Juvenile Huntington Disease

THE RAREST HD VARIANT

…when the disease
starts before
20 years of age…

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Head of the HD Unit, IRCCS Casa Sollievo della Sofferenza &
CSS - Mendel, Rome – Italy

EHA CONFERENCE - Sofia, Sept 22-24, 2017

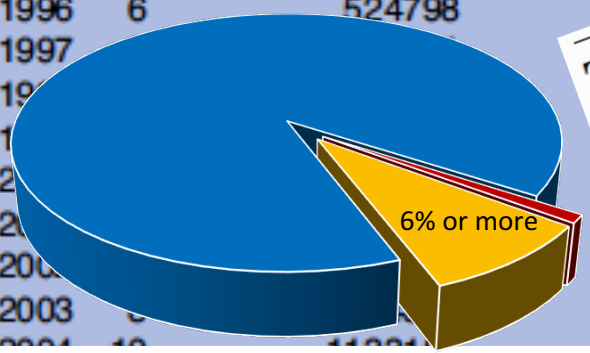
JHD frequency: some examples

BMJ open

Prevalence estimates of juvenile Huntington's in the UK

2013

Year	Prevalent cases	Numbers in GPRD aged less than 21 years	Prevalence per million (95% CI)
1990	1	248518	(0.1 to 22.4)
1991	1	304836	(18.3)
1992	1	350401	
1993	5	376180	
1994	5	406351	
1995	6	434286	13.8 (
1996	6	524798	11
1997			
19			
1			(3.3 to 17.0)
2			6.3 (2.3 to 13.8)
2			5.9 (2.2 to 12.9)
200			6.5 (2.6 to 13.4)
2003			7.2 (3.1 to 14.3)
2008	8	1184231	6.8 (2.9 to 13.3)
2009	3	1175793	2.6 (0.5 to 7.5)
2010	3	1167683	2.6 (0.5 to 7.5)



Juvenile Huntington disease in Argentina

Doença de Huntington juvenil na Argentina

Juvenile Huntington Disease

Juvenile-onset Huntington

Intergenic disease family

The Gender Effe Patients of Italian

Morocco

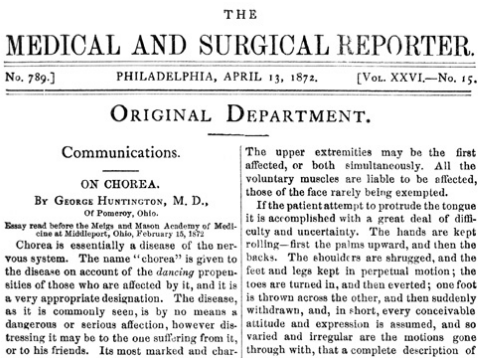
In general between 5 and 10% of all HD cases:
from *Europe, Asia, North America, South America, Africa*

Roos, R., 2011. Juvenile Huntington disease. Available at: http://www.orpha.net/consor/cgi-bin/Disease_Search.php?lng=EN&data_id=19562 [Accessed October 24, 2014].

ABOUT 6% FREQUENCY

Also reported by EMA

What's Huntington's disease



THE
MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

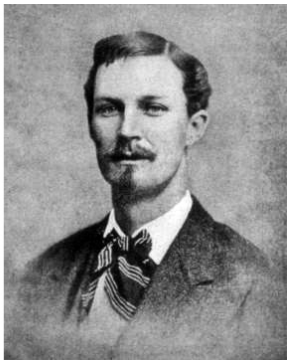
By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

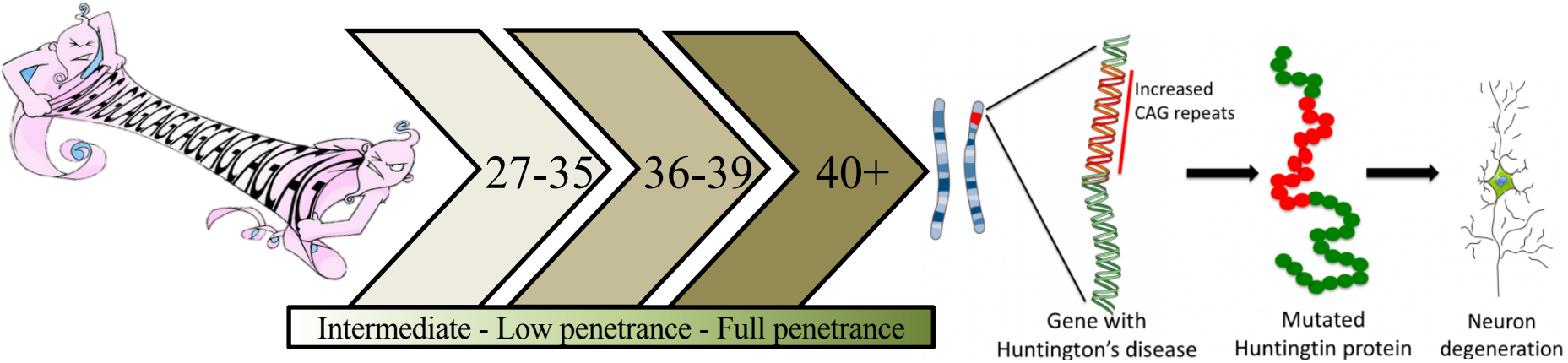
Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and char-

