

Observational Cohort Study Dedicated to Autism Spectrum Disorder: Milestone Steps, Results Updates, Perspectives

Mohamed BEN SAID^{a,1}, Laurence ROBEL^b, Fanny KPENOU^a, Jean-Philippe JAIS^a, Mario SPERANZA^c and TEDIS Study Group

^a AP-HP Necker-Enfants Malades Hospital· *Biostatistics Unit, Paris Cité University, Paris, France*

^b *Dept of Child and Adolescent Psychiatry, GHU Psychiatry and Neuroscience, Paris, France, INSERM UMR 1018 CESP Paris-Saclay University, France.*

^c *Dept of Child and Adolescent Psychiatry, Versailles Hospital, Versailles, France, INSERM UMR 1018 CESP Paris-Saclay University, France.*

Abstract. Autism Spectrum Disorder (ASD) is a neurodevelopmental condition characterized by persistent difficulties in two domains: social communication and interaction, alongside with restricted, repetitive pattern of behaviors. It affects children and persists into adolescence and adulthood. Its causes and underlying psychopathological mechanisms are unknown and remain to be discovered. TEDIS cohort study developed over the decade 2010-2022, in Ile-de-France region, includes 1300 patients' files up to date, with valuable health information drawn from ASD evaluation. It provides researchers and decision makers with reliable data source to improve knowledge and practice in the context of ASD patients.

Keywords. Autism Spectrum Disorder, TEDIS, Cohort Study, Neurodevelopmental disorder, ASD

1. Introduction

Autism Spectrum Disorder (ASD) is a neurodevelopmental condition with an estimated median prevalence of 100/10,000 and a median percentage of autism cases co-occurring with intellectual disability of 32% [1]. ASD are characterized by persistent difficulties in two domains: social communication and interaction, alongside with restricted, repetitive pattern of behaviors [2]. Diagnosis is based upon precise behavioral and communication analysis of children of three-to-five years old [3]. Children and adults with autism can have a happy and healthy life but urgent action is required to promote these outcomes [4]. Expert evaluations of ASD' patients in specialized medical centers in Ile-de-France region called « Centre de Diagnostic et d'Evaluation de l'Autisme (CDE) » and « Plateforme Autisme de Proximité (PDAP) » are organized around in-depth psychopathological assessment besides multidisciplinary domains investigations. It

¹ Corresponding Author: Mohamed Ben Said, Biostatistics Unit, Necker University Hospital. 149 rue de Sèvres. 75015, Paris. France. E-mails : mohamed.bensaid@aphp.fr, mohamed.ben-said@ext.paris-descartes.fr.

generates valuable health information for apprehending underlying psychopathological, physiological processes of the ASD' affection. An information system called TEDIS, was developed to manage such information, in the context of a) ease-of-use in daily practice in clinical settings, b) respect of privacy, ethics, data integrity and security, c) being adaptable to knowledge domain evolutions, e) expandable to new participating centers. This article aims at presenting major milestone steps during the last decade and the solutions brought at each step. Excerpts of data analyses results will be discussed in relation with governance, and collaboration perspectives.

2. Methods

Four major phases punctuate TEDIS evolution during the last decade (2011-2022).

2.1. TEDIS Milestone steps

Phase 1 [2009-2010]: Dedicated to the development of conceptual data model and the application system. TEDIS was implemented in relational MySQL™ database, within an n-tiers architecture web information system, using light-weight client engineering and free-license software: HTML, CSS, JavaScript, Apache-tomcat and Java™ language.

Phase 2 [2011–2017]: TEDIS system was tested in a stand-alone mode by psychiatrists, psychologists, and medical residents at Necker university hospital.

Phase 3 [2017 – 2019]: Institutional endorsement and support from the regional public health agency in parallel with multi-centers deployment through the Assistance Publique des Hôpitaux de Paris (APHP) Intranet.

