



**TITE: ESTABLISHING AN INTEGRATED DIAGNOSTIC  
PROFILE OF AUTISM SPECTRUM DISORDER (ASD)  
THROUGH THE USE OF ESSENCE FRAMEWORK.  
THE CASE STUDY OF A 3-YEAR-OLD INFANT**

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**Abstract:**

Neurodevelopmental disorders appear in early childhood and cause serious impairments in several areas. These are characterized by damages or delays in development of functions closely associated with the biological aging of the central nervous system. Neurodevelopmental disorders include speech and language disorders, learning disorders, motor and divisive disorders such as Autism Spectrum Disorder (ASD). Aiming to explore the various phenotypic characteristics of these disorders as well as their co-morbidity or coexistence, an emerging body of studies stressed the importance of both early multidisciplinary assessment and intervention in the framework of these disorders. Due to the complexity of neurodevelopmental disorders there should be specific diagnostic groups so as to apply timely and multifactorial diagnoses. Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) are considered as the assessment concept that could contribute to multifactorial early diagnosis of neurodevelopmental disorders. Early, adequate, and comprehensive diagnosis conduces to early, effective, and well adapted to individual's needs intervention programs. In the current study, the ESSENCE

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framework was used as the key diagnostic approach for both definitive and multifactorial diagnosis of a 3-year-old infant with a wide range of impairments.

**Keywords:** neurodevelopmental disorders, ESSENCE model, differential diagnosis, multifactorial approach, autistic spectrum disorder

## 1. Introduction

### 1.1 Complexity and coexistence of Neurodevelopmental Disorders. The Autism Spectrum Disorder (ASD)

Neurodevelopmental disorders are a group of conditions that usually manifest early in the developmental period, usually before the child enters primary school. They are underline developmental deficits that reflect personal, social, academic or occupational impairments (American Psychiatric Association, 2010).

Symptoms or indicators of Neurodevelopmental Disorders (NDD) involve problems within the overall development, motor coordination, perception, communication, language, impulsivity, attention, social interaction/reciprocity, behavior including insistence on sameness, tic and obsessive compulsive disorder, mood swings/emotional dysfunction and problems associated with sleep and/or the feeding (Bourgeron, 2016; Gillberg et. al., 2013; Sim, 2015).

At least 10% of children under the age of 18 are or have been affected by NDD, including among others, Attention Deficit Hyperactivity Disorder (ADHD), Autism Spectrum Disorder (ASD), Autism and Epilepsy, Behavioral Disorder (BD), Intellectual Disability (ID), Specific Learning Disabilities (SLD) and Developmental Coordination Disorder (DCD) (Ehninger, 2008).

An emerging body of literature suggests that the assessment of the early onset of NDD should focus on disturbances on structural and functional cerebral connectivity and/or network organization, in terms of the early diagnosis as well as the early re-education (Anderson, Miniscalco, Gillberg, 2014; Ball et al., 2017; Levy et al., 2009).

ASD is considered as a serious, complex and heterogeneous neurodevelopmental disorder with a distinctive structure of cognitive deficits, a range of clinical descriptions and a strong genetic substrate (Carlsson et al., 2013; Fernell, Eriksson and Gillberg, 2013).

The most common, as well as core, symptoms of ASD refer to impaired atypical or non-verbal communication and social interaction with others, reduced attention to salient social stimuli and facts and obsessive repetitive behaviors and activities (Bujnakova et al., 2016; Odriozola, 2016; Zilbovicious et al., 2006).

In several studies, (Carlsson et al., 2013; Levy et al., 2010) a strong coexistence between ASD and additional developmental disorders is well demonstrated, such as ID, ADHD (Frazier et al., 2001), Specific Language Impairment (SLI) (Miniscalco et al., 2006), SLD (O'Brien and Pearson, 2004), Epilepsy, behavioral and emotional disorders (Simonoff et al., 2008).

