

## DIVERSITIES of CLINICAL course in ASD



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## Playing Bach

- Case 1. A boy aged 14 y with ASD comorbid with ADHD.
- In the elementary school he was in a normal class in an unfavourable setting: critical attitude and alarm on behalf of teachers. He had difficulties in learning and had mood disorders with severe excitement.

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## Playing Bach

- In the following years he changed school and the general atmosphere was more favourable: 'Autism friendly'. He was more relaxed, his learning improved.
- At 12 years he was tested with Leiter=73.

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## Playing Bach

- He was very repetitive about the sound of bells and at age 14 his parents sent him to play piano. With two lectures per week and two afternoons of practice in 5 months he has revealed an unexpected talent in playing piano.

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## bullyism and decline

- Case 2 is a 18 yrs old boy with high functioning autism and normal I.Q.
- Seen a year ago he was victim of bullyism: good in scholastic activities no one of his peers wanted to sit near him. He was attacked in various ways.
- In the last year he had a prolonged, severe depression, was in hospital in 2 occasions, refused to go to school from october to a month ago. Has developed OCD.

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## Imitation&improvement

- Case 3. Little boy with AR at 2 yrs seen at 4 yrs 6 months: mute with no verbal understanding. Sugg. Teacch&CAA.
- At 5 yrs begins to imitate gestures.
- At 5 yrs 6 m: speaks in short phrases, good verbal understanding.

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## Children with ASD

- Can follow different pathways.
- In single cases important progress can be obtained revealing talents and unexpected improvements as in the boys just described

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## copy number variations

- begin to be associated with some, rare phenotype (Kakinuma, Sato 2008)

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## in contrast, many children with ASD

- have a relatively stable behaviour along their clinical course

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## phenotype-genotype correlation

- begins to be obtained for some subgroups

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## PTEN mutation & macroc. + ASD

- an example are children with ASD and macrocephaly with PTEN mutation.
- Prevalence of 8.3% (Varga et al, 2009) or more if macrocephaly is pronounced (Butler et al 2005)

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## regression (AR) is common in ASD

- it accounts for about 30% of the cases usually in the 2d or 3d year
- followed in most cases by a relatively stable level of abilities and of autistic symptoms

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## but great improvement

- can follow
- in single cases,
- in groups of cases
- and in well defined conditions

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## concerning

- 1. general or special abilities leaving intact Autistic features
- 2. radical changes: with disappearance of Autistic features
- and recovering general abilities within the norm

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## in the following situations

- 1. in a variant of RTT: Z-RTT
- 2. early onset epilepsy(L-K, early onset partial complex seizures, West s)
- 3. at the edge of GTS, ADHD, A: dysmaturational syndrome

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## relevant progress without AR

- 1. early&severely depriving institutions  
(Rutter 1999; 2001) and in RAD (Motavalli 2004)
- 2. single cases
- 3. intrauterine rubella(Chess, 1977)

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## in connection with RTT

- In the Zappella variant(Z-RTT) of Rett syndrome, affecting only girls, in most case with ASD

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## AR followed by late improvement

- is present in the Zappella Variant of the Rett syndrome, where initial regression is followed some years later by slow, continuous progress in language& use of hands.
- These girls are in most cases(76%) within the ASD

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## Z-RTT shares with classic RTT

- a preclinical period
- a disease structured in 3(4) stages
- hand dyspraxia
- hand stereotypic activities (hand washing, rubbing, etc)
- and MECP2 mutation

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## In classic RTT abnormalities in

- CNS: alalia, ataxia, hand apraxia, hand stereotypies, epilepsy
- Soma: microcephalic, microsomic, scoliosis
- Neurovegetative s: breathing, cardiac, g-esophageal reflux, stypsis

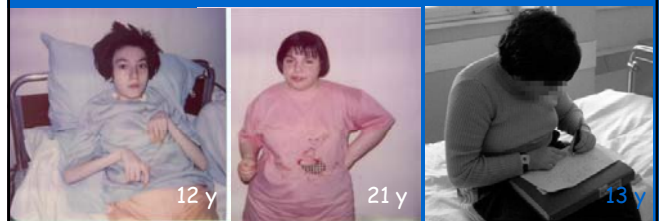
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## in Z-RTT abnormalities in

- CNS: late recovery of speech and partial of hand use, hand stereotypies less intense
- soma: normal head circumference, height, weight, no scoliosis
- neurovegetative s: absent or greatly reduced

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## The continuous spectrum of phenotype



classic >>>> PSV >>>> PSV high functioning.

