Service des troubles du spectre de l'autisme & apparentés
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Etiological diagnosis in young children with Autism Spectrum Disorder: A pilot study in a Swiss tertiary center

Introduction

Clarification of the DSM 5 diagnosis criteria, scientific research on early biomarkers, and progressive enhanced awareness of its general neuro-developmental dimensions, have contributed to early Autism Spectrum Disorder (ASD) diagnosis.

Concerning etiological investigations, the recommendation is that any children receiving an ASD diagnosis should have a genetic assessment; there exists no consensus for brain imaging, EEG and metabolic assessments indications in this clinical population (1-4; 10).

Assuming that some disorders like epilepsy and certain inborn errors of metabolism (IEM) are treatable, early ASD diagnosis might drive changes in terms of recommendations in the etiological investigations panel.

The contribution and interpretation of etiological investigations like brain MRI and EEG to the follow-up is debated.

Aims

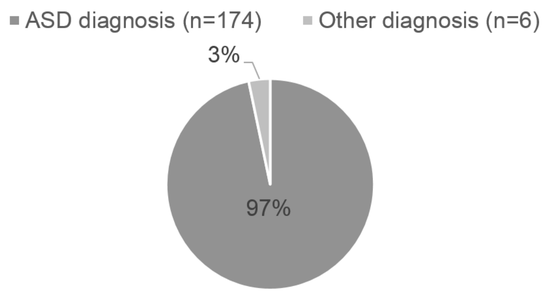
- **Description** of the etiological investigations in a young children cohort assessed for an ASD diagnosis.
- **Effectiveness 'assessment** of the clinical investigations to find an **etiology** in suspected syndromic ASD.

Study design and Methods

- Pilot monocentric retrospective study on the children aged 0 to 18 yo assessed for ASD diagnosis following the DSM-5 criteria in the Service des Troubles du Spectre de l'Autisme et Apparentés (STSA-A) during a two-year period 2017-2018.
- Descriptive statistics of the cohort, the etiological investigations performed and their yield.
- Comparison with the existing literature.

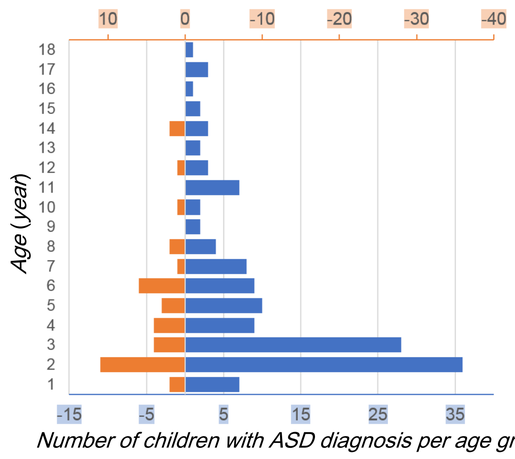
Results

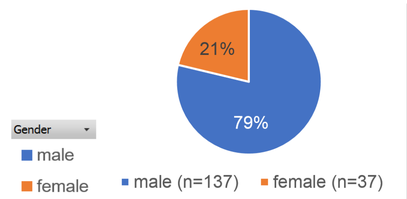
Children aged 0 -18 yo assessed at the STSA during the **period 2017-2018**



Age at the ASD diagnosis (mean):

5.14 yo (SD 4.02)





M/F **gender** ratio: 3.7:1

Children with ASD diagnosis (n=174) assessed with **etiological investigations**

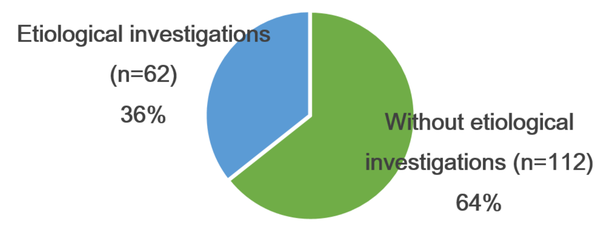
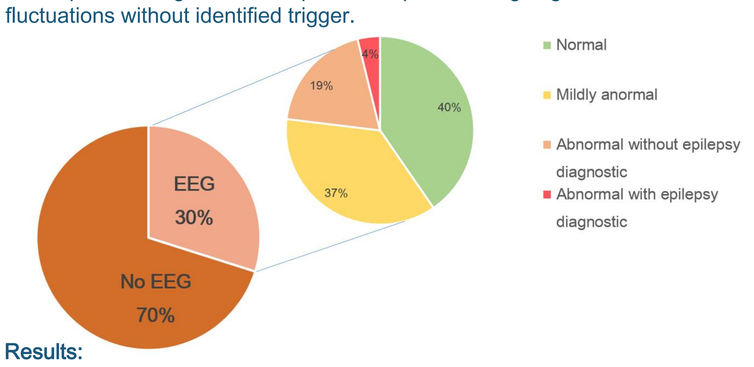


Fig.1 Description of the children referred to the STSA diagnostic centre over a 2-year period (2017-2018). Etiological investigations were performed in only a third of the children diagnosed with ASD. Alerting signs and symptoms additional to ASD (perinatal history, dysmorphic features, severe developmental delay) oriented towards a neurological assessment and when indicated, to etiological investigations in 36% patients (n=62). Indications are listed below.

