Prospective investigation of early clinical predictors of Autism Spectrum Disorders in infants with Tuberous Sclerosis Complex: First analysis from the EPISTOP Project

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Background:

Tuberous Sclerosis Complex (TSC) is a rare, autosomal dominant genetic syndrome that confers significantly increased risk for Autism Spectrum Disorder (ASD), with about 50% of infants with TSC meeting criteria for ASD by 3 years of age. The fact that TSC is diagnosed early in development, often prenatally, facilitates the prospective investigation of developmental trajectories and of early markers of ASD. Emerging evidences demonstrate that infants with TSC/ASD begin to show early deviation from normal development starting from 9 months of age, with relative specificity to the visual domain that generalize to a significant decline in non verbal developmental quotient between 12 and 36 months.
However, the specific phenotypic profile and the prognostic value of early clinical predictors of ASD in TSC has not been well-established.

Methods:

SAMPLE: 99 infants with TSC

RECRUITMENT PROCEDURES: multi-center EPISTOP project

STUDY DESIGN: Prospective study (end of the study in October 2018, data collection still ongoing)

TIME OF NEURODEVELOPMENTAL ASSESSMENT: 6, 12, 18 and 24 months of age

OUTCOME MEASURES:

- Developmental level: Bayley Scales of Infant and Toddler Development Third Edition (BSID-III)
- ASD symptoms: Autism Diagnostic Observational Schedule- Toddler Module (ADOS)

STATISTICAL ANALYSIS: ADOS and BSID changes over time were evaluated with paired samples t-test. Comparisons between groups were performed with two-sample t test, ANOVA models, and Pearson's correlations.
An alpha level of 0.05 was used for all statistical analyses, which were performed using SPSS v. 23.0 (IBM Corp., Armonk, NY, USA).

Objectives:

EPISTOP project is a multi-center prospective European study focused on evaluating clinical and molecular biomarkers of epileptogenesis and neurodevelopmental disorders in the genetic model of TSC.
The objective of the Italian team of WP7 is to identify early clinical markers of epilepsy comorbidities, as autism spectrum disorder and neurodevelopmental delay, in a very early age of life.
The main goals of this preliminary analysis are the identification of:

1. **Early deviation in developmental trajectories**: in order to identify if the baseline global developmental profile and/or some specific skills can be helpful to predict developmental outcome at 24 months.
2. **Developmental trajectories potentially associated with ASD:** in order to identify if the early impairment of developmental profile and of some specific sub-quotients can be predictive of ASD onset at 24 months of age.

Results:

Data is available for 69 children at age 6 months and 46 at 24 months

1. Developmental quotients trends and correlations

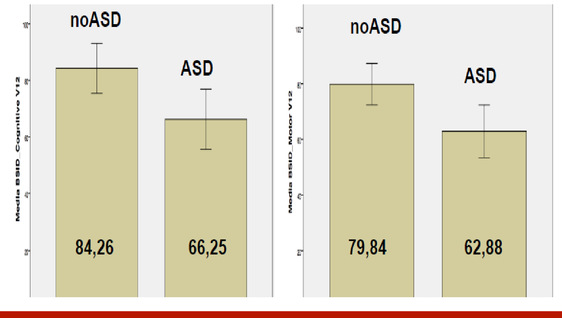
- At 6 months, 50% of children present developmental delay in motor area and 20% in language and cognitive area
- At 24 months, developmental delay can be observed in all BSID area in about 36% of children
- At V6, BSID scores correlates positively with BSID quotients at V24 months in cognitive and motor area

	COGNITIVE V24
COGNITIVE V6	r .423 P .001
	LANGUAGE V24
LANGUAGE V6	r .204 P .189
	MOTOR V24
MOTOR V6	r .393 P .009

2. Developmental trajectories associated with ASD onset

- At 6 months, no significant correlations were found between BSID subscores and ADOS risk at 24 months
- At 12 months, lower scores in cognitive and motor quotients are significantly associated with an higher risk of developing ASD at 24 months.
- The statistical significance of this correlation increases to 18 months and involves all developmental quotients.

BSID SCORES AT V12 AND ADOS RISK AT V24



BSID cognitive **p 0.018;** BSID motor **p 0.010**

Conclusion:

Our preliminary observations show an early deviation from a normal developmental trajectory in infants with TSC in the first 6 months of life, particularly in the motor area. Impairment in cognitive and language level at 12 months could be predictive of ASD at 24 months in these high-risk children. Prospective neurodevelopmental assessment associated with a close neurological and EEG follow-up could be useful to identify early correlation between clinical and neurobiological markers of ASD, to design individualized treatment strategies and to improve both short and long term outcomes for this population.

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