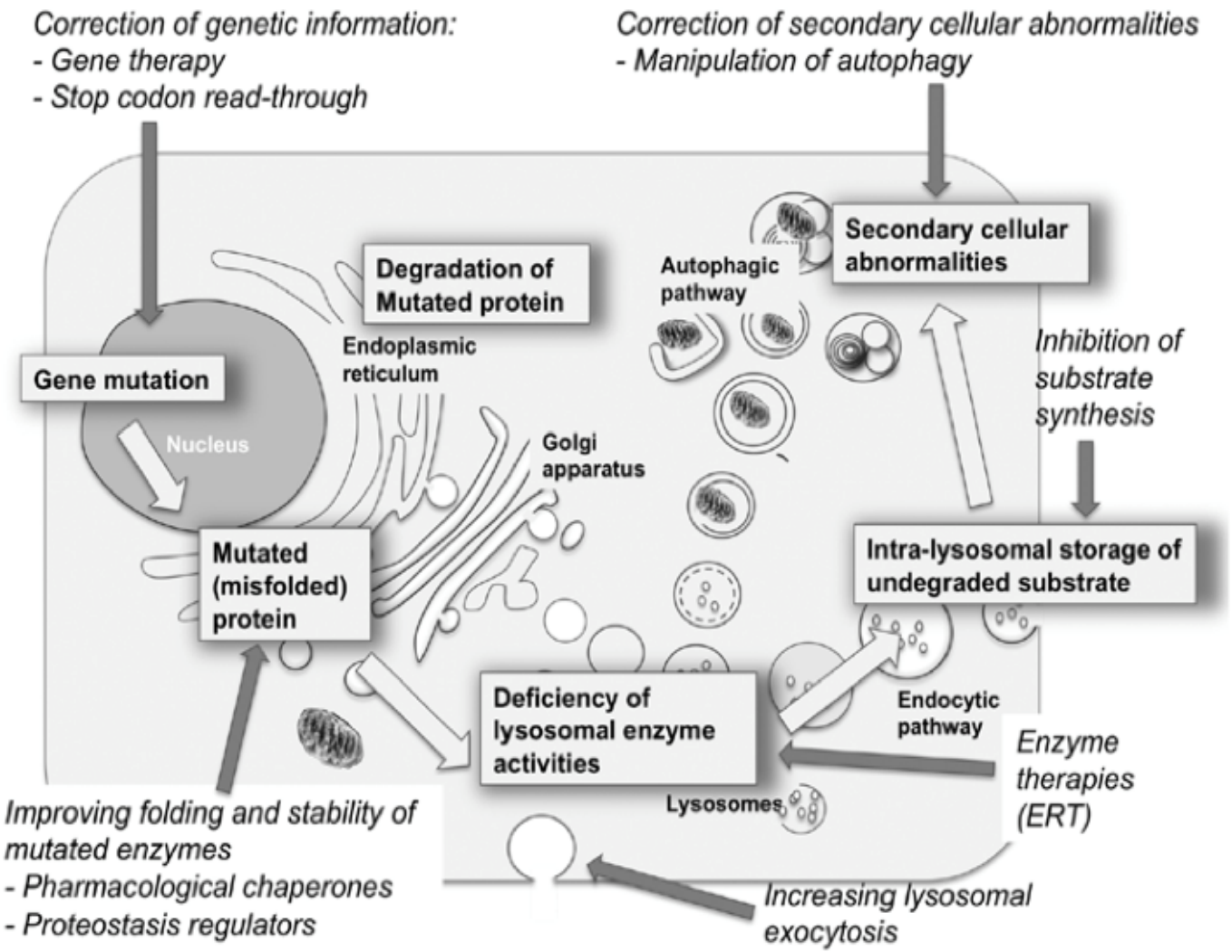
Cross correction cellulare: **terapie cellulari**

Uptake ed esocitosi**: ERT**

Pathway biochimico**: terapia con piccole molecole**



Cascata patogenetica delle LSD e relativi approcci terapeutici



Parenti et al, 2015

Malattie lisosomiali: Strategie terapeutiche

BMT= Bone Marrow Transplantation

HSCT= Haematopoietic Stem Cells Transplantation

ERT= Enzyme Replacement Therapy

GT= Gene Therapy

PCT= Pharmacological Chaperone Therapy

[CCT= Chemical Chaperone Therapy

(Enzyme Enhancement Therapy)]

SRT = Substrate Reduction Therapy

Substrate Deprivation Therapy

Increasing enzyme activity

Substrate deprivation

Future: Stop codon read-through therapy

RNA-based gene therapy

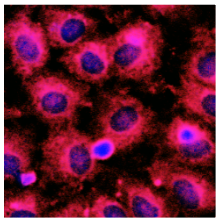
Prevention throught carrier testing, and potentially with newborn screening

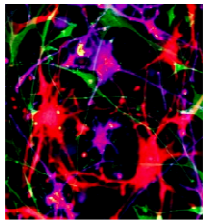
STRATEGIE TERAPEUTICHE PER LE MALATTIE LISOSOMIALI

1. **AUMENTO DELLA DISPONIBILITA' DELL'ENZIMA**
2. **DEPRIVAZIONE DEL SUBSTRATO**
3. **AUMENTO DELL'ATTIVITA' ENZIMATICA RESIDUA**
4. **TERAPIA GENICA**
5. **ANTI INFIAMMATORI**
6. **……**

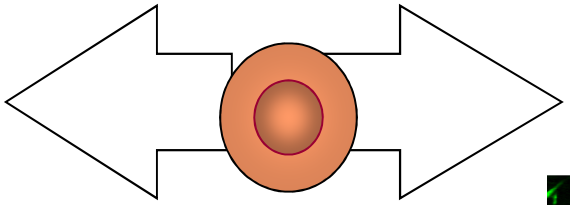
Trapianto di midollo/HSCT

hepatocytes

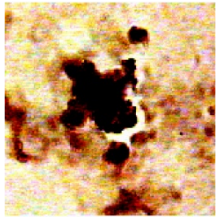


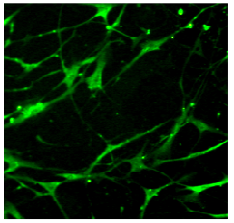


neurons, astrocytes
oligodendrocytes

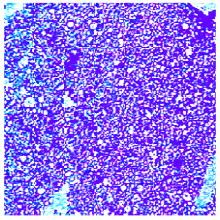


osteoblasts

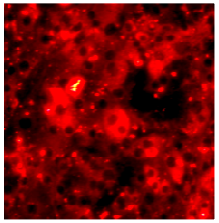




myoblasts



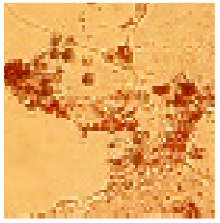
chondroblasts

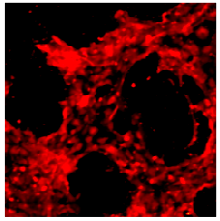


cardiac
myoblasts

Stem Cell INSTITUTE
UNIVERSITY OF MINNESOTA

adipocytes



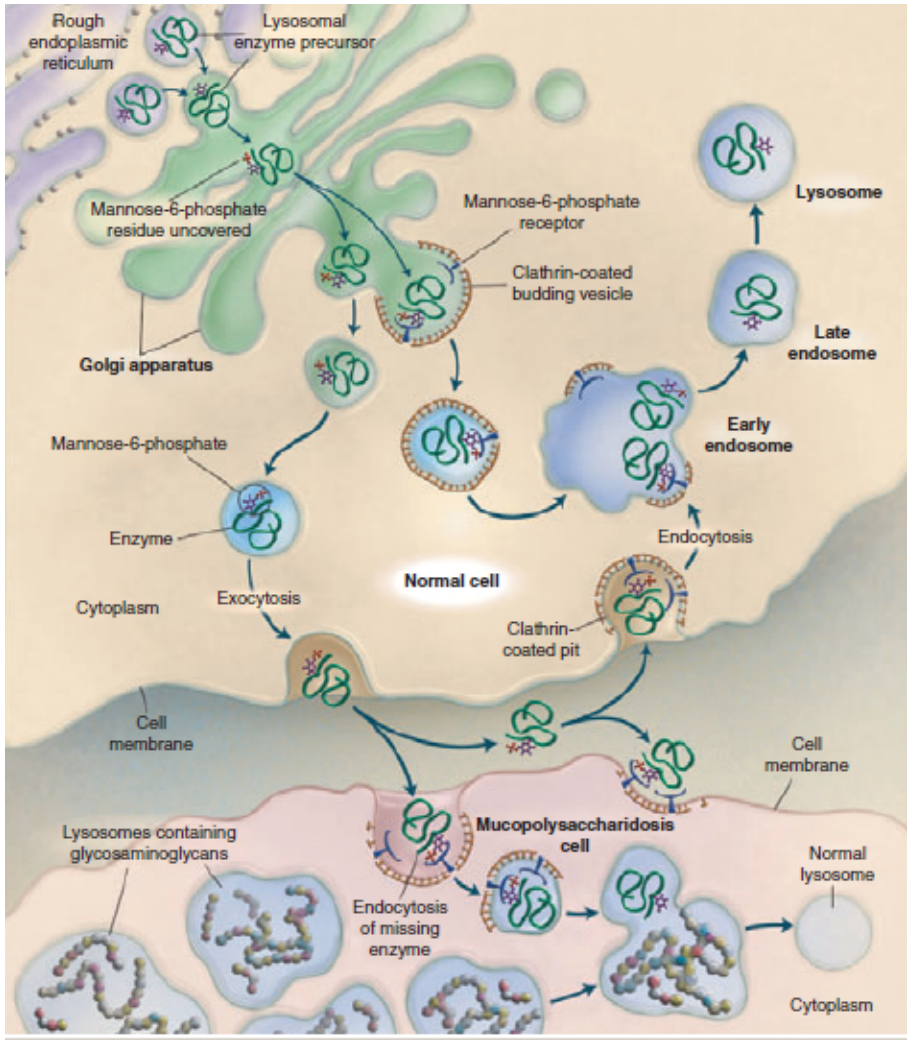


UNIVERSITY OF MINNESOTA

Ad oggi sono più di
2000
>500 casi di MPS I

Cross correction, a form of «cellular enzyme therapy»

Gli enzimi lisosomiali secreti dalle cellule normali vengono captate dalle cellule del ricevente con conseguente clearance del substrato metabolico o materiale d'accumulo



Muenzer , J and Fisher, 2004

bjh british journal of haematology

Vinod K. Prasad and Joanne Kurtzberg 2009 Blackwell Publishing Ltd, *British Journal of Haematology*, **148**, 356–372

Table I. HSCT for various IMD: Reports from literature and our recommendations.