87%

10%

3%

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## Z-RTT and Autism

- profound difficulty in relationship, ecolalias, speech in second-third person, no phantasy in 76%

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## Z-RTT improvement

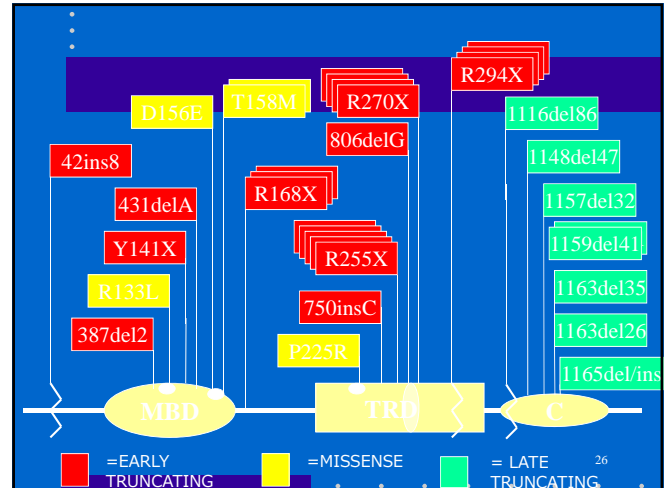
- manual, verbal, intellectual abilities begin to increase around 5-6 yrs or later, often more markedly at the end of the first decade, reaching in some case an I.Q. of 50

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## MECP2 mutation

- is present in these girls as in classic Rett in PSV with a particularly frequency for some missense as R133C(7/3 i.e. 23.3%)
- or for late deletions(13/3 i.e. 33.3%).
- In contrast with the great majority of mutations in classic Rett(early truncating)

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## specific genetic advises

- risk of recurrence around 1%
- possibility of intrauterine diagnosis
- regression is related to devel. periods when MECP2, a silencing gene, becomes more active

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## education

- favour emotionally positive interactions,
- language development, autonomy, music, swimming& motor activities
- avoid Teacch&ABA

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## Improvements in Z-RTT

- are not induced by therapies but by the nature of the disease
- education and therapies can favour a positive outcome

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## another different clinical course

- is represented by children who(can) go off autism a controversial and important subject

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## children off autism

- have been described since the seventies:
- but results vary from 1.5% (Rutter, 1970)
- to 17% (Sigman et al 1999; Suttera et al 2007)
- and to 47% (Lovaas 1987, Sallow&Graupner 2005).
- Great differences favour confusion and criticism: no attention paid to phamily history, neurologic symptoms, comorbidities

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## Children go off A in 3 situations

- 1. early onset epilepsy: LKS, early complex part.seizures (Deonna, 1993; 1995; 2004)
- 2. develop. disorder w.features of GTS& ADHD & transient ASD(dysmaturational syndrome) (Zappella, 1994; 1996; 1999; 2002;2005)
- 3. severely depriving institutions (Rutter1999; 2001)/child abuse, RAD (motavalli, 2004)  
*these 3 situations have been reported in separate studies*

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## The following study

- is a recent attempt to better define children who go off autism, their occurrence in clinical practice and their common features

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## This study

- is a follow up of 534 children with ASD aged 5 or less seen in a private outpatient's specific syndromes with ASD(tuberous sclerosis, fragile X, Down s, etc) were excluded

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## 534 young children with ASD

- total 534
- males 446
- females 88
- AR 167(31.8%)
- social AR 57
- language&social AR 110
- no AR 367(68.2%)

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## Tics(motor and/or vocal) in AR

- AR 119/167(70%)
- no AR 70/367(20%)

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## 39 children off autism

- total cases 39
- LKS 1
- w.abnormal EEG(treated) 1
- w.abnormal EEG(not treated) 1
- dysmaturational syndrome 36

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## Landau&Kleffner s.(LKS)

- Case a. Girl normal up to 3 yrs6m.
- At this age: myoclonic jerks of the head&rapid regression. Language& social skills lost.
- Seen at 1 y later: EEG multifocal spikes&spike-waves, subcontinuous general discharges in sleep.
- ASD: CARS 35, ABC 60

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## Landau&Kleffner S(LKS)

- treated with valproate(20 mg/kg) she quickly improved: at 5 y 6m she had recovered language, IQ=75, ABC=12.
- Now at 12 yr.s has adequate social life,
- still needs some support in teaching

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## Early onset epilepsy

- Autistic behaviour in these case is the result of foci discharging subcontinuously in networks concerned with communication and interaction

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## Early onset epilepsy

- Appropriate diagnosis and pharmacological treatment can determine complete recovery of symptoms of autistic behaviour and of cognitive abilities in a few, well documented cases.
- (Deonna et al, 1993, 1995; Deonna 1995; 2004)

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## case b: abnormal EEG, no drugs

- A boy with normal development up to 2 yr.s: then AR with ecolalias, unable to relate. Never had tics.
- At 2 y8m: EEG with multifocal biphasic sharp waves in P-T-O. Had ASD, CARS=34.
- At 3 y6m he began to recover.
- At 4 y had ABC=8; DSM IV n. EEG n. At 5 y: ABC=1, no ASD.