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of



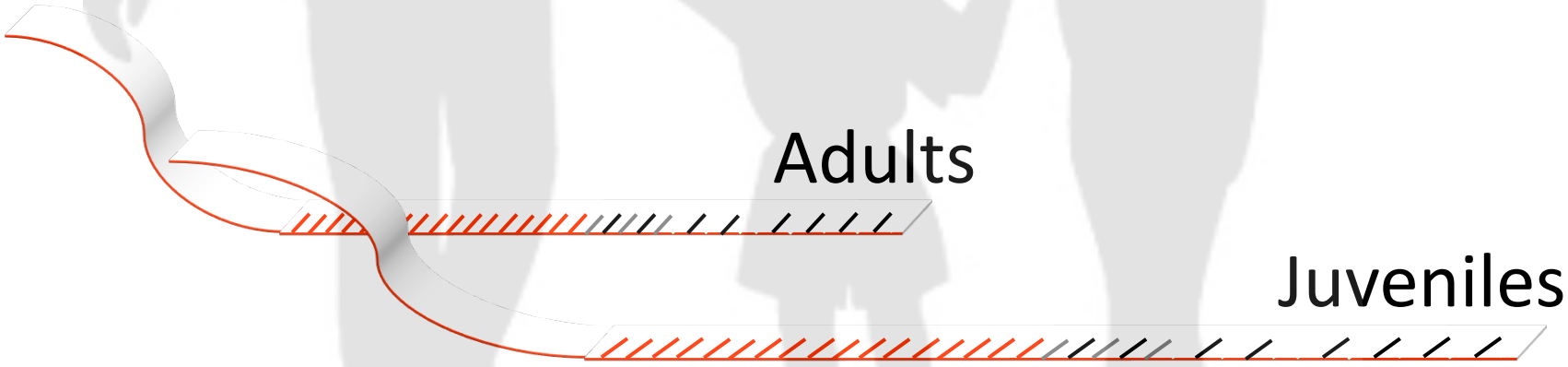
- Rare and Hereditary
- Caused by an expanded CAG mutation in the *HTT* gene
- Dominantly transmitted with 50% risk to develop the disease in each child