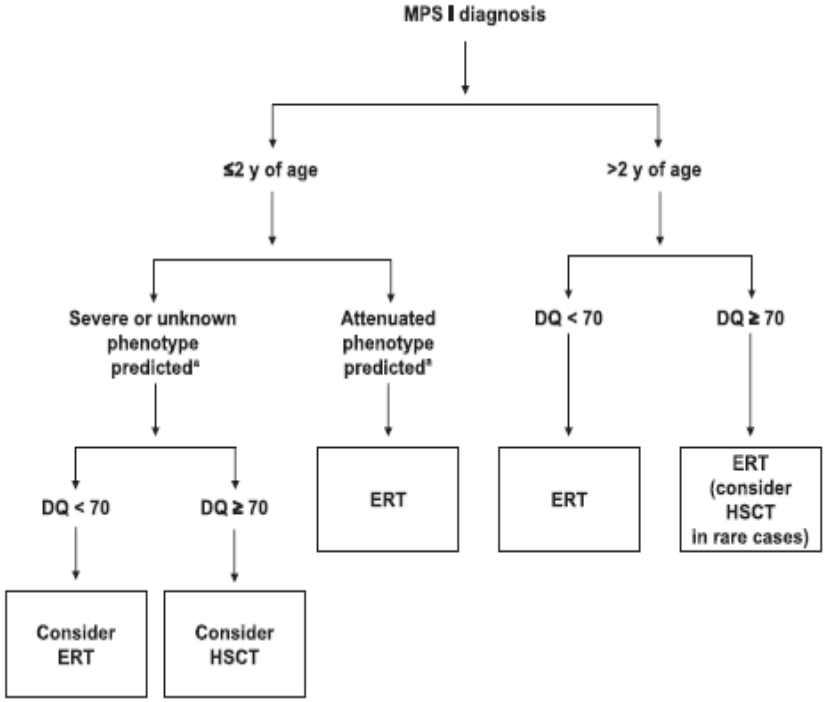
Category	Diagnosis	HSCT reported	Current status of HSCT
Mucopolysaccharidosis	MPS I, severe phenotype	BMT[1], UCBT[2]	Standard of care
	MPS II with CNS disease	BMT[3], UCBT[4]	Investigational
	MPS III A-D	BMT[5], UCBT[6]	Investigational
	MPS IV A-B	BMT[7]	Investigational
	MPS VI	BMT[8], UCBT[9]	If failed ERT
	MPS VII		Investigational
Glycoproteinosis	Aspartylglucosaminuria	BMT[10]	Standard of care
	Fucosidosis	BMT[11]	Standard of care
	Alpha-Mannosidosis	BMT[12], UCBT[13]	Standard of care
	Farber	BMT[16]	Investigational
	Gaucher	BMT[17]	Investigational for CNS involvement
	GM1 gangliosidosis	BMT[18], UCBT[19]	Investigational
	Niemann-Pick disease A and B	BMT[20], UCBT[21]	Investigational
	Tay-Sachs disease	BMT[22], UCBT[23]	Investigational
	Sandhoff sisease	UCBT[24]	Investigational
	Globoid leucodystrophy	BMT[25], UCBT[26]	Standard of care
	Metachromatic leucodystrophy	BMT[27], UCBT[28]	Standard of care
Other lipidosis	Niemann-Pick disease C		Not Indicated
	Wolman disease	BMT[29]	Standard of care
	Ceroid lipofuscinosis	BMT[30]	Investigational
Glycogen storage disorders	GSD type II, early infantile	BMT[31]	Investigational
Peroxisomal storage disorders (PSD)	Adrenoleucodystrophy	BMT[32], UCBT[33]	Standard of care
	Adrenomyeloneuropathy	BMT, UCBT[34]	Investigational
Other	Pelizaeus-Merzbacher disease	UBCT[34]	Investigational
	Lesch-Nyhan	UCBT[34]	Investigational

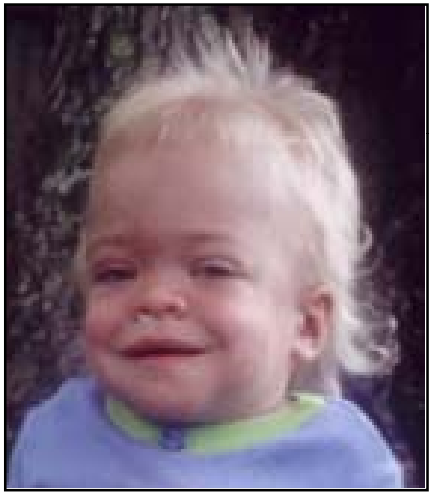
MPS 1, fenotipo severo BMT, UCBT Standard of care

Mucopolysaccharidosis I: Management and Treatment Guidelines

Joseph Muenzer, MD, PhD[a], James E. Wraith, MB, ChB[b], Lorne A. Clarke, MD[c], and the International Consensus Panel on the Management and Treatment of Mucopolysaccharidosis I

[a]Division of Genetics and Metabolism, Department of Pediatrics, University of North Carolina, Chapel Hill, North Carolina; [b]Willink Biochemical Genetics Unit, Royal Manchester Children's Hospital, Manchester, United Kingdom; [c]Department of Medical Genetics, University of British Columbia, Vancouver, British Columbia, Canada





Pediatrics 2009;123;19

de Ru *et al. Orphanet Journal of Rare Diseases* 2011, **6**:55
http://www.ojrd.com/content/6/1/55

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Enzyme replacement therapy and/or hematopoietic stem cell transplantation at diagnosis in patients with mucopolysaccharidosis type I: results of a European consensus procedure

Minke H de Ru[1], Jaap J Boelens[2], Anibh M Das[3], Simon A Jones[4], Johanna H van der Lee[5], Nizar Mahlaoui[6], Eugen Mengel[7], Martin Offringa[5], Anne O'Meara[8], Rossella Parini[9], Attilio Rovelli[10], Karl-Walter Sykora[11], Vassili Valayannopoulos[12], Ashok Vellodi[13], Robert F Wynn[14] and Frits A Wijburg[1*]

Results: Full consensus was reached on several important issues, including the following: 1) The preferred treatment for patients with MPS I-H diagnosed before age 2.5 yrs is HSCT; 2) In individual patients with an intermediate phenotype HSCT may be considered if there is a suitable donor. However, there are no data on efficacy of HSCT in patients with this phenotype; 3) All MPS I patients including those who have not been transplanted or whose graft has failed may benefit significantly from ERT; 4) ERT should be started at diagnosis and may be of value in patients awaiting HSCT.

de Ru *et al. Orphanet Journal of Rare Diseases* 2011, **6**:55
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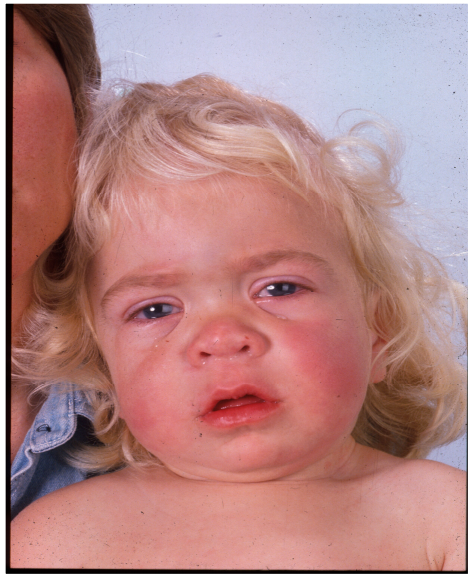


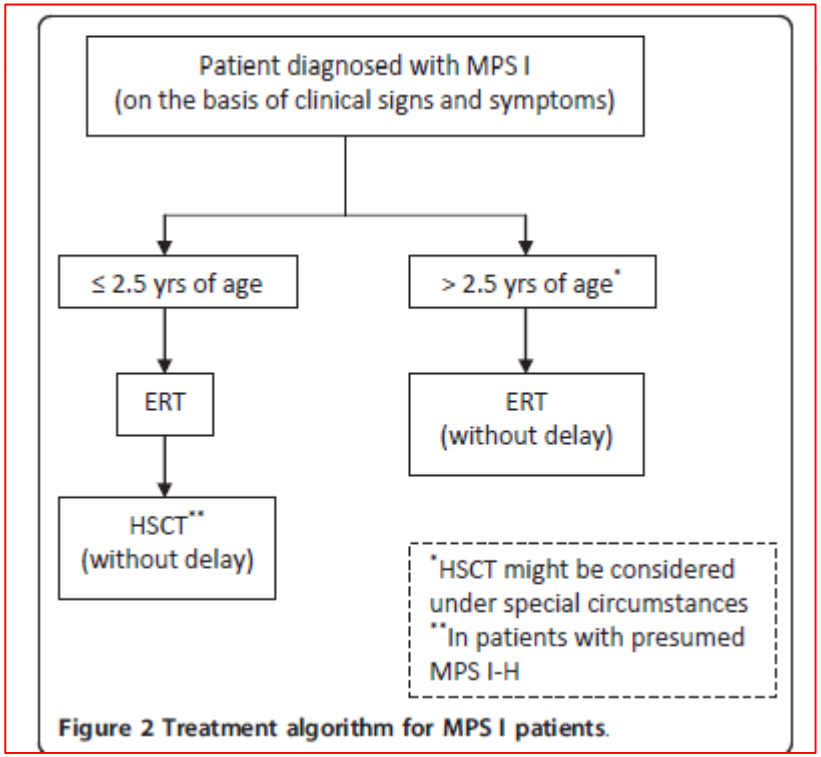
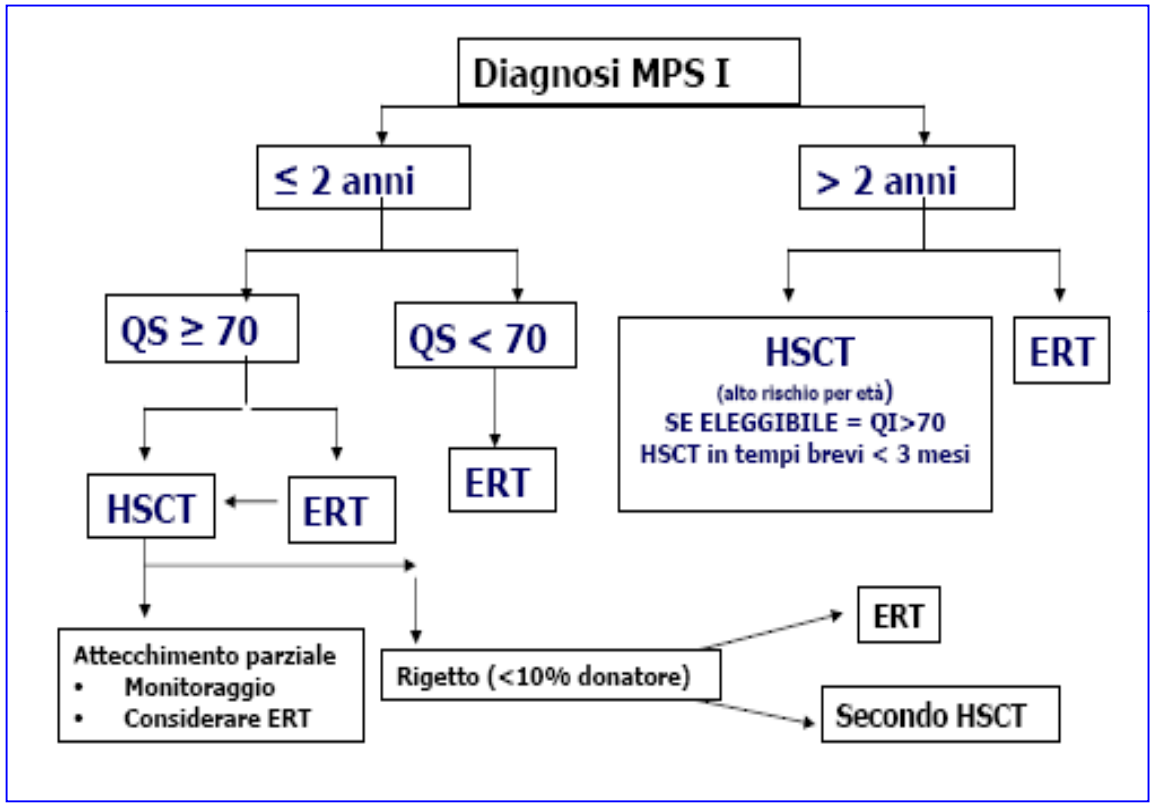


Figure 2 Treatment algorithm for MPS I patients.