## 1.2 The approach of ESSENCE

Due to the aforementioned coexistence, in early stages of the development, it seems difficult to clarify the dominating disorder and/or to define certain and constant diagnostic profiles of developmental disorders. Thus, it becomes of high importance to apply broader assessments, exploring a wide range of symptoms and phenotypic characteristics, such as the concept of the Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) (Gillberg, 2010). ESSENCE framework concerns the entire group of neurodevelopmental/neuropsychiatric disorders which are presented with disabling symptoms in early childhood and include ADHD, ASD, Developmental Coordination Disorder (DCD), ID, SLI, Tourette's syndrome, early onset Bipolar Disorder (BD) and a variety of neurological disorders that occur with significant behavioral/cognitive problems at a young age. All these disturbances can usually coexist and therefore they are difficult to separate from one another during the early diagnostic evaluation (Bourgeron, 2016; Carlsson et al., 2013; Plenty et al., 2013).

ESSENCE represents a step as to alert clinicians and researchers to be constantly aware of the enormous variety of problems that arise in children, adolescents and adults with any kind of early onset neurodevelopmental problem. The treatment of the aforementioned disorders often includes a combination of professional treatment, pharmaceutical programs at home and at school-based programs (Gillberg, 2010). The causes included in ESSENCE range from severe social deprivation, genetic risk factors, metabolic diseases, immune disorders, infectious diseases, nutritional factors, physical trauma and toxic and environmental factors.

Accurate diagnosis is essential in the "time of ESSENCE", but diagnosing individual phenotypic symptoms is likely to be inaccurate and in most cases will need diagnostic reassessment over time.

Specifically, ESSENCE:

1. Is an acronym of thinking about early onset of childhood problems that continue to affect the development of children long after the preschool years.

2. Is introduced so as to reduce the current trend of separation of syndromes in child and adolescent psychiatry and developmental medicine in so far as Autism and ADHD are considered "boxes" which are entirely separable from each other.
3. Is a term that draws attention to the fact that there is no easy way to diagnose preschoolers which are presented with symptoms of ESSENCE. All children which are presented with a problem of ESSENCE must be examined in terms of multifactorial and interdisciplinary evaluation.
4. Children assessed by ESSENCE receive a holistic approach, from diagnosis to treatment. If an infant presents ASD, it is likely to present ADHD, language delay and other disorders, too. The approach to diagnosis may not contribute if the goal is solely to the diagnosis of a discrete entity.
5. The coating of the problems encountered in ESSENCE refers not to the existence of distinct disorders or syndromes, but mostly to brain/neuro multifunctions, reflecting collapse or malfunctioning of the brain network; decreased, abnormal or increased connectivity or even in many cases, normal function of brain variants. Therefore, it would be inappropriate to seek for a diagnosis of a separate problem without considering any potential connectivity with other coexisting problems (Gillberg, 2010; Gillberg et al., 2013).

In the light of the above, the present study attempts to:

1. investigate the complex and multifactorial entity of ASD, exploring dysfunctions of more than one biological, neurological, cognitive, and psycho-emotional factors;
2. test the hypothesis that ASD coexists with other developmental disorders;
3. recommend the effectiveness of a holistic interpretative model of early-stage diagnosis of neurodevelopmental disorders as the ESSENCE concept demonstrates.

## 2. Case report

In the current paper, we present the case study of K. a 4year-old boy with reference to severe psychomotor retardation. Aiming to an accurate diagnosis as well as an effective intervention, a multivariate and multidisciplinary diagnostic process was used including a crowd of examinations.

The following evaluations were performed (see Supplement Table 1):

### I. Laboratory Evaluation:

- **Neuroimaging evaluation:** *Magnetic Resonance Imaging (MRI) of Brain:* on the medial surface of the left temporal lobe a cystic formation was identified of

the following dimensions: 13.4 mm height, 16.6 mm width and anteroposterior diameter of 25 mm. The formation, in all sequences, presented signal intensity similar to that of the cerebrospinal fluid with illustrative features of an arachnoid cyst. The bladder was in contact with the left parahippocampalis proeller causing mild pressing effects. No other mass lesions were revealed in cerebral hemispheres, while at the periventricular white matter attached to the occipital horn bilaterally, minor increased signal intensity area was observed on T2-weighted sequences of symmetrical distribution. The brainstem and cerebellum emerged without evidence of relocation of the midline or dilatation of the ventricular system and with absence of bleeding elements in the T2 sequence. The fate of the intracranial optic nerve, optic chiasm and the area of sella turcica were visualized without pathological findings. Similarly, the ocular bulbs and oculomotor muscles were controlled, with normal morphology and symmetrical size.