Phase 4 [2019 – Now] Strengthen applications' protection of patient private information before Internet deployment in mid-2019. Hosting new participating centers was facilitated but requiring data model evolutions to fit with local clinical practice [5].

2.2. TEDIS data

TEDIS ASD' patient inclusion is based on ICD-10' F84 class codes reported in the patient discharge summary. The main diagnosis points to the reason which mobilized the most of the medical, clinical and care resources. F84 class codes, may also be present in one of three associated diagnoses, referenced usually to enrich patient' medical characterization. A selection of patients of interest subsets, whose diagnoses are uncertain at the moment of the assessment and whose discharge summary include results of two out of three gold standard ASD' assessment tests², are included in TEDIS' cohort. The data production workload, followed the chronology of expert centers joining the study. Data quality was ensured by medical residents in phase 2 and in phase 3, then by the clinical research assistant. Main statistical descriptive analyses results are introduced in this paper. They are developed in R statistics software and integrated in an R-Markdown programs, adapted to the cohort evolution and growth.

² CARS: Childhood Autism Rating Scale; ADI-R: Autism Diagnostic Interview – Revised; ADOS: Autism Diagnostic Observation Schedule

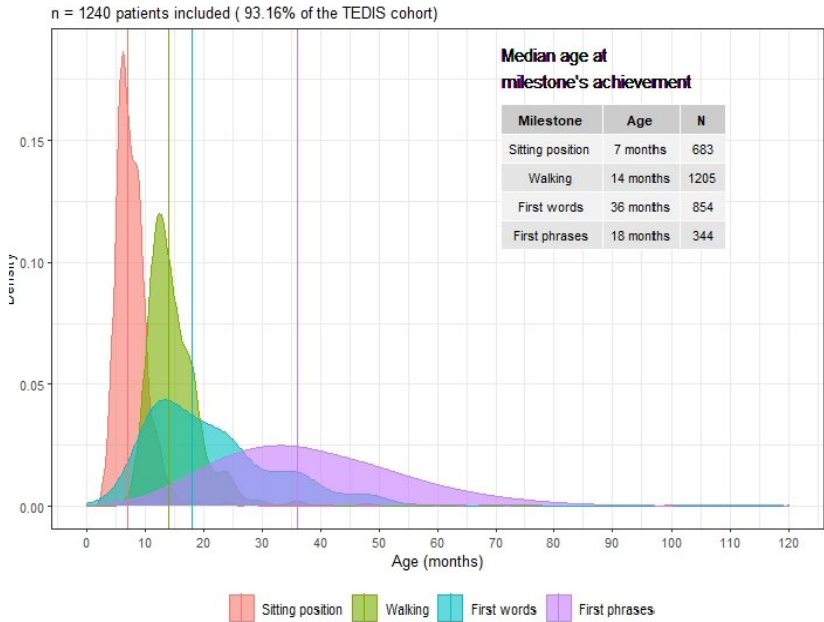


Figure 1. Motor and speech development ages distributions. Documented cases n=1240 with at least one out four information documented: Median age for sitting: 7 months old. Walking median age: 14 months. Median age at first words: 18 months, and median age at first phrases: 36 months old.

3. Results

TEDIS' cohort included as of January 20th 2023, 1331 ASD' patient records. Patients diagnosed with an F84 ICD-10 class code represent 90% of the participants. Patient ratio confirms the four males to one female and the median age of 5 years old for expert' ASD diagnosis. 1255 patients, reside in Ile-de France region. Most of the ASD patients belong to bi-parental family structures: 973 cases (73%). The mean father age is of 36 years old in 944 cases and the mean mother age is of 32 years old in 958 cases. Parents belong to all socio-professional categories, according to the national institute of statics INSEE, with a noticeable proportion of women without professional activity: 30% in both the bi-parental families and the 279 mono-parental families. There are no noticeable psychological difficulties during pregnancy period (18.7% cases) with 157 reported cases among women (including 73 cases of anxiety) and 65 cases including 8 anxiety situations among the fathers. Pregnancies were carried to term in 1024 cases (77%), and the birth parameters are in normal boundaries in the majority of cases (85%). The absence of language capacity is reported in 477 cases, mostly (92%) with F84 diagnosis. Motor and speech median acquisition age results are reported in Figure 1. First wording capacity acquisition age distribution in figure 1, shows the influence of the extreme values (120 months). Feeding and sleeping habits are reported in 726 ASD patient cases of ASD patients, with absence of disorder in 18% cases of sleeping and in 23% cases of feeding habits. Feeding selectivity is observed in 49% of cases and nocturnal awakening are observed in 29% of cases. Achieving toilet control mean age is about 39.1 months. Most of study ASD' patient population, 1163 cases, beneficiated from schooling, ambulatory specific health care and social measure, before ASD expert assessment.