RACCOMANDAZIONI PER LA DIAGNOSI E CURA DELLA MUCOPOLISACCARIDOSI DI TIPO I

AIEOP-SIMMESN / Raccomandazioni MPS I / 25.10.2010



HSCT e MPS I

- Miglioramento/stabilizzazione/ prevenzione
  - Organomegalia, udito
  - Funzione cardiaca e polmonare
  - Opacità corneale
- Outcome muscolo scheletrico
  - Miglioramento della mobilità articolare
  - Residua patologia ortopedica
- Outcome neurospicologico
  - Stabilizzazione con IQ finale tra normale e Ritardo lieve-moderato
  - Dipende da età e IQ al trapianto

HSCT: vantaggi e limiti

- E' efficace per molti aspetti somatici della malattia
- E' in grado di modificare l'outcome neuropsichico del paziente

- Elevata morbilità e mortalità
- Non è efficace sull'interessamento scheletrico, cardiaco, oculare
- Efficacia limitata nelle MPS II e VI

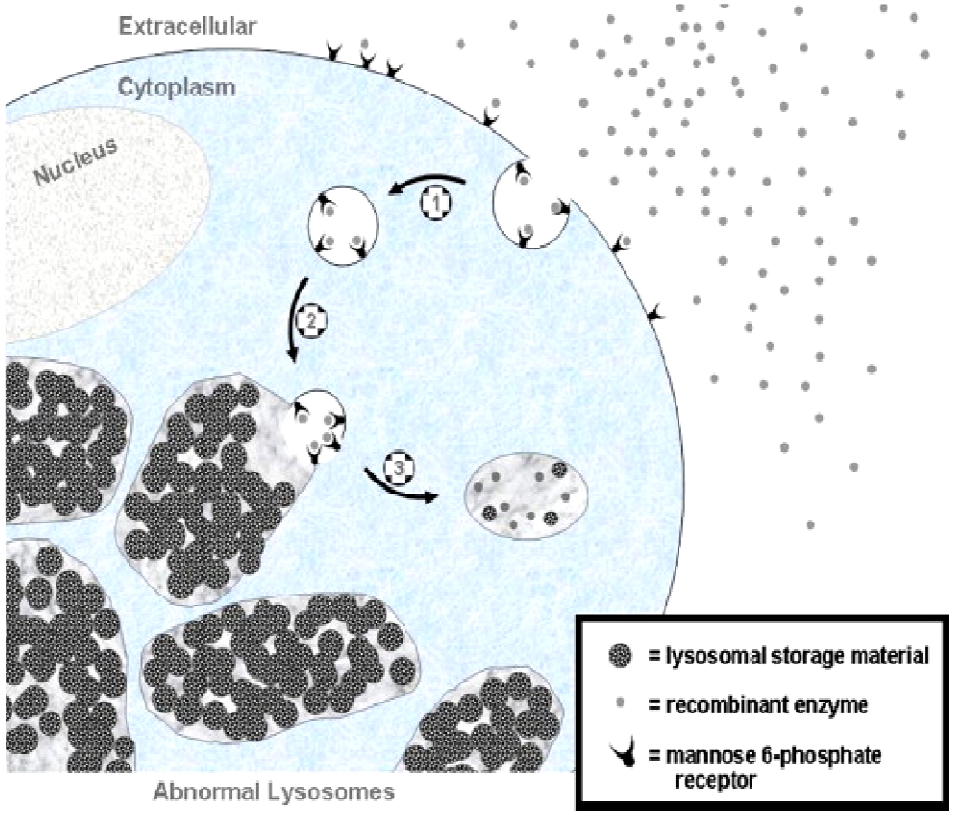
HSCT e LSD: indicazioni

Patologia	Terapia standard^	Opzionale*	Sperimentale §	Controindicato $	Riferimenti bibliografici
MPS I H	Se il paziente ha un DQ ≥ 80.			Se malattia avanzata	Aldenhoven et al., 2015
MPS I H/S, MPS I S, MPS IIB, MPS IV, MPS VI		Da valutare su base individuale insieme ad altre opzioni			Boelens et al., 2014
MPS III				Sempre	Welling et al., 2015
Adrenoleucodistrofia X-linked; MLD; GLD	Se paziente asintomatico o segni lievissimi			Se malattia avanzata	Boelens et al., 2014
Farber; Tay-Sachs; Sandhoff			Se paziente asintomatico o segni lievissimi	Se malattia avanzata	Boelens et al., 2014
Pompe			Si		Boelens et al., 2014
Niemann-Pick A e B			Se paziente asintomatico o segni lievissimi		Boelens et al., 2014
Niemann-Pick C tipo 1				Sempre	Vanier, 2010
Niemann-Pick C tipo 2			Si		Vanier, 2010; Breen et al., 2013
Deficit multiplo di solfatasi			Si		Boelens et al., 2014
MNGIE			Si		Halter et al., 2015

^ Terapia di prima linea
* È fattibile e può dare risultati ma non è la terapia di prima linea
§ Non sono disponibili evidenze di efficacia sufficienti ma è possibile che sia efficace
$ Quando è noto o si suppone che la malattia non possa rispondere al trapianto

Parini et al, 2016

TERAPIA ENZIMATICA SOSTITUTIVA (ERT)

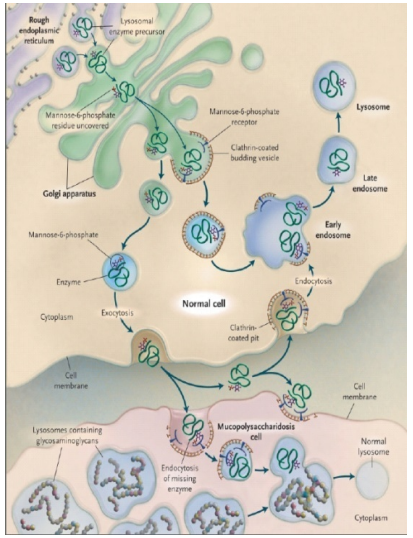


L'obiettivo è di fornire l'enzima carente

- **degradazione del materiale accumulato nei vari organi**
- **prevenzione di ulteriore deposito**

TERAPIA ENZIMATICA SOSTITUTIVA (ERT)

M. di Hurler (MPS I) (Laronidasi)
M. di Hunter (MPS II) (Idursulfase)
M. di Morquio (MPS IV) Elosulfase
M. di Marataux-Lamy (MPS VI) (Galsulfase)
M. di Sly (MPS VII) (Vestronidase Alfa)



Terapia enzimatica sostitutiva

Patologia	ERT disponibile	ERT attualmente in trial	Riferimenti bibliografici o codice identificativo in https://clinicaltrials.gov
MPS I	ERT: Laronidase (Aldurazyme®)	ERT intratecale associata a HSCT	Hollak e Wijburg, 2014 NCT00638547
MPS II	ERT: Idursulfase (Elaprase®)	ERT intratecale	Hollak e Wijburg, 2014 NCT02055118 e altri
MPS III A MPS III B		ERT intratecale ERT intratecale	NCT02716246 NCT02324049
MPS IV	ERT: Elosulfase (Vimizim®)		Hendriksz et al., 2014
MPS VI	ERT: Galsulfase (Naglazyme®)		Hollak e Wijburg, 2014
MPS VII		ERT	NCT02432144
Gaucher	ERT: Imiglucerase (Cerezyme®) Velaglucerase alfa (Vpriv®) Taliglucerase (Elelyso®)		Hollak and Wijburg, 2014
Fabry	ERT: Agalsidasi alfa (Replagal®); Agalsidasi beta (Fabrazyme®)		El Dib et al., 2013
Pompe	ERT (Myozyme®)	ERT modificato + Chaperone (ATB200/AT2221)	Kishnani et al. 2009a NCT00976352
Niemann-Pick tipo B		ERT (sfingomielinasi ricombinante)	NCT02292654
Deficit di lipasi acida lisosomiale (LAL)		ERT Sebelipase alfa	NCT01757184
Alfa mannosidosi		ERT alfa mannosidasi ricombinante (Lamazym®)	NCT01285700
Ceroidolipofuscinosi tipo 2		ERT intratecale (Rh Tripeptidyl peptidase 1- BMN190)	Ortolano et al., 2014

R. Parini et al.

Enzyme replacement therapy with laronidase (Aldurazyme®) for treating mucopolysaccharidosis type I (Review)

Jameson E, Jones S, Remmington T

The current evidence demonstrates that laronidase is effective when compared to placebo in the treatment of mucopolysaccharidosis type I.

- Reduce urine glycosaminoglycan excretion
- Improve functional capacity as assessed by forced vital capacity and the six-minute - walk test
- Laronidase appeared to be safe

de Ru *et al. Orphanet Journal of Rare Diseases* 2011, **6**:55
http://www.ojrd.com/content/6/1/55

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ERT e MPS II

IDURSULFASE (ELAPRASE)

elaprase (idursulfase)

Tomanin *et al. Orphanet Journal of Rare Diseases* 2014, **9**:129
http://www.ojrd.com/content/9/1/129

ORPHANET JOURNAL OF RARE DISEASES

RESEARCH Open Access

Clinical efficacy of Enzyme Replacement Therapy in paediatric Hunter patients, an independent study of 3.5 years

Rosella Tomanin[1†], Alessandra Zanetti[1†], Francesca D'Avanzo[1], Angelica Rampazzo[1], Nicoletta Gasparotto[1], Rossella Parini[2], Antonia Pascarella[3], Daniela Concolino[4], Elena Procopio[5], Agata Fiumara[6], Andrea Borgo[7], Anna Chiara Frigo[8] and Maurizio Scarpa[1*]

ERT for MPS II can prolong survival but disease progresses and quality of life can decline

SSIEM 2018

ERT e MPS IV

ELOSULFASE (VIMIZIM)

BIOMARIN

VIMIZIM™
(elosulfase alfa)

J Inherit Metab Dis (2014) 37:979–990
DOI 10.1007/s10545-014-9715-6

ORIGINAL ARTICLE

Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis IVA): a phase 3 randomised placebo-controlled study

Christian J. Hendriksz · Barbara Burton · Thomas R. Fleming · Paul Harmatz · Derralynn Hughes · Simon A. Jones · Shuan-Pei Lin · Eugen Mengel · Maurizio Scarpa · Vassili Valayannopoulos · Roberto Giugliani · STRIVE Investigators · Peter Slasor · Debra Lounsbury · Wolfgang Dummer

Conclusions: Elosulfase alfa improved endurance as measured by the 6MWT in the weekly but not qow dose group, did not improve endurance on the 3MSCT, reduced urine KS, and had an acceptable safety profile.