Indications:
Reported or observed behavioural arrest, severe sleep disorders, recent developmental regression, frequent unexplained laughing, severe behavioural fluctuations without identified trigger.

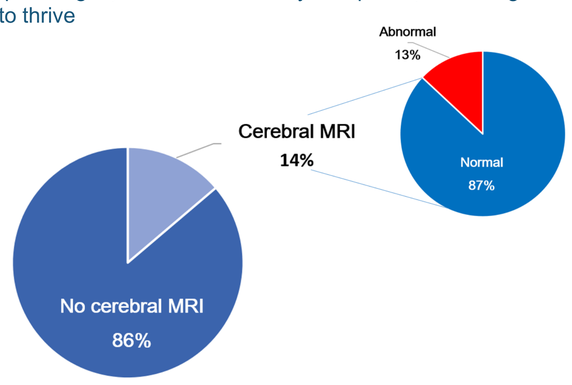


Results:
52/174 ASD children (30%) were assessed with an EEG. ***Mean age when EEG performed: 3yo 11m*** (SD 2yo 6m); M:F gender ratio was 2.2:1
The majority of abnormal EEG showed sleep abnormalities (paroxystic hypersynchronous waves, altered sleep structures, extreme spindles).
Abnormal EEG without epilepsy diagnostic displayed focal or diffuse irritative discharges or slowings, or absence of sleep structures.
2 ASD children investigated with an EEG presented with epilepsy (4%); 1 lesional poly-focal epilepsy in a patient with Tuberous Sclerosis; 1 with a left temporal epileptic focus with behavioural seizures.
So far we did not correlate the presence of EEG abnormalities with IQ or ADOS severity.

Epilepsy associated with ASD correlates with lower IQ (5). Presence of epileptic discharges in ASD children might be predictive of epilepsy later in life (6)

Fig.2 EEG awake and sleep

Indications: Global developmental delay (DD), developmental regression, dysmorphic signs, creatin deficiency suspicion, neurological disorder, failure to thrive



Results:
24/174 ASD children (14%) were assessed with a cerebral MRI with spectroscopy.
Among them, only 3 were abnormal (13%); 1 with jugular bulb ectopia; 1 pituitary hypoplasia without endocrine disorders, 1 with perivascular dilatations in white matter.

None of these findings could explain the clinical presentation despite restrictive indications to perform cerebral MRI.

Other cohort studies described clinically non significant cerebral MRI abnormalities (7) associated, but non specific, to ASD. Potential structural biomarkers in ASD are inconsistently reported (for review see (8)

Fig.3 Brain MRI with spectroscopy

Indications: DD, developmental regression, dysmorphic signs, neurological disorder, failure to thrive
Investigations:
Plasma amino acids, urine organic acids, lactate, acyl-carnitine profile, thyroid function, urine purines/pyrimidine, creatin metabolism, glycosaminoglycan
Results:
Normal for the 26/174 ASD children (15%) assessed with metabolic screening.

IEM associated with ASD are rare, and often associated with additional disorders (epilepsy) (9). In non syndromic ASD the yield of IEM investigations seems to be low

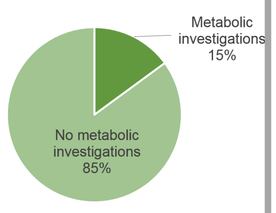


Fig.4 Metabolic investigations

Indications: DD, dysmorphic signs, neurological disorder, required genetic counselling
Investigations:
Comparative genomic hybridization (CGH) microarray, Fragile-X, exome on a gene panel (>1400 genes).
Results:
No fragile-X diagnosed in the 32/174 ASD children investigated for genetic disorder (18%) .
CGH array showed a 16q23 duplication in 1 participant, most probably pathogenic.
Exome on a >1000 genes panel reported no pathogenic genetic alteration in this small cohort.
CGH array showed the highest yield with an etiology found in 3% of the investigated ASD children.
In a recent pediatric cohort with DD and ASD, CGH array has a yield of 7% (10)

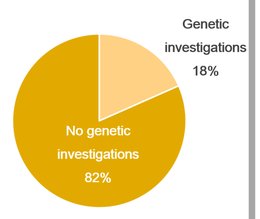


Fig.5 Genetic investigations

Discussion and perspectives

The majority of the etiological investigations did not contribute to a diagnosis. In our ASD pediatric population CGH array and EEG seem to be of clinical significance for etiological diagnosis and follow-up.

Recommendations in clinical practices regarding etiological investigations in ASD pediatric population should be carefully considered in terms of children general health benefits, limited invasiveness for the child, and health system cost limitations.

Standardized guidelines on etiological investigations in ASD at different developmental time-points are needed.

In the future, the output of these clinical data analysis could lead to open new perspectives for research on ASD, either on biomarkers, or on general health and intervention's follow-up.

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References:
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