The CAG mutation is the cause

- The mutation length may influence the age at onset (*for about 60-70%)*

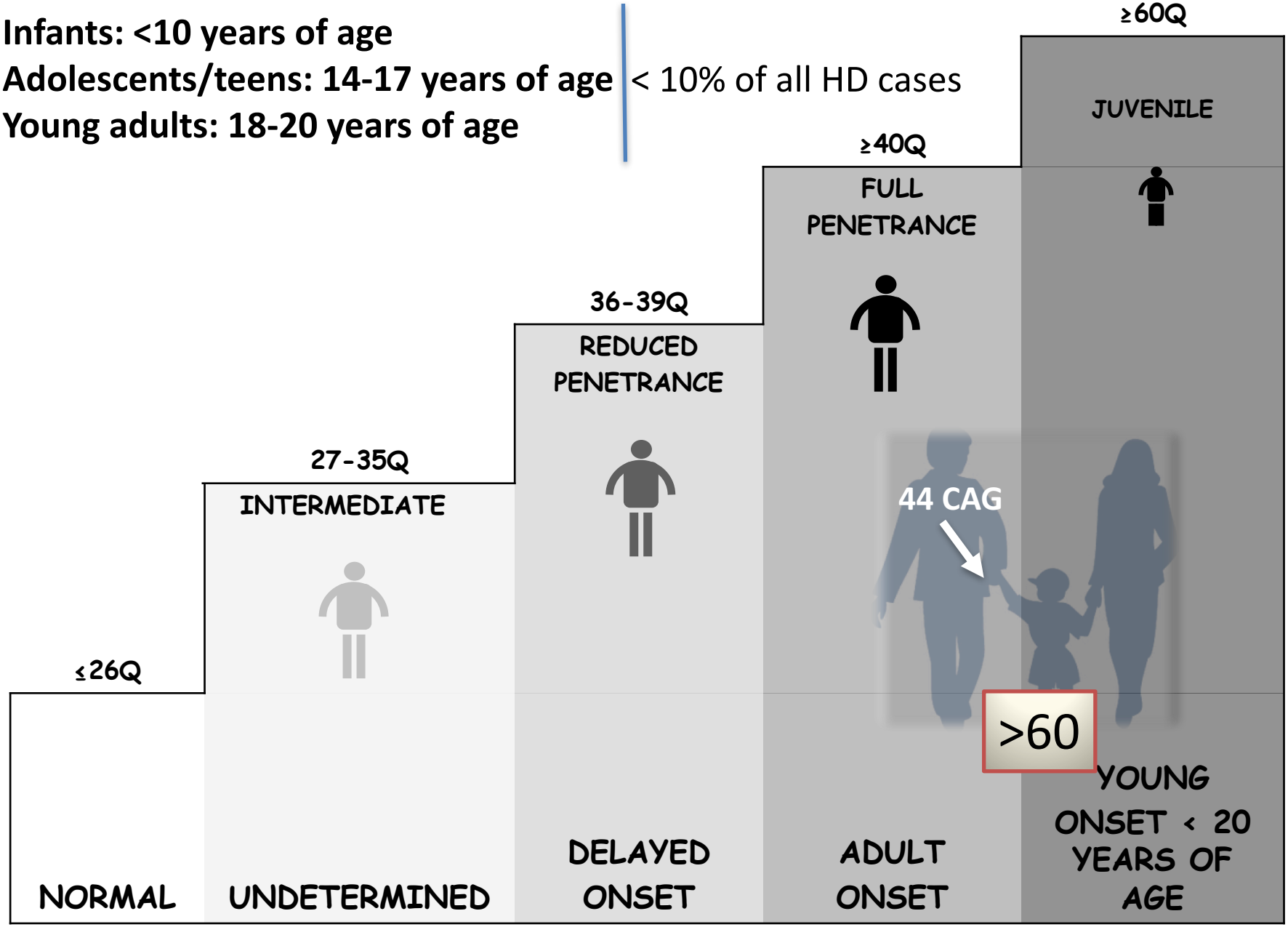
- The paternal transmission is frequently associated with juvenile age at onset



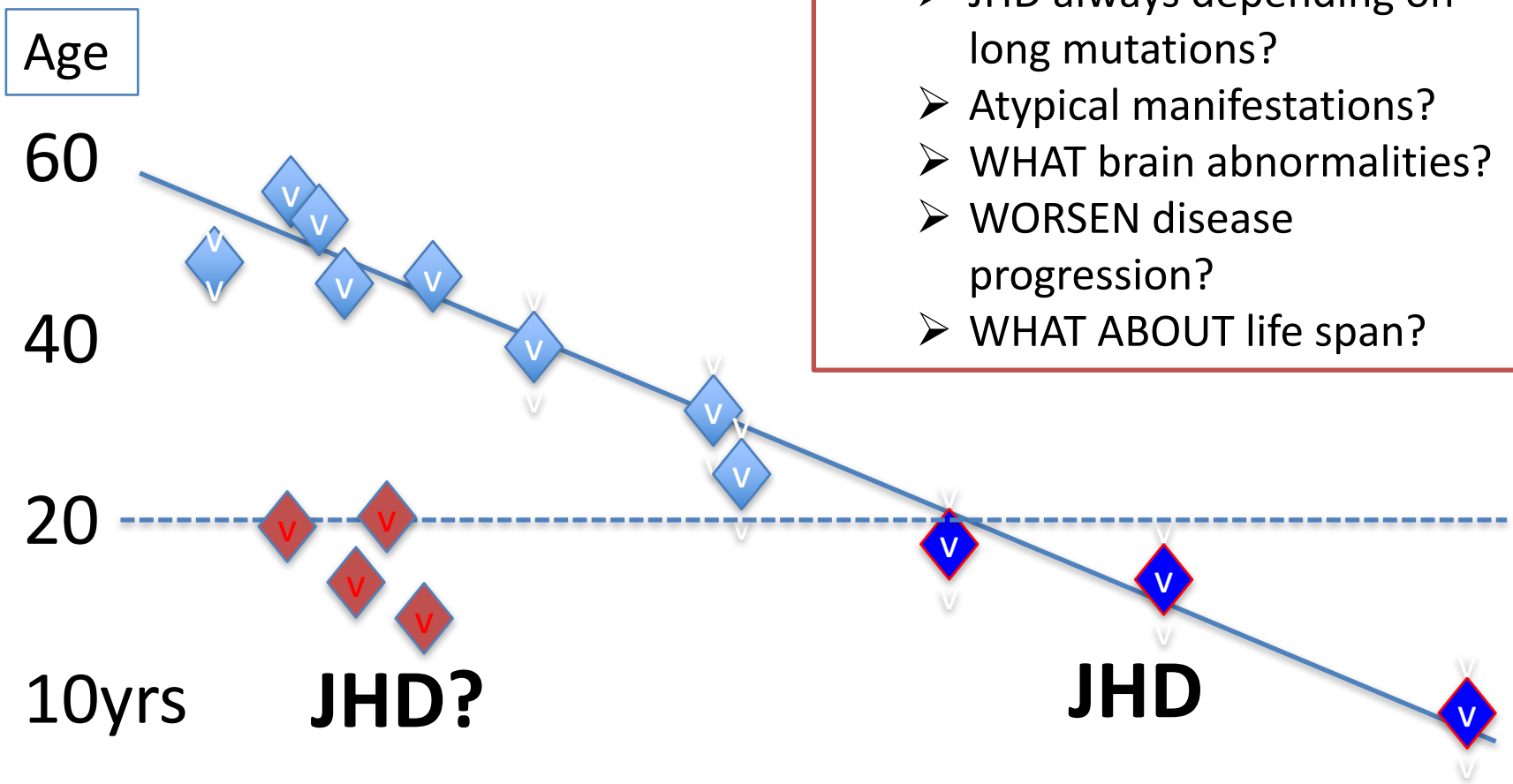
JHD:

- **Infants: <10 years of age**
- **Adolescents/teens: 14-17 years of age**
- **Young adults: 18-20 years of age**

< 10% of all HD cases



MUTATION BURDEN ON AGE AT ONSET



- JHD always depending on long mutations?
- Atypical manifestations?
- WHAT brain abnormalities?
- WORSEN disease progression?
- WHAT ABOUT life span?

40 45 50 55 60 65 70 75 CAG

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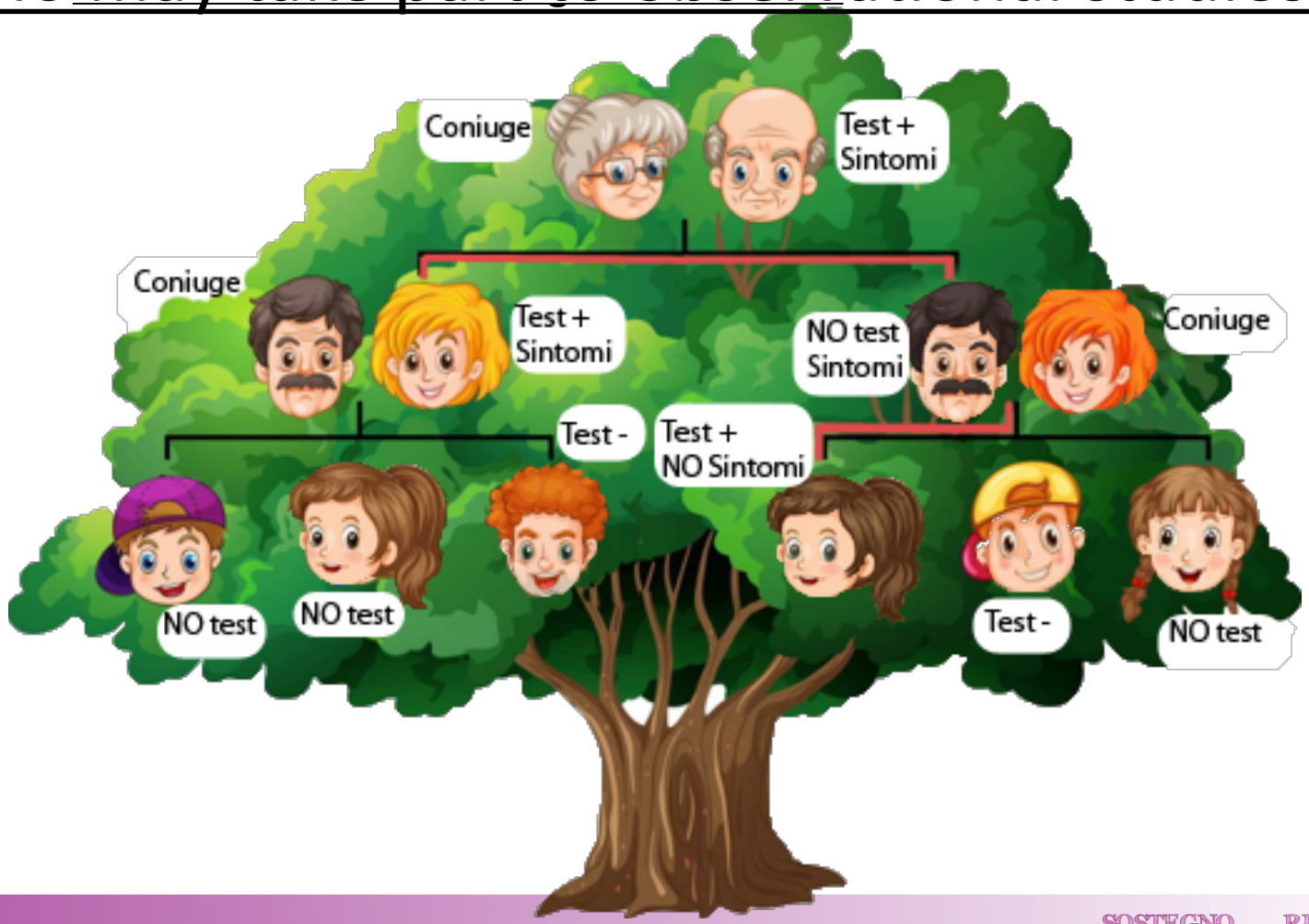
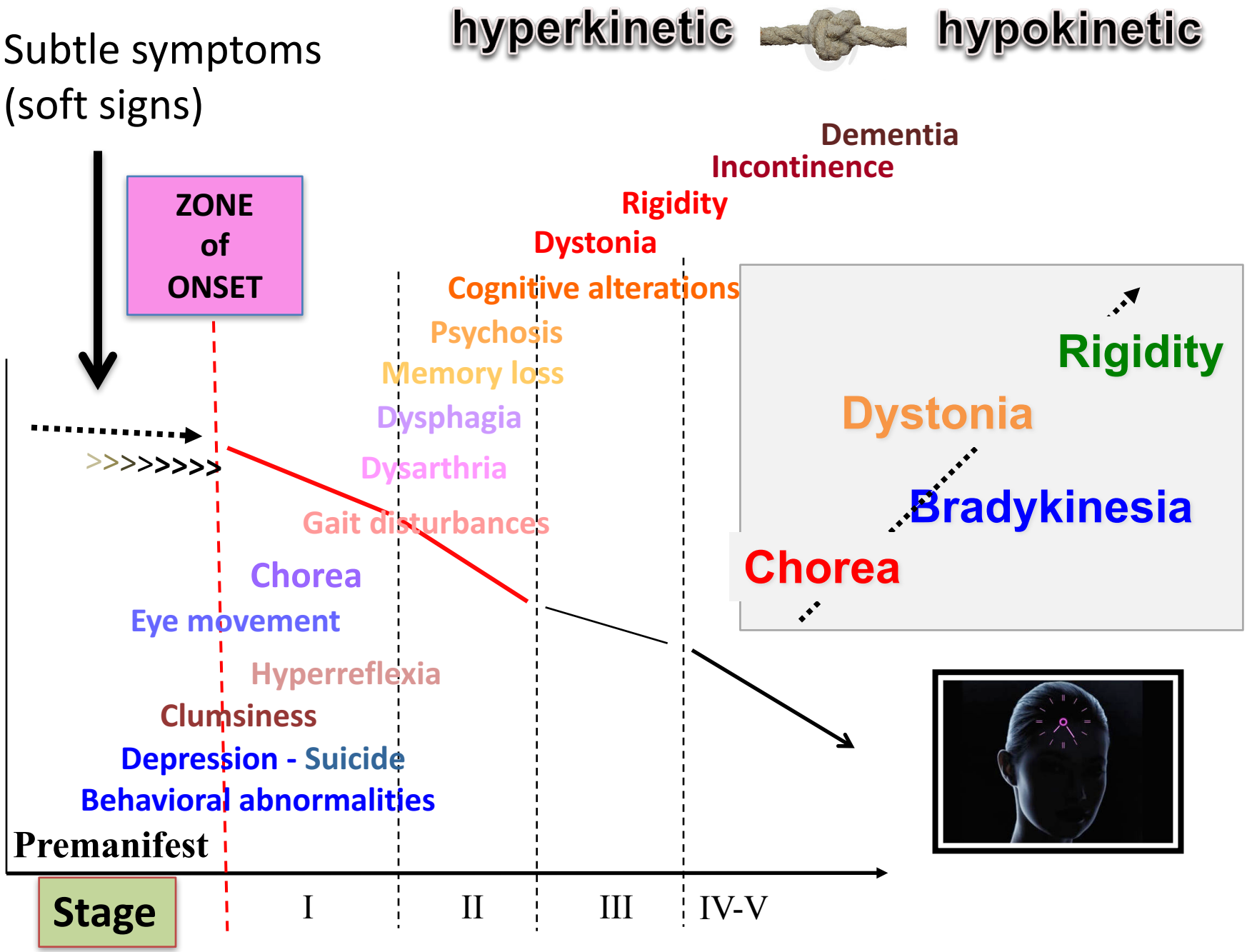
LEGA ITALIANA RICERCA HUNTINGTON E MALATTIE CORRELATE - ONLUS