ERT e MPS VI

GALSULFASE (NAGLAZYME)

Naglazyme™
(GALSULFASE - rch)

Cochrane Library

Cochrane Database of Systematic Reviews

Enzyme replacement therapy with galsulfase for mucopolysaccharidosis type VI (Review)

Brunelli MJ, Atallah ÁN, da Silva EMK

Long-term patients treated with galsulfase were associated with improvements in pulmonary function and endurance.

The 6MWT was considered to determine endurance, mobility and also to provide an indication of cardiopulmonary health.

The levels of uGAG decreased by 87.9%

Futher studies are required to obtain evidence on long-term effectiveness and safety of ERT with galsulfase.

Autorizzazione EMA: Mepsevii per il trattamento di MPS7 23-08-2018

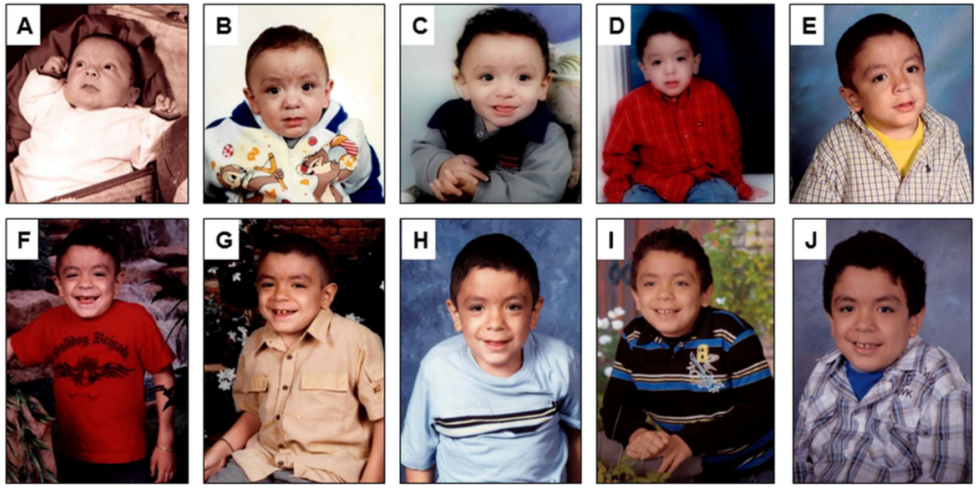


Figure 1 Serial pictures of a male patient who survived a stormy early course, beginning with neonatal hydrops and subsequently progressed more slowly with cognitive impairment, hepatosplenomegaly, obstructive airway disease, heart valve abnormalities and dysostosis multiplex including progressive hip dysplasia. This patient died undergoing anaesthesia from a dental procedure at age 12 years, which is a complication from which these patients often suffer. (A) 2.5 months old, (B) 6 months old, (C) 1 year old, (D) 3 years old, (E) 5 years old, (F) 6 years old, (G) 7 years old, (H) 8 years old, (I) 9 years old and (J) 11 years old. Photographs of the deceased patient were obtained and approved for publication with maternal consent. X-rays are shown below in the section clinical course of the disease (figures 12 and 13).

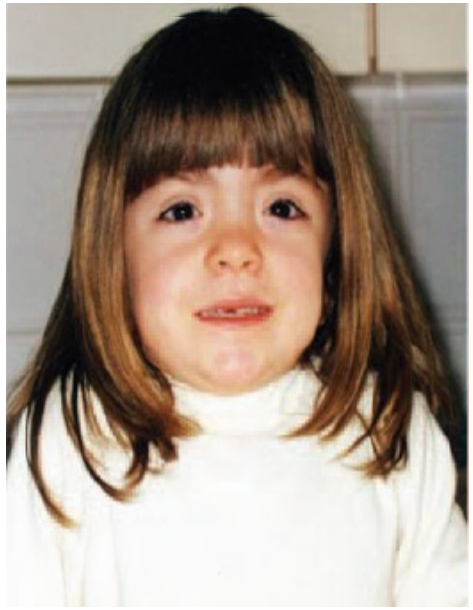
Montaño AM, *et al*. *J Med Genet* 2016;**53**:403–418. doi:10.1136/jmedgenet-2015-103322

PEDIATRICS
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Enzyme-Replacement Therapy in a 5-Month-Old Boy With Attenuated Presymptomatic MPS I: 5-Year Follow-up

Orazio Gabrielli, Lorne A. Clarke, Stefano Bruni and Giovanni V. Coppa

Pediatrics 2010;125;e183-e187; originally published online Dec 21, 2009;



Gabrielli *et al. BMC Medical Genetics* (2016) 17:19
DOI 10.1186/s12881-016-0284-4

BMC Medical Genetics

CASE REPORT Open Access

12 year follow up of enzyme-replacement therapy in two siblings with attenuated mucopolysaccharidosis I: the important role of early treatment

Orazio Gabrielli[1*], Lorne A. Clarke[2], Anna Ficcadenti[1], Lucia Santoro[1], Lucia Zampini[1], Nicola Volpi[3] and Giovanni V. Coppa[1]

Conclusioni: "This study demonstrates that early diagnosis and early initiation of enzyme-replacement therapy substantially modify the natural history of the attenuated form of Mucopolysaccharidosis type I."

Fig. 1 Patient M at the age of 10 years and Patient F at the age of 14.5 years

Molecular Genetics and Metabolism 111 (2014) 63–72

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: www.elsevier.com/locate/ymgme

Minireview

Early initiation of enzyme replacement therapy for the mucopolysaccharidoses☆☆

Joseph Muenzer *

Division of Genetics and Metabolism, Department of Pediatrics, CB 7487, Medical School Wing E Room 117, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7487, USA

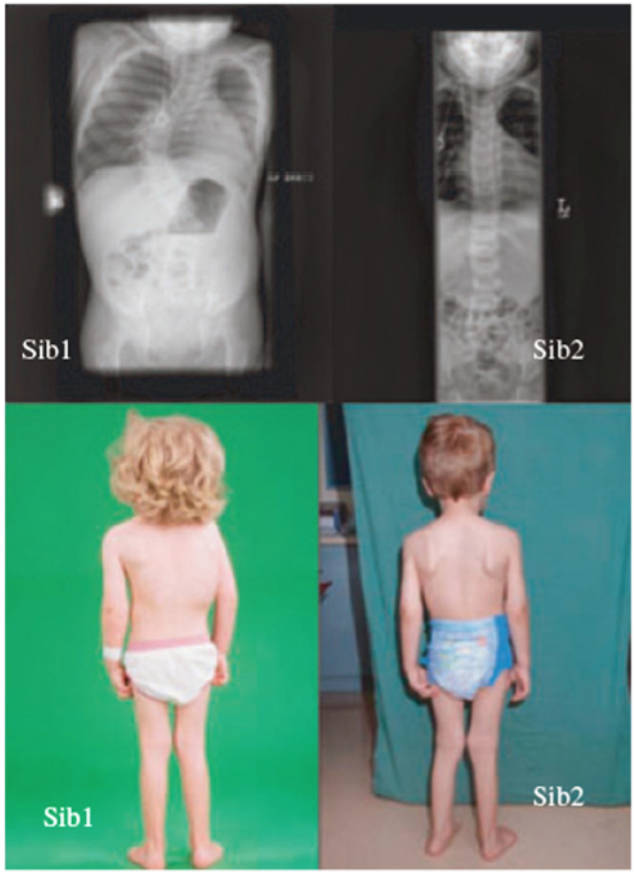


Fig. 2. **Scoliosis in the older affected sister (left) of the sibling pair with MPS I at 3.6 years of age. Sibling 1 and Sibling 2 are both affected with MPS I and are both pictured at 3.6 years of age. Sibling 1 had not received laronidase at this time, while Sibling 2 had received 182 weeks of laronidase after being diagnosed prenatally.**

Short Communication

Impact of early enzyme-replacement therapy for mucopolysaccharidosis VI: results of a long-term follow-up of Brazilian siblings

J.F. Franco[1], D.C. Soares[1], L.C. Torres[2], G.N. Leal[1], M.T. Cunha[1], R.S. Honjo[1], D.R. Bertola[1] and C.A. Kim[1]

Diagnosi precoce = outcome migliore

ERT a 9 aa e 1.5 aa

85 mesi di follow up

- statura >
- 6MWT >
- < dismorfismi
- < progressione della valvulopatia
- assenza di mielopatia

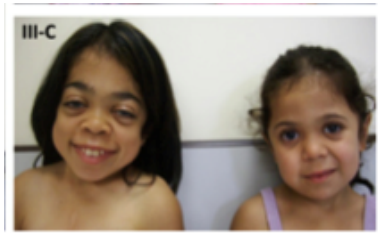
MPS VI

McGill et al 2010

3.6 anni follow up

Franco et al 2016

7 anni follow up



Furujo et al 2017

10 anni follow up

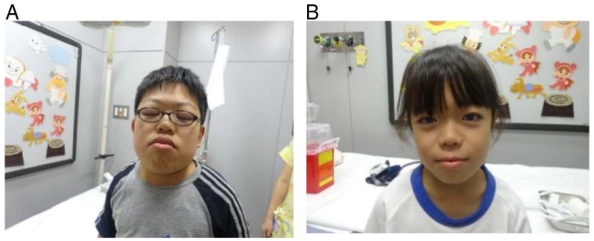


Table 3 | **Approved therapies**

Disease	Type of therapy	Drug name	Comments
Gaucher disease	Recombinant enzyme[a]	• Imiglucerase • Velaglucerase alfa • Taliglucerase alfa	ERT is effective only for type I Gaucher disease (the non-neuronopathic phenotype) and is not effective for types II and III (neuronopathic phenotypes)
	Substrate reduction therapy	• Miglustat • Eliglustat	Effective only for non-neuronopathic Gaucher disease
Fabry disease	Recombinant enzyme	• Agalsidase beta • Agalsidase alfa	• Agalsidase alfa and beta have the same amino acid composition but different glycosylation • Agalsidase beta was approved by the US FDA, although both drugs are approved by the EMA
MPS I (Hurler–Scheie and Scheie syndromes)	Recombinant enzyme	Laronidase	Effective for attenuated forms of MPS I (Hurler–Scheie and Scheie syndromes) but is not effective for severe form of MPS I (Hurler syndrome)
MPS II (Hunter syndrome)	Recombinant enzyme	• Idursulfase • Idursulfase beta	• Not effective for CNS or skeletal disease • Idursulfase beta approval by Korean Ministry of Food and Drug Safety
MPS VI (Maroteaux–Lamy syndrome)	Recombinant enzyme	Galsulfase	Efficacy variable and depends on the severity of the disease and the age at which ERT was started
MPS IV (Morquio syndrome A)	Recombinant enzyme	Elosulfase	Not effective on bone disease, which might need surgical intervention
MPS VII (Sly syndrome)	Recombinant enzyme	Vestronidase alfa	Approved for use in paediatric and adult patients
syndrome A)	Recombinant enzyme	Elosulfase	intervention
MPS VII (Sly syndrome)	Recombinant enzyme	Vestronidase alfa	Approved for use in paediatric and adult patients
Lysosomal acid lipase deficiency	Recombinant enzyme	Sebelipase alfa	Multiple disease-related lipid abnormalities reduced
Late infantile neuronal ceroid lipofuscinosis type 2 (CLN2 disease)	Recombinant enzyme	Cerliponase alfa	First treatment available for any form of Batten disease; requires intracerebroventricular administration
Niemann–Pick disease type C	Substrate reduction therapy	Miglustat	First small-molecule modifier of CNS disease in an LSD