ICD-10 codes distribution

n = 1311 primary diagnosis,
n = 601 secondary diagnosis 1,
n = 122 secondary diagnosis 2,
n = 19 secondary diagnosis 3.

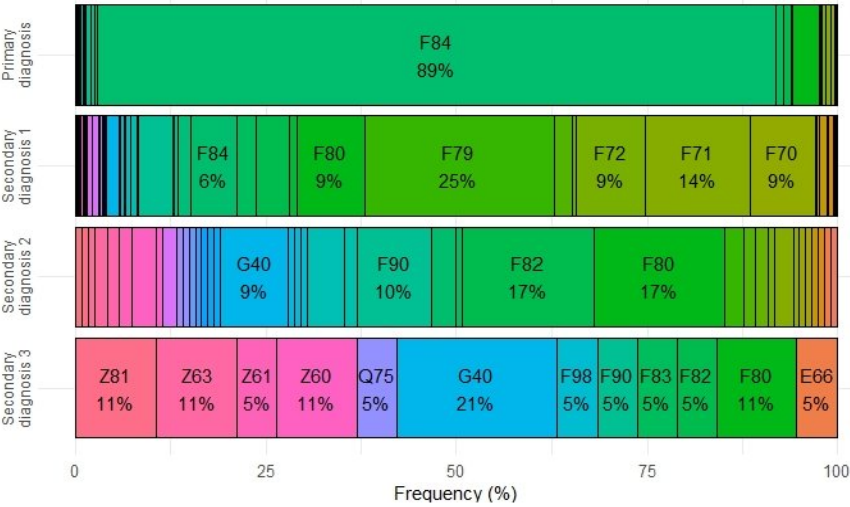


Figure 2. ICD-10 codes distribution in TEDIS' cohort. Documented cases n=1311.89% belong to ASD class coding class F84 for the main diagnosis. In the first associated diagnosis position, F7 class codes of intellectual deficiency represents 57%. In the second diagnosis position there is a mixture of attention deficit-hyperactivity disorders, speech and language disorders, epilepsy and seizures, while in forth associated diagnosis position, we find a mixture of neurological and developmental disorders.

Ambulatory care consisted mainly in speech (21%) and motor (21%) supporting measures and 56% benefited from social measures and handicap status recognition opening facilities for free public health care and social accompaniment.

Psychiatry and psychology assessment tests results are reported in 1233 (93%) cases. Reported cases are of 874 for ADI-R, 593 for CARS, 534 for ADOS and ADOS-2, wheschler scales : 221 reported cases. There are a mean of 2.7 Psychiatry and psychology assessment tests for each patient record. Figure 2, shows the main diagnosis dominance of the ICD-10 class codes F84, characterizing ASD' patients. Intellectual deficiency, attention deficiency-hyperactivity and neurological symptomatology are frequently present in ASD' symptomatology. TEDIS' cohort patient data specific subsets, already permitted six medical academic research works and publications in neuro-psychiatry. A similar number of methodological indexed articles were published in medical informatics communities. The presentations to the psychiatrics participating in the study cohort of the of data analysis automatic report were encouraging and motivating for pursuing feeding the cohort with the expert information of ASD patients' assessments.