- *Ultrasound Colon-abdominal and retroperitoneal space:* liver dimensions and ichomorfologia were in normal range. The gallbladder was found contorted because of food intake, but no pathology was detected. The spleen was also controlled in normal position with normal for the age of the examinee measuring.
- *Ultrasound kidney-bladder:* The intrahepatic and extrahepatic cholangia were pointed with normal morphology and range as well as the kidneys were of normal size, shape with smooth edge of their contour and ichodomi, in regard to the age of the examinee. Dilatation of renal pelvic cavitation was not observed kidneys. Moderate filling of the bladder did not bring clear pathology existence in it.
- *Thyroid testing:* normal thyroid stimulating hormone (TSH) was measured.
- *Echocardiographic evaluation:* normal position viscera and heart chambers. Additionally, it was localized the presence of a small atrial communication into the foramen oval level without hemodynamic burden.
- *DOPPLER (PW-CW-colored) evaluation:* instantaneous maximum systolic pressure of the right ventricle (RVSP = 25 mmHg). The function of the diastolic left ventricular was within normal limits.
- **Genetic Evaluation:** *Cytogenetic analysis:* in peripheral blood sample, 28 metaphases from two cultures of peripheral blood lymphocytes stimulated with phytohemagglutinin, were studied. The analysis figured out a karyotype composed of 47 chromosomes and XY sex chromosomes. Furthermore, in all metaphases a supernumerary chromosome, Extra Structurally Abnormal

Chromosome (ESAC-marker) was identified. The conclusion drawn is that the karyotype is 47, XY, + mar.

- *Molecular karyotype analysis (comparative genomic hybridization array- CGH):* the finding of witness of Hybridization Promega male ref. G147A indicates the occurrence of psychomotor retardation (Friedman et al., 2006; Vermeesch et al., 2007). The molecular karyotype analysis lead to the following:
  - a. In the 15q11.1q13.2 genomic region a 10.3 Mb doubling was observed. Doublings in this genomic region have been associated with phenotypes of psychomotor delay and neurodevelopmental/autism spectrum disorders (Kitsiou–Tzeli et al., 2012; Marini et al., 2013).
  - b. The remaining areas of micro-defects and micro-duplications identified through the technical array CGH (AGILENT 4X180K) include CNPs (polymorphic copy number sequences) typically observed in general population without being associated with pathological phenotype so far, internationally (Kidd, 2010).
- *Molecular control using DNA analysis:* (probability of Carrier Spinal Muscular Atrophy (CSMA): the absence of homozygous or heterozygous deficiency in exons 7 and 8 of SMN1 gene eliminated the appearance of SMA Carrier with effect to safety about 92%.
- **Auditory evaluation:** *Transient evoked otoacoustic emissions:* Transient evoked otoacoustic emissions were released bilaterally. *Tympanogram:* The tympanogram did not reveal any findings because of liquid location in one of the two ears. In regard to the auditory perception, he observed around him when a sound was produced and he was accurately oriented towards the sound source, while he did not directly react on hearing his name and did not understand verbal instructions.
- *Blood tests and urine tests:* In regard to blood tests, the child did not face any metabolic disease.

## **II. Clinical Evaluation: involved physical examination, history taking and clinical observation:**

- *Full physical examination:* emphasis was given to the morphological evaluation (head shape and circumference, hair line, ear shape, eyebrows and eyelashes morphology, auricle shape anomalies, cleft lip/ palate, palate shape, teeth formation, palm lines, extremities anomalies, thoracic cavity shape) targeting to detect phenotypic abnormalities

In addition, an extensive neurological evaluation took place (irritability, lethargy, muscle tone and strength evaluation, reflexes evaluation, superficial and deep sensation

evaluation). The findings included the following: extrusion of the tongue, mouth open and hypotonia resulting in the appearance of salivation. With intervention by orofacial exercises, salivation and hypotonia of his mouth had been quite reduced. Also, weakness occurred in chewing; he did not chew well and the lateral movement of the tongue was absent, while he consumed