CNS, central nervous system; EMA, European Medicines Agency; ERT, enzyme replacement therapy; LSD, lysosomal storage disease; MPS, mucopolysaccharidosis.
[a]The names of the recombinant enzymes represent the generic name. The use of α and β in the name of the natural enzyme is to distinguish between different preparations of the recombinant enzymes.

F M. Platt et al *Nature Reviews Disease Primers 2018*

Terapia enzimatica sostitutiva (ERT)
Limiti

Estrema variabilità
Outcomes clinici

Spettro fenotipico
Fenotipo/genotipo
Risposta individuale

Insufficiente
in tessuti chiavi

Osso, cartilagine, valvole cardiache
SNC

Risposta
immune

CRIM

Terapia
invasiva
per tutta la
vita

Costi elevati

ERT e prospettive terapeutiche

Delivery a siti quali osso, cartilagine SNC

Aumento del contenuto di M6P
Proteine di fusione con trasportatori BEE
nuove formulazioni: intratecale, intranasale
enzimi incapsulati, nanocarriers, PEGylazione

Management della risposta immune

Determinazione precoce stato CRIM/immunomodulazione

Terapie combinate

Individuazione biomarkers clinici, biologici, imaging

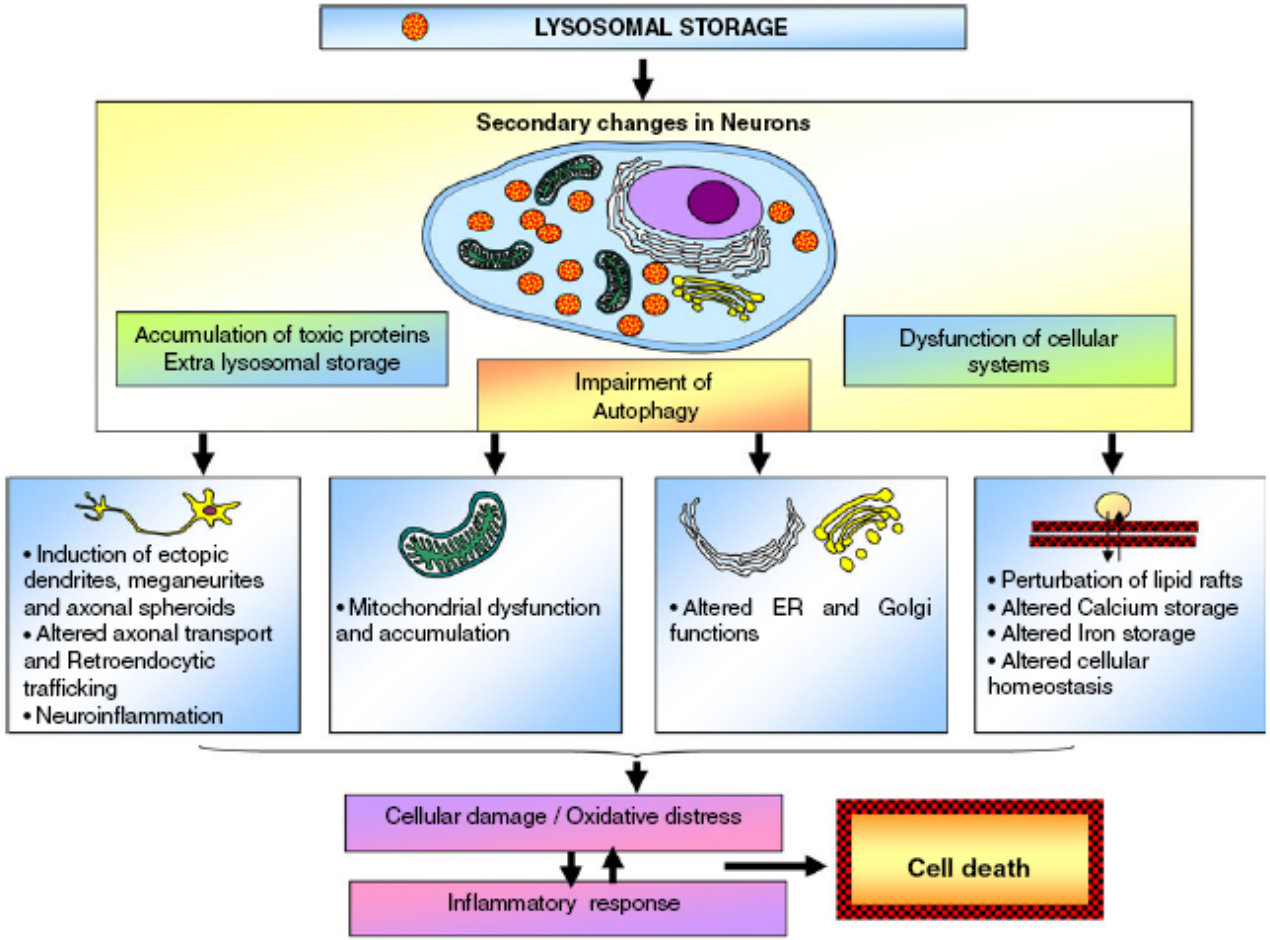
proteomica, metabolomica

Diagnosi precoce e terapia precoce

NBS

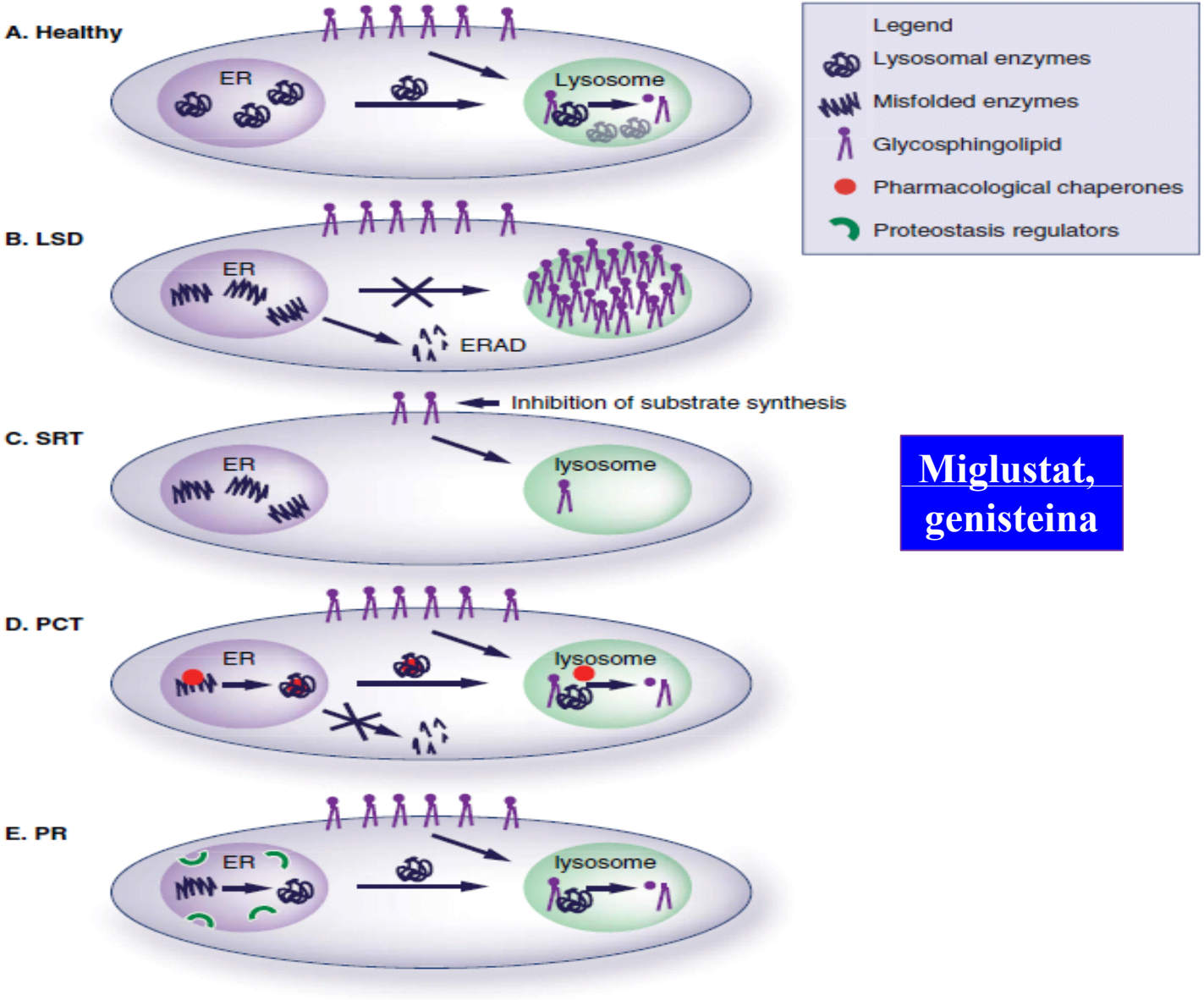
Gestione Costi e accessibilità alla terapia

Fisiopatologia delle LSD con interessamento neurologico



J Inherit Metab Dis (2010) 33:347–362

Nuovi approcci terapeutici con piccole molecole



Miglustat, genisteina

BE Smid, JMFG Aerts, RG Boot, GE Linthorst & CEM Hollak[T]
Expert Opin. Investig. Drugs (2010) 19(11):1367-1379

Nuovi approcci terapeutici

- Somministrazione orale vs e.v.
- Riduzione effetti tossici (SRTs di seconda generazione)
- Miglioramento della stabilità dell'enzima
- Riduzione risposta anticorpale alle proteine infuse
- Chaperones
- Terapia genica
- Terapia intratecale