Enroll-HD ?

Who may take part to observational studies and why?



SOSTEGNO RICERCA CURA


hyperkinetic
hypokinetic
Subtle symptoms
(soft signs)
ZONE
of
ONSET
Dementia
Incontinence
Rigidity
Dystonia
Cognitive alterations
Psychosis
Memory loss
Dysphagia
Dysarthria
Gait disturbances
Chorea
Eye movement
Hyperreflexia
Clumsiness
Depression - Suicide
Behavioral abnormalities
Premanifest
Rigidity
Dystonia
Bradykinesia
Chorea
Stage
I
II
III
IV-V

Adult and JHD patients' shared symptoms	Additional symptoms predominantly manifested in Infantile HD
• Behavioural abnormalities	• Autism, severe behavioural changes
• Depression and psychosis	• Seizures and myoclonic epilepsy
• Clumsiness	• Predominant cerebellar features
• Cognitive alteration	• Learning problems
• Eye movement abnormalities	• Intellectual development and delay
• Chorea and tourettisms	• School failure
• Dysphagia	• Spasticity
• Dysarthria	• Muscular pain (due to severe dystonia)
• Memory loss	• EEG abnormalities
• Gait disturbances	
• Hyperreflexia and Incontinence	
• Bradykinesia	
• Rigidity	
• Dystonia	

Roger Barker and Ferdinando Squitieri Chapter 4 in JHD (and other trinucleotide repeat disorders), Oxford University Press Book, 2009

Squitieri et al., 2006

Diagnostic criteria for childhood-onset Huntington's disease (< 10 years)

A FAMILY HISTORY OF HUNTINGTON'S DISEASE (USUALLY THE FATHER) AND TWO OR MORE OF:

- Declining school performance
- Seizures
- Oral motor dysfunction
- Rigidity
- Gait disturbance

Summary of Huntington's disease symptoms that require treatment

- Movement disorder:
  - Involuntary movements
  - Incoordination of voluntary movements
  - Rigidity/dystonia
  - Oral–motor dysfunction
- Cognitive disorder:
  - Progressive cognitive dysfunction (treated by repeated testing, and creation of appropriate school or vocational programs and goals)
- Psychological/behavioral disorder:
  - Depression
  - Anxiety
  - Obsessiveness
  - Inattention/ADHD
  - Apathy
  - Impulsiveness
  - Irritability
- Family issues:
  - Caregiver stress
  - School placement
  - Work placement
- Other:
  - Weight loss
  - Poor oral hygiene
  - Aspiration pneumonia (late)

Nance MA. US Huntington Disease Genetic Testing Group. Genetic testing of children at risk for Huntington's disease. Neurology. 1997; 49:1048–1053. Summarizes the clinical features of very young individuals with JHD. Diagnostic criteria were proposed to aid diagnosis for those cases with disease onset at ≤10 years. [PubMed: 9339688]

What is happening in a JHD brain?

Kindly provided by Jean Paul Vonsattel, New York Brain Bank at Columbia University, New York, USA

From LIRH Foundation archives, Rome, Italy

CURRENT TREATMENTS

- MANY LIMITATIONS
- MOSTLY SYMPTOMATIC (*no therapeutic trails so far allowed*)
- UNEFFECTIVE IN MOST CASES
  - USUALLY FOCUSED AGAINST:
    - *SEIZURES (often drug resistant)*
    - *PAIN management*
    - *BEHAVIORAL CHANGES*
    - *MOTOR AND COGNITIVE REHABILITATION*

FAMILIES PERSPECTIVES:

From Quarrell, Nance, Nopoulos, Paulsen, Smith and Squitieri, in "Managing juvenile HD" – Neurodegener Dis Manag 2013

When questioned about their experience, parents/care providers reported that they slowly became aware that something was wrong: at times, this could be based on nonspecific observations with small gradual changes often not noticed by others. Carers spoke about the physical symptoms and were distressed by falls, epilepsy and pain. Similarly, problems with communication and progressive isolation from friends caused distress for the parents. The behavioral problems were difficult for carers, especially when these occurred in public and resulted in perceived criticism from others. Carers also spoke of the slow and relentless nature of the condition. Aspects of helpful and unhelpful support and of feeling isolated were described in separate reports [58,65]. A study employing the same methodology to examine the experiences of parents in different European countries has recently been completed and reports similar findings [66].