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### Case c: abnormal EEG, treated

- A boy. Abnormal behaviour & language from first y. NMR(2y4m) possible arrested hydrocephalus.
- Seen at 3y8m: ASD, ABC=48, DSM IV +.
- EEG sharp w.s L.occ.&slow w.s R.occ.
- Treated with valproate(20 mg/kg):
- followed by rapid improvement in language, relations, symbolic play.

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### Case 3: abnormal EEG treated

- After 4 months: EEG n.
- At 5y2m ABC=1 & no more signs of ASD; WPPSI 81. Treatment interrupted.
- At 7 y6m he has ADD, shy, adequate progress in school.

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### 36 children w.dysmaturational s.

- **Family history**
- Cases n=36
- tics in 3 generations 19/36(52%)
- tics in parents 15/36(41%)
- ADHD(f) 4/36(11%)
- mood disorders(m) 3/36(8%)
- ASD in 3 generations 0/36(0%)

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### 36 children w.dysmaturational s.

- **Initial development**
- normal first year 36/36
- AR second year 36/36
- tics in second year 36/36
- 1sr visit(2-4 yrs) 2 yrs 11m(m.r.)
- DSM-IV(A&PDD) 32/36
- ABC 43(m.r.)
- EEG n 24/25

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### 36 children w.dysmaturational s.

- **Outcome at follow up(1-6yrs)**
- DSM-IV(A&PDD) 0/36
- ABC 2(m.r.)
- IQ 84-111(94 m.r.)
- Tics 10/17(56%)
- ADHD 12/17(70%)

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### Previous studies on dysmaturat.s

- Series of 12 children
- Zappella M(2002) Eur.Child.Adolescent Psych.

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## Family history

- Tics in parents 8/12
- ADHD in parents 2/12

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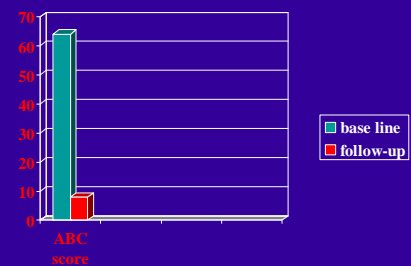
	N=12
Normal 1st y	12/12
First words 1 y	5/12
First words 18-36 m	6/12
Walks alone 12-14 m	8/12
Walks alone 15-18m	4/12
Tics start 1-2 y	12/12
Tics observed in 1st v.	12/12

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## Course of disorder

- DSM-IV for A&PDD at first visit: + in all
- At follow up(2 to 10 yrs, m.r. 5 yrs): 0

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## at follow up(2 to 10 y 8m m.r. 5y)

- GTS in all
- YGTSS=28 m.r. between 6-9y
- YGTSS=52 m.r. between 10-14y
- IQ(Wisc-R) 71 in two
- 92-112 in 10(mr 94)
- ADHD in 9
- OCD in 3
- Dyslexia in 3

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## Series of 11 children

- Zappella M
- in Riva D&Rapin I(Ed.s): Autistic Spectrum Disorders N.Y.: J.Libbey, 2005

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## 1st visit(2-4 y): 2y10m(mr)

- parents with tics 6/11
- fathers with ADHD 2/11
- normal 1st y 10/11
- regression 2d y 11/11
- TS in 2d y 11/11
- DSM IV(A&PDD) 11/11
- ABC 49(m.r.)

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## Follow up(1-4y)

- DSM IV(A&PDD) 0/11
- ABC 3.7(mr)
- IQ 76-114 or n
- TS 7/11
- mult. motor tics 2/11
- ADHD 9/11
- no TS or ADHD 2/11

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## The dysmaturational syndrome

- is the more common condition where an autistic behaviour is subsequently lost

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## Dysmaturational syndrome

- **Diagnostic criteria**
- 1. sex: males (M:F ratio 19:1)
- 2. positive family history for tics and ADHD
- 3. normal first year

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## diagnostic criteria

- 4. regression in second year with motor&vocal tics
- 5. absent dysmorphic features
- 6. normal routine lab results
- 7. respond rapidly to physical play
- 8. rapid recovery with uneven improvements in various areas

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## differential diagnosis

- a subgroup: children with A and GTS wit rapid improvement but remain within the autistic spectrum. (Kereshian&Burd, 1992;1994).
- But many children with AR have tics after regression and remain within ASD

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## treatment

- Based on parents & teachers in nursery.
- Poor or lacking reciprocal interaction is the major deficit in AR young children(mirror neurons dysfunction?).
- Therefore: physical play, face-to-face body interaction with intense cuddling, favouring attachment, affiliation exploration of the other. Favour verbal and gestural imitation.