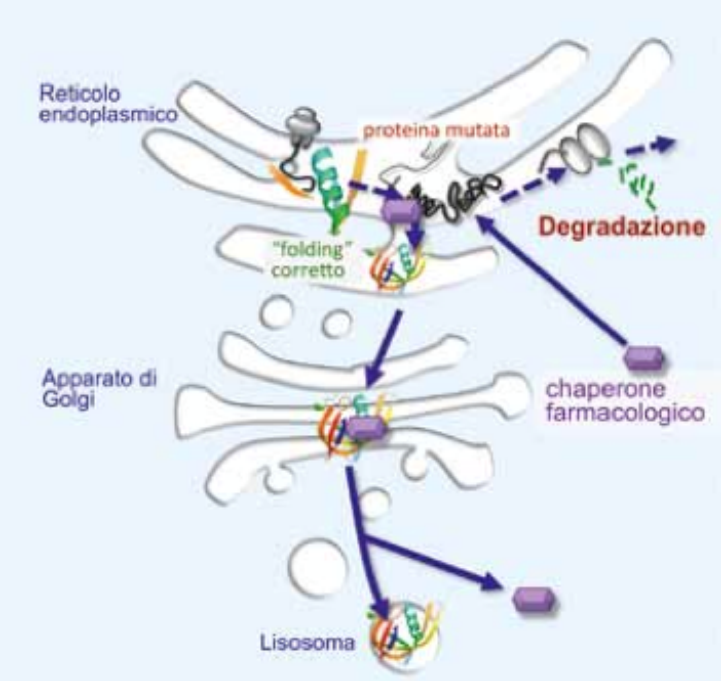
PCT/CCT

Chemical Chaperone Therapy
(Enzyme Enhancement Therapy)

Acquisizione di una struttura terziaria corretta («folding»)

Necessaria attività enzimatica residua

A causa di mutazioni missenso gli enzimi lisosomiali mutati sono alterati nella loro conformazione tridimensionale, riconosciuti dalla cellula e degradati.
Gli chaperones farmacologici possono interagire fisicamente con la proteina mutata, favorendone la corretta conformazione, migliorandone la stabilità e favorendone il corretto traffico verso i lisosomi, dove il complesso chaperone-enzima si dissocia.
Come risultato l'attività enzimatica della proteina mutata viene parzialmente recuperata.



The cellular pathways that control folding of lysosomal enzyme

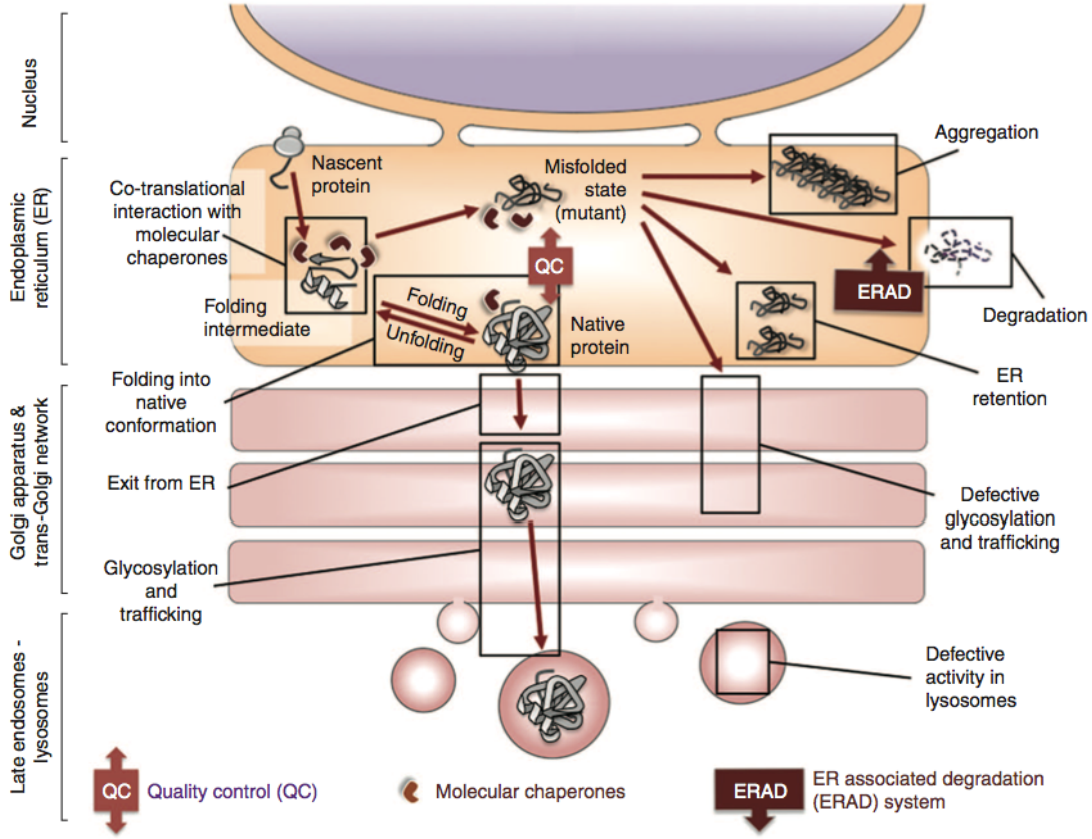


Figure 1 The cellular pathways that control folding of lysosomal enzymes. During synthesis, proteins (in this case, lysosomal enzymes or proteins) are cotranslationally assisted by molecular chaperones and folding factors (*e.g.*, heat-shock proteins) that interact with partially folded, aggregation-prone structural motifs of the nascent protein. Upon recognition and binding to the nascent polypeptide, molecular chaperones can stabilize protein conformation, inhibit premature misfolding, and prevent aggregation. Enzymes that are correctly folded and stable pass the quality control (QC) of the endoplasmic reticulum (ER), exit the ER efficiently, and traffic to lysosomes. Mutant, misfolded enzymes may undergo ER retention or be recognized by the ER QC, retro-translocated to the cytosol, and degraded by ER-associated degradation systems (ERAD).

Parenti G, et al www.moleculartherapy.org vol. 23 no. 7, 1138–1148 jul. 2015

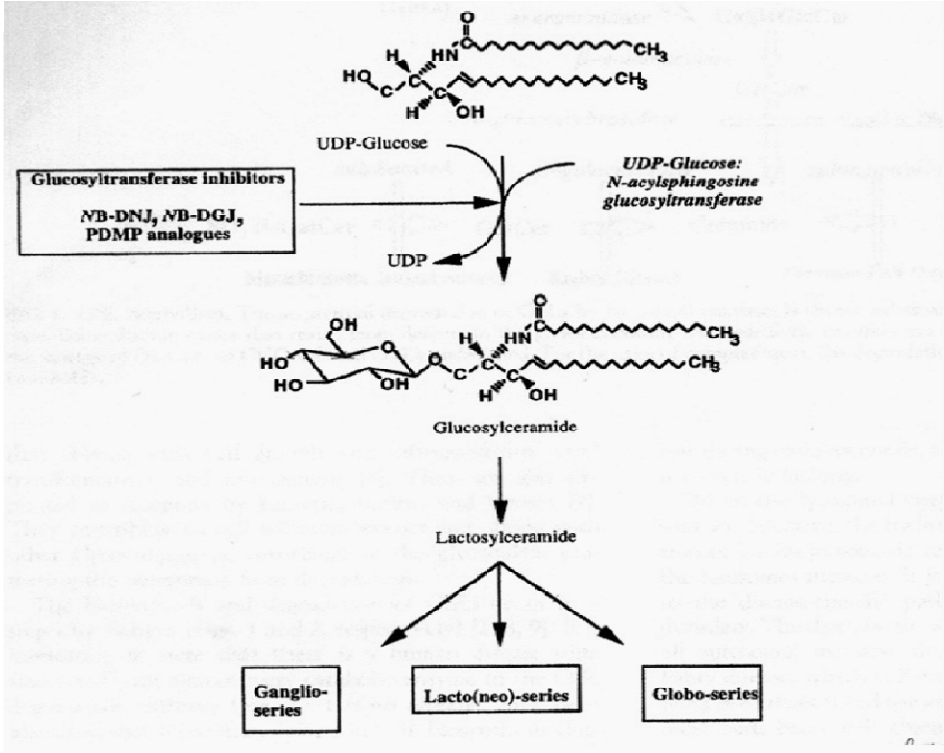
INIBITORI DI SUBSTRATO

RIDURRE LA QUANTITÀ DI GLICOSFINGOLIPIDI SINTETIZZATI

Inibitori biosintesi glicosfingolipidi (NB-DNJ, DGJ): Gaucher, Fabry, Sandhoff, Tay-Sachs, Niemann-Pick tipo C

NB-DNJ e DGJ sono imino zuccheri che inibiscono la prima fase della biosintesi dei glicosfingolipidi, ovvero il trasferimento di glucosio alla ceramide con formazione della glucosilceramide (GlcCer)

Miglustat
Migalastat
Eliglustat



SRT (Inibitori di substrato)

- Attraversano la BEE
- Non inducono risposta immune
- Somministrabili per os

Terapia con piccole molecole

Patologia	SRT	Stabilizzazione con *chaperone*	Altro meccanismo	Terapia associata/ efficacia	Riferimenti bibliografici
Tirosinemia tipo I	Nitisinone (Orfadin®)			Dieta ipoproteica/ottima	Mayorandan et al., 2014b
Cistinosi			Cisteamina bitartrato (Cystagon®)	Sintomatica/limitata	Weinreb, 2013
Alcaptonuria	Nitisinone *trial* in corso			Dieta ipoproteica	Arnoux et al., 2015
Gaucher	1) Miglustat (Zavesca®)			1) restrizione latticini/ buona viscerale e ossa, non efficace su sistema nervoso centrale, effetti collaterali	Weinreb et al., 2013
	2) Eliglustat (Cerdelga®)			2) -/buona viscerale e ossa, non efficace su sistema nervoso centrale, dose individualizzata	Sechi et al., 2016
MPS III	Genisteina			-/in attesa di risultati del *trial* in corso	Piotrowska et al., 2011; Kim et al., 2013
Niemann-Pick C	Miglustat (Zavesca®)			Restrizione latticini/ limitata	Fecarotta et al., 2015
Niemnn-Pick C			HSP70	-/in attesa di risultati del *trial* che inizierà a breve	Ingemann e Kirkegaard, 2014
			Ciclodestrina	-/in attesa di risultati del *trial* che inizierà a breve	Pontikis et al., 2013
Fabry		DGJ- Migalastat monoterapia o in associazione a ERT		-/risultati preliminari incoraggianti	Germain et al., 2012; Warnock et al., 2015
Pompe		Miglustat (Zavesca®) in associazione a ERT		-/risultati preliminari incoraggianti	Parenti et al., 2014