SUBTLE

SOCIALITY

ATYPICAL

STIGMA

Neurodegener Dis Manag. 2013 June 1; 3(3): . doi:10.2217/nmt.13.18.

Managing juvenile Huntington's disease

Oliver W. J. Quarrell[1,*], **Martha A. Nance**[2], **Peggy Nopoulos**[3], **Jane S. Paulsen**[4], **Jonathan A. Smith**[5], and **Ferdinando Squitieri**[6]

Professionals involved in the care of patients with juvenile Huntington's disease.

Professional	Potential role
General pediatrician/community pediatrician	Address general health needs and act as a focal point for specialist input
Pediatric neurologist possibly supplemented by a clinician (neurologist, psychiatrist or geneticist) with a specific interest in HD	Advice on pharmacological management and assessment of the disease stage
Child psychiatrist	Advise on management of the family and pharmacotherapy for behavioral disorders
Child psychologist or neuropsychologist	Assess cognition, provide strengths and weaknesses, assist with educational curriculum and recommend compensatory strategies for cognitive losses
Dietician	Manage the weight loss that is associated with HD
Nonclinical case manager able to coordinate non-medical services for the family (could be a social worker or nurse)	Relate to school teachers, arrange respite care, provide support for the family and arrange for adaptations to the house if necessary
Dentist	Dental hygiene may become a challenge given the problems with movement and behavior
Speech therapist	Advise on aspects of communication and swallowing difficulties
Physiotherapist and occupational therapist	Important for maintaining independence for as long as possible
Palliative care specialist	Important for the end stage of illness, which may last for many years

Several different situations may affect families

- Early symptomatic parent, child with clear symptoms
- Parent died with HD, child with very suspicious motor manifestations
- Parent with HD mutation, child with behavioral changes, i.e. autistic spectrum, learning difficulties, school related issues

Some examples:
Sofía and her way to communicate

- Born in 1989
- First time I've met in 2006 (17yo)
- First reported issues at age 11 (attention, learning)
- First motor manifestations af age 15 (jerky, incoordinat, clumsiness)
- Genetic test at age 19 (65 CAG)
- Main manifestations: Dystonia, Parkinsonism and epileptic-like seizures. Progressive dysartria

- Irritability
- Obsessions and Perseveration
- Depression
- Insomnia

- Treated by low doses of benzodiazepines and antidepressants.
- Physical rehabilitation

I aspire to the stars
I cannot reach…

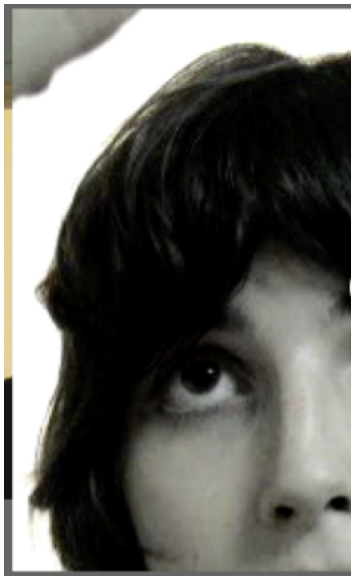
SPECIAL
AWARD
BY THE ITALIAN
“ISTITUTO
SUPERIORE
DI SANITA’”
Rome - 2014

Pain management since 2016:

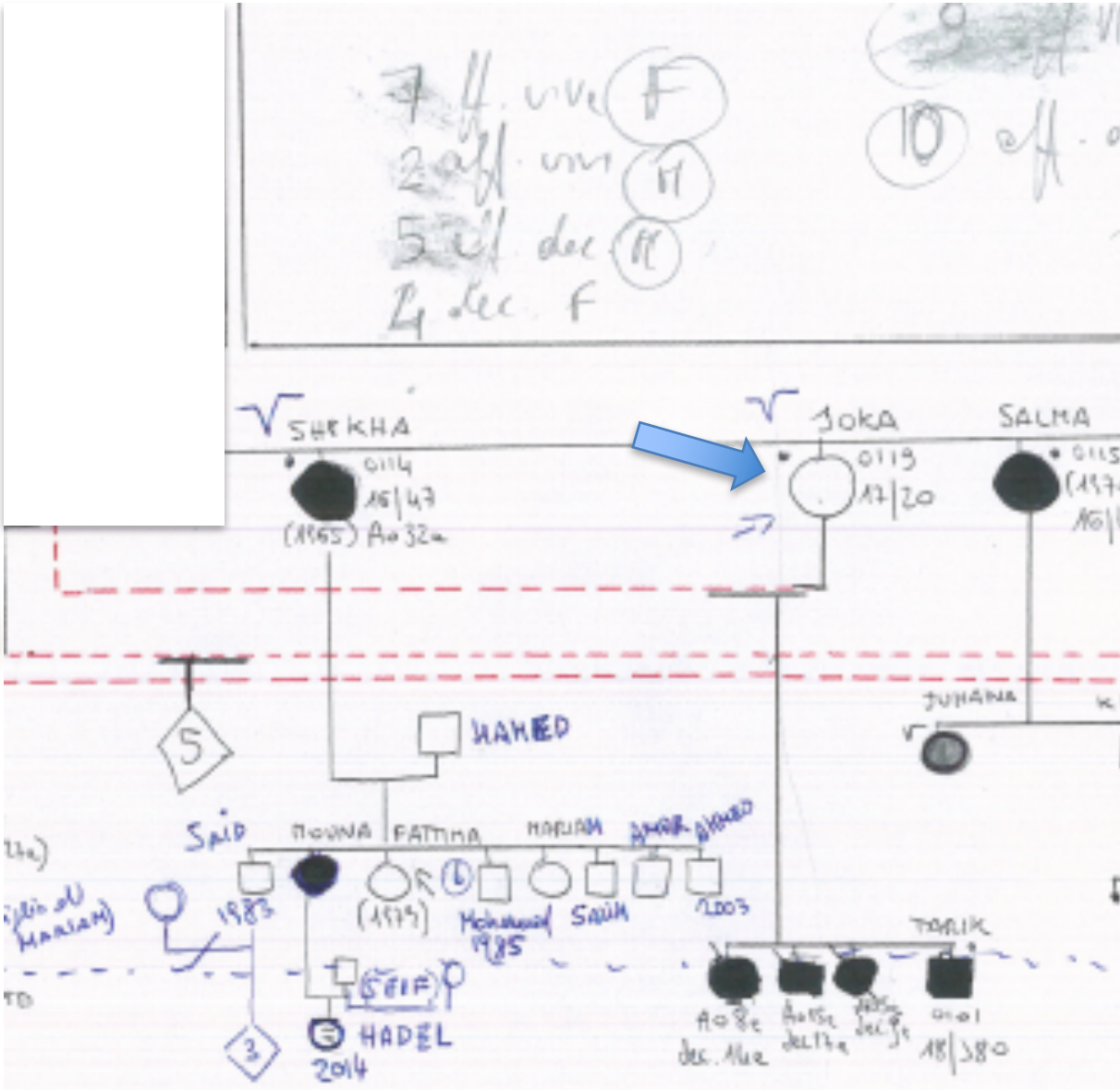
Morphine (12mg)
Midazolam i.v.
Paroxetine
Lorazepam
Food supplements

Emanuele:
a positive approach to the disease

Many little children…



Case 4



From Quarrell, Nance, Nopoulos, Paulsen, Smith and Squitieri, in "Managing juvenile HD" - Neurodegener Dis Manag 2013 -

Practice Points

- Juvenile Huntington's disease (JHD) is defined as Huntington's disease (HD) with an age of onset ≤20 years and accounts for approximately 5% of all HD cases.
- Individuals with a CAG repeat length of >60 usually have JHD, but a significant proportion of JHD cases (~50%) have <60 CAG repeats.
- The transmitting parent is frequently the father (~70–80% of cases), but this is not an absolute even in those cases with very large CAG repeat lengths.
- Issues of disease duration and disease progression are contested, and it is wise to avoid categorical statements when talking to families.
- If a young individual from a HD family has behavioral problems, it is important for clinicians to avoid implying that these result from 'poor parenting skills'.
- The disease duration is prolonged; therefore, a multiprofessional approach is required for management.
- Pharmacological treatment is aimed at symptomatic and supportive care.
- End-of-life issues have to be considered on an individual basis.

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CASA SOLLIEVO DELLA SOFFERENZA • SAN GIOVANNI ROTONDO •

SOSTEGNO + RICERCA = CURA