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## treatment

- pedagogic guidance(ex. Portage method)
- support reciprocal interactions with peers: role play or else
- deal with ADHD features if present
- Speech therapy is often useful

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## treatment

- Rapid recovery initially, i.e. making two or more items a normal child would do in the same period of time
- Rapid decrease of ABC, CARS, ICD10

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## treatment

- The type of treatment&course of disorder(rapid recovery) is similar to what occurs in children coming from depriving institution, reared in normal families and recovering from A

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## course of the disorder

- autistic features absent by six years
- I.Q. in the normal range
- ADHD (often)
- GTS prolonged into adolescence(often)
- OCD, dyslexia(occasionally)

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## Dysmaturational syndrome

- Total of published cases: 85(82 M 3 F)
- plus the present 36(33 M 3 F): total 121(115 M 6 F, ratio 19:1)
- described in: Zappella M: Ter Famil 1994
- Zappella M: Autismo Infantile, 1996
- Zappella M: Infanto Rev Neuropsiquiatria 1999
- Zappella M chapter in Richer&Coates: Autism, J.Kingsley: 2001
- Zappella M: Eur Child Adolesc Psychiatry 2002
- Zappella M chapter in Riva&Rapin(Ed.s): Autistic Spectrum Disorders Libbey, 2005

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## genetic aspects

- ASD was never reported in 2 generations in these families.
- Tics were frequently present in the family.
- In parents: 27/59(45.7%)
- 1 couple of homozygotic twins
- 1 couple of heterozygotic twins (Zappella 2005)

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## genetic aspects

- ASD has a recurrence risk of 10% in brothers(Constantuno et al 2006)
- GTS has a high presence of tics in parents(up to 70%) (Freeman et al, 2000).

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## genetic aspects

- Therefore the dysmaturational syndrome is genetically similar to GTS
- and different from most cases of ASD

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## consequence in treatment

- doubts on the need of intensive(many hours per days) treatments for getting optimal results.
- We are dealing with a disorder which is genetically and biologically different from most cases of ASD.

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## consequences for treatment

- A recent study in 48 young children diagnosed as ASD at 2 yrs:
- at follow up at 4 almost a third lost this diagnosis.
- The amount of intervention did not differ between those who remained ASD and those who lost this diagnosis (Turner&Stone 2007)

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## consequences for treatment

- In education/treatment child should be kept with normal peers in the nursery
- parents and teachers guided to help him
- some rehabilitation(speech therapy) useful

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## how does recovery occur?

- We can look at other situations within the ASD where an improvement has occurred

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## A silencing gene for improvement?

- is one of different hypothesis to explain an easy(or relatively easy) recovery in the dysmaturational syndrome.
- Remember that a mutation of KCNQ2 is expressed at birth and subsequently becomes silent in neon.ben.fam.conv.
- (Kanaumi et al, 2008)

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## If not recognized

- Children who potentially can go off Autism may lose the opportunity of appropriate treatment:
- the wrong diagnosis fulfills its prophecy
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## Reversible autism

- can be suspected in:
- AR with rapid loss of language+fits
- AR followed by improvement in child with tics(familial or not), reacting well to physical play
- Sleep EEG should be done

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## There are many diversities

- in the clinical course of ASD.
- The additional presence of comorbidities of different kinds make even more complex an appropriate way of dealing with these conditions.

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## The clinician can be helped

- by knowledge of definite subgroups and syndromes where often the counterpart is a more precise therapy, education and rehabilitation.

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## analytic evaluation of the child

- 1. the evaluation of children with ASD should be analytic&comprehensive of:
- family history for developmental disorders& other conditions,
- comorbidities, verbal comprehension, manual/oral abilities,
- neurological symptoms,
- general abilities
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## and its environment

- It should include a careful analysis of the places where his daily life is organized.

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## Nature/nurture

- environment can have a great importance in situations like case 2 and probably also case 1.
- It can only favour a progress in Z-RTT where as yet unknown genetic factors play the main role.
- In the dysmaturational syndrome both environment and genetics often play a role

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## What can we learn

- Therapy should be based on knowledge of special conditions and accurate evaluation of the child and his environment and make use of existing therapies or fragments of them
- The advantages of intensive therapies, many hours per day, are questionable.

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