R. Parini et al.

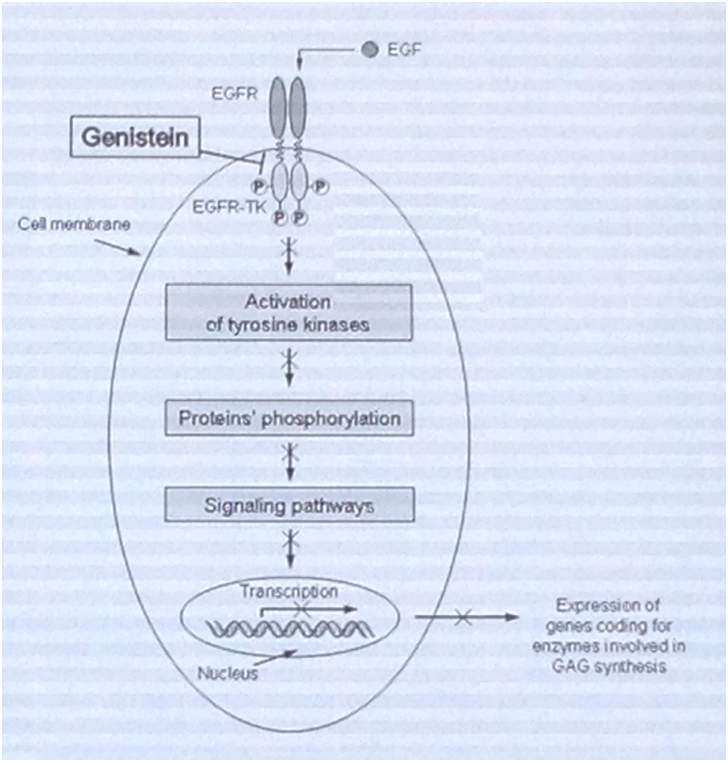
SRT e MPS
Genisteina e MPSIII

Inibisce la sintesi dei GAG in vitro e nel modello animale attraverso l'inibizione della tirosin kinasi

Attraversa la BBE

Trial Open label in MPS III A e B (n=10): 12 mesi->2 aa: miglioramento del comportamento e rallentamento del deterioramento cognitivo (Piotrowska 2008)

Trial clinico placebo-controllato non ha mostrato significativi benefici



Nuovi approcci terapeutici con piccole molecole

ORIGINAL ARTICLES

www.jpeds.com • THE JOURNAL OF PEDIATRICS

Evaluation of Miglustat Treatment in Patients with Type III Mucopolysaccharidosis: A Randomized, Double-Blind, Placebo-Controlled Study

Nathalie Guffon, MD, Sylvie Bin-Dorel, MD, Evelyne Decullier, PhD, Carole Paillet, PharmD, Jérôme Guitton, PharmD, PhD, and Alain Fouilhoux, MD

Objective To evaluate the efficacy and safety of oral miglustat treatment in patients with mucopolysaccharidosis type III. The primary outcome was efficacy with improvement or stabilization in at least two domains of Vineland Adaptative Behavior Scales at 6 months. The secondary outcome measured the evolution of other cognitive tests at 12 months. The safety and tolerability were assessed throughout the study.

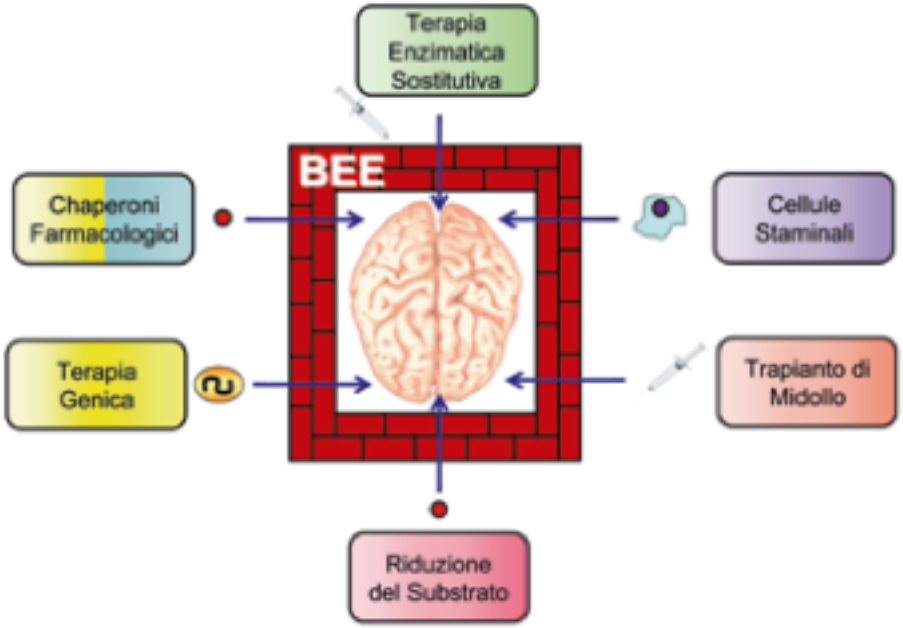
Study design This was a randomized, double-blind, placebo-controlled, monocenter, institutional, phase IIb to III study. In case of efficacy at 6 months, the study would go on for another 6 months on an open design with all patients receiving miglustat. In the absence of efficacy at 6 months, the trial had to be continued for 6 more months with the initial design.

Results After 6 months, efficacy was not superior in patients with miglustat. The independent review board confirmed continuing the study until 12 months.

Conclusion Miglustat treatment was not associated with any improvement/stabilization in behavior problems in patients with mucopolysaccharidosis type III. Miglustat has an acceptable safety profile. However, the study has confirmed that miglustat is able to pass through the blood-brain barrier without significantly decreasing ganglioside levels. *(J Pediatr 2011;159:838-44).*

MPS e SNC

ERT
SRT
PC
GT
BMT
NSC



Practice points

- Despite huge advances in drug discovery, the neuronopathic LSDs still represent a major challenge for successful therapy.
- LSDs constitute excellent models for studying and understanding the processes that control the ability to deliver drugs directly to the brain.
- The clinical failure of many potentially effective therapeutics is often due to the fact that, as they cannot cross the BBB, they cannot fulfill their pharmacological action in the CNS.

M. Scarpa et al. / Best Practice & Research Clinical Endocrinology & Metabolism 29 (2015) 159–171

Futuri approcci terapeutici con piccole molecole

Infiammazione in particolare nella MPS I

Adalimumab in MPS I

Read through stop codon therapy (Ataluren in MPS I)

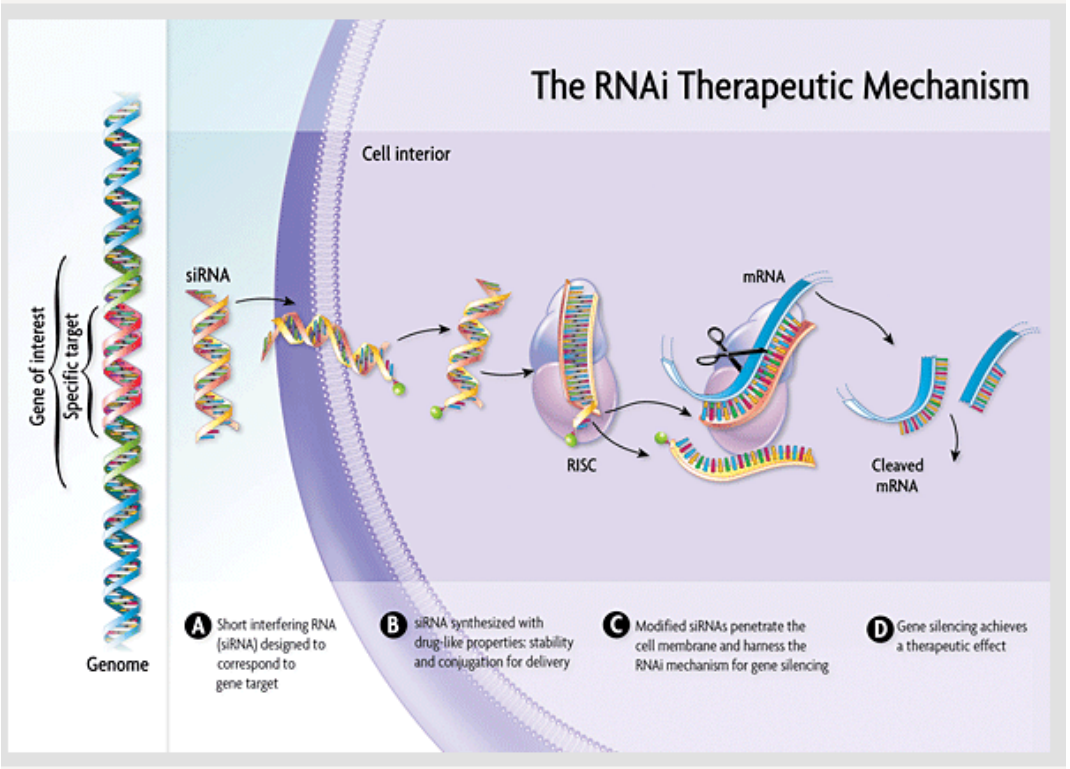
Nuovi targets per il trattamento delle LSD

RNAi interference “Genetic SRT”

Processo di silenziamento del gene

Inibisce il gene della GlcCer sintasi nella GD

siRNA inibisce la sintesi dei GAG
in topi MPSIIIA e
nelle cellule di pz. MPSIIIC



Summary of current trials in MPS

MPS I	Gene therapy	Intravenous AAV/ SB-318-IDUA	NCT02702115
	Anti-inflammatory	Adalimumab	NCT03153319
MPS II	Anti-inflammatory	Adalimumab	NCT03153319
	Gene therapy	AAV/SB-913-IDS	NCT03041324
MPS IIIA (Sanfilippo syndrome A)	Recombinant enzyme	rhHNS	NCT01299727
	Gene therapy	Intravenous scAAV9.U1a.hSGSH	NCT02716246
MPS IIIB (Sanfilippo syndrome B)	Recombinant enzyme	BMN250	NCT02754076
	Substrate reduction therapy	Genistein	EudraCT: 2013-001479-18
	Gene therapy	Intracerebral rAAV2/5-hNAGLU	NCT03300453
	Gene therapy	Intravenous rAAV9.CMV.hNAGLU	NCT03315182
MPS VI	Gene therapy	AAV2/8.TBG.hARSB	NCT03173521

Trials are listed on publicly available databases and are available at ClinicalTrials.gov. AAV, adeno-associated virus; ARSA, arylsulfatase A; HSC, haematopoietic stem cell; LSD, lysosomal storage disease; LV, lentivirus; MPS, mucopolysaccharidosis.

F M. Platt et al *Nature Reviews Disease Primers 2018*

……sulla base delle più recenti acquisizioni emerge l'importanza di una diagnosi precoce che, oltre a costituire la base per un corretto consiglio genetico, è il presupposto fondamentale per consentire un precoce approccio terapeutico prima che si siano verificati danni irreversibili in quelle malattie per le quali è attualmente disponibile una terapia efficace.