4. Discussion

TEDIS cohort tries to keep up with daily practice in clinical settings. This objective is challenged by recurrent evolutions in ASD' medical codification and assessment criteria during the last decade, besides new versions of assessment scales and psychometrics testing and variations in assessment practice in the participating centers need. The partnership between clinicians and methodologists and the data quality control by the

clinical research assistant, try to guarantee development, evolution, and maintenance of a reliable data source. Building a structured data model is a long process. It offers however facilities for statistical quantitative and qualitative analyses, allowing rapid advances in producing research results. Participating psychiatrists adopted a governance schema with a steering committee and a scientific committee. A charter commits participants to the cohort study project and aggregated, de-identified patient data sets will be made available for researchers on demand, to be addressed to the scientific committee.

5. Conclusion

Building a reliable clinical data source for research and public health policies remains a challenge, involving domains experts and methodologists. Structured data modeling is helpful for rapidly advancing research and taking advantages from available statistical tools and capacities. Data quality control is evident in modern data source development. Governance and data sharing need to guarantee a safe use of the data with respect of ethics, privacy, scientific objectives, and benefits to the community.

Acknowledgement

Psychiatrists in the centers participating in TEDIS cohort study (TEDIS study group), are fully thanked for their support. The Centre Ressource Autisme Ile de France (CRAIF) and the Agence Regionale de Santé Ile de France (ARS-IDF) are thanked for supporting and funding TEDIS study ASD patient cohort.

References

- [1] Zeidan J, Fombonne E, Scorah J, Ibrahim A, Durkin MS, Saxena S, Yusuf A, Shih A, Elsabbagh M. Global prevalence of autism: A systematic review update. *Autism Res.* 2022 May;15(5):778-790. doi: 10.1002/aur.2696. Epub 2022 Mar 3. PMID: 35238171; PMCID: PMC9310578.
- [2] Hyman SL, Levy SE, Myers SM; COUNCIL ON CHILDREN WITH DISABILITIES, SECTION ON DEVELOPMENTAL AND BEHAVIORAL PEDIATRICS. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics.* 2020 Jan;145(1):e20193447. doi:10.1542/peds.2019-3447. Epub 2019 Dec 16. PMID: 31843864.
- [3] Ashwood KL, Buitelaar J, Murphy D, Spooren W, Charman T. European clinical network: autism spectrum disorder assessments and patient characterisation. *Eur Child Adolesc Psychiatry.* 2015 Aug;24(8):985-95. doi: 10.1007/s00787-014-0648-2. Epub 2014 Dec 4. PMID: 25471824.
- [4] Lord C, Charman T, Havdahl A, Carbone P, Anagnostou E, Boyd B, Carr T, de Vries PJ, Dissanayake C, Divan G, Freitag CM, Gotelli MM, Kasari C, Knapp M, Mundy P, Plank A, Scahill L, Servili C, Shattuck P, Simonoff E, Singer AT, Slonims V, Wang PP, Ysrraelit MC, Jellet R, Pickles A, Cusack J, Howlin P, Szatmari P, Holbrook A, Toolan C, McCauley JB. The Lancet Commission on the future of care and clinical research in autism. *Lancet.* 2022 Jan 15;399(10321):271-334. doi: 10.1016/S0140-6736(21)01541-5. Epub 2021 Dec 6. Erratum in: *Lancet.* 2022 Dec 3;400(10367):1926. PMID: 34883054.
- [5] Ben Said M, Robel L, Chaste P, Perisse D, Oreve MJ, Zylberberg P, Philippe A, Joussemme C, Lacoste S, Speranza M, Hafsa I, Cisse F, Cherqaoui Z, Jais JP. TEDIS, a Comprehensive Data Model for In-Depth Clinical Assessment of Patients Affected with Neuro-Developmental Disorders Including Autism. *Stud Health Technol Inform.* 2020 Jun 16;270:1401-1402. doi: 10.3233/SHTI200462. PMID: 32570679.