THE JOURNAL OF PEDIATRICS • www.jpeds.com MEDICAL PROGRESS

Newborn Bloodspot Screening for Lysosomal Storage Disorders

Hui Zhou, MD, PhD, Paul Fernhoff, MD, and Robert F. Vogt, PhD

LSD candidati allo screening neonatale

Malattia	Enzima deficitario	Età di esordio	Terapia
Fabry	α-galattosidasi	Infanzia/adulto	ERT
Gaucher	β-glucocerebrosidasi	Neonato/infanzia/adulto	ERT SRT
Krabbe	β-galattocerebrosidasi	Early onset Late onset	HSCT
MPS I	α-iduronidasi	Hurler/Hurler-Schie/Schie	HSCT ERT ERT/HSCT
MPS II	Iduronato-2 solfatasi	Variabile	ERT
MPS VI	Arilsulfatasi B	Infanzia	ERT
Leucodistrofia metacromatica	Arilsulfatasi A	Infantile/giovanile/adulto	HSCT ERT (trial clinico)
Niemann Pick A/B	Sfingomielinasi	Neonatale/infanzia	HSCT
X-ALD	Proteina ALD	Infanzia/adulto	HSCT

Box 1 | **Newborn screening for LSDs**

Universal screening for lysosomal storage diseases (LSDs) is mandated in the following regions and is under development or in pilot phases in several other regions:

- Pompe disease: Taiwan and, in the United States, Illinois, Kentucky, Minnesota, Missouri, New York, Pennsylvania and Tennessee
- Mucopolysaccharidosis I: Illinois, Kentucky, Minnesota, Missouri, New York, Pennsylvania and Tennessee
- Krabbe disease: Illinois, Kentucky, New Mexico, New York and Pennsylvania
- Fabry disease: Illinois and Missouri
- Gaucher disease: Illinois and Missouri
- Niemann–Pick disease types A and B: Illinois

F M. Platt et al Nature Reviews Disease Primers 2018

THE JOURNAL OF PEDIATRICS • www.jpeds.com

MEDICAL PROGRESS

Newborn Bloodspot Screening for Lysosomal Storage Disorders

Hui Zhou, MD, PhD, Paul Fernhoff, MD, and Robert F. Vogt, PhD

Clinica Chimica Acta 413 (2012) 1827–1831

Contents lists available at SciVerse ScienceDirect

Clinica Chimica Acta

journal homepage: www.elsevier.com/locate/clinchim

First pilot newborn screening for four lysosomal storage diseases in an Italian region: Identification and analysis of a putative causative mutation in the GBA gene

Silvia Paciotti [a], Emanuele Persichetti [a], Severo Pagliardini [b], Marta Deganuto [c], Camillo Rosano [d], Chiara Balducci [a], Michela Codini [a], Mirella Filocamo [e], Anna Rita Menghini [f], Veronica Pagliardini [g], Silvio Pasqui [h], Bruno Bembi [c], Andrea Dardis [c], Tommaso Beccari [a,*]

PROGRAMMA DI SCREENING NEONATALE PILOTA

MEDIANTE SPETTROMETRIA DI MASSA PER LE MALATTIE DA ACCUMULO LISOSOMIALE:

MALATTIA DI POMPE, MALATTIA DI FABRY E MUCOPOLISACCARIDOSI I

Comitato Etico Regione Toscana
18-03-2014: parere favorevole

OBBIETTIVO PRINCIPALE: Screening neonatale per la m. di Pompe, m. di Fabry e Mucopolisaccaridosi I nei nati in Toscana e Umbria

DURATA PROGETTO: 3 anni **INIZIO 1 NOVEMBRE 2014**

PROGRAMMA di SCREENING NEONATALE PILOTA LC-MS/MS per MALATTIE da ACCUMULO LISOSOMIALE: M. di POMPE, M. di FABRY, MUCOPOLISACCARIDOSI I

PUNTI NASCITA RACCOLTA SPOT SANGUE

STESSO CARTONCINO E SPOT SCREENING DI LEGGE

TOSCANA-UMBRIA

Consenso informato multilingua

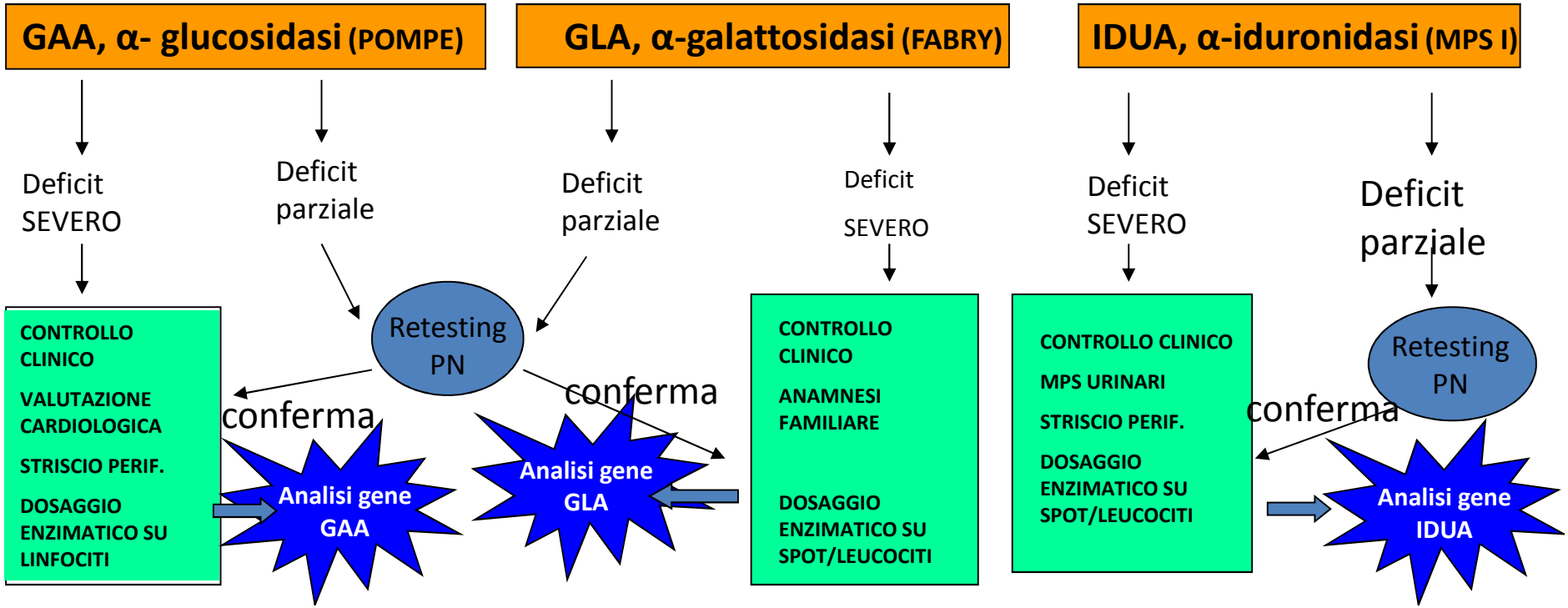
INFORMATIVA MULTILINGUA

OSPEDALE PEDIATRICO MEYER AZIENDA OSPEDALIERA

Analisi in LC- MS/MS

GAA, GLA, IDUA + enzima di controllo

SF36-STAI-BDI



SCREENING NEONATALE LSD
CRITICITA'

ANALISI MOLECOLARE
ANALISI CLINICO-STRUMENTALI
ANALISI ENZIMA FIBROBLASTI

ATTIVITA' ENZIMATICA:

NON DISCRIMINA IL FENOTIPO

FALSO POSITIVO IN PSEUDO-DEFICIT

FALSO POSITIVO IN ETEROZIGOTE

ANALISI GENETICO-MOLECOLARE:

STRESS FAMIGLIA

NON CORRELAZIONE GENOTIPO-FENOTIPO

MUTAZIONI NUOVE DI INCERTO SIGNIFICATO

DIAGNOSI :

FORMA CLINICA NON/PARZ RESPONSIVA(es coinvolgimento neurologico)

PZ CHE SVILUPPANO RESISTENZA per RISPOSTA IMMUNE

FORMA AD ESORDIO TARDIVO/ASINTOMATICI

SEMINARS IN PERINATOLOGY 39 (2015) 206–216

Available online at www.sciencedirect.com

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Newborn screening for lysosomal storage disorders

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Costi

Sensibilità specificità esame

Alta recall rate

Correlazione genotipo/fenotipo

SCREENING NEONATALE MPS I
CRITICITA'

ATTIVITA' ENZIMATICA:

PSEUDO-DEFICIT PIU' COMUNE DI QUANTO AD OGGI NOTO

SPECIE IN AFROAMERICANI

8 PSEUDODEFICIT IDUA, 1 eterozigote

IMPORTANTE ANALISI GENETICO-MOLECOLARE

- **NON FACILE SPIEGARE ALLA FAMIGLIA CONCETTO PSEUDODEFICIT**

- **FOLLOW UP DEI NEONATI CON ATTIVITA' IDUA IN ZONA GRIGIA?**

- **DEVONO ESSERE TRATTATI I NEONATI IN RANGE IDUA AFFETTI ASINTOMATICI CON MUTAZIONI NON NOTE?**

Conclusioni

Negli ultimi 20 anni abbiamo assistito a notevoli progressi nel trattamento delle MPS

Disponiamo di diverse opzioni terapeutiche e
molte sono in valutazione in studi clinici e pre-clinici

Necessaria una migliore conoscenza della storia naturale della malattia
al fine di meglio valutare gli effetti delle terapie

Linee guida e Consensus su diagnosi, follow-up, inizio e cessazione terapia

Possibilità di combinare terapie al fine di ottimizzare l'efficacia terapeutica e
personalizzare il trattamento per ogni malattia e per ogni paziente

Conclusioni

Migliorare la biodisponibilità e il targeting dei farmaci

Ridurre l’impatto delle terapie sulla qualità di vita del paziente

Ridurre i costi delle terapie

- CU, maschio 3 aa
- Unicogenito di genitori non consanguinei
- Peso alla nascita Kg 3.900 l 53 cm cc 36 cm

- Sin dai primi mesi di vita pectus carinatum
- Bronchiti asmatiformi
- 18 mesi Ricovero per broncopolmonite: escluso rachitismo
- Follow up presso Broncopneumologia
- Visita ortopedica: rivalutazione dopo 2 aa
- Visita allergologica
- Visita oculistica: ndp
- Visita fisiatrica: prescritti plantari
- Visita ORL: ndn

- 3 aa: Visita endocrinologica per deflessione curva staturale: escluso rachitismo → Visita genetica per displasia scheletrica

- → Visita metabolica DIAGNOSI MPS IV

Conclusioni

- Il sospetto diagnostico permette l'invio in un centro di riferimento…..

- Evitare il ritardo diagnostico
- Sono attualmente disponibili terapie specifiche
- Più precoce è il trattamento, migliore è l'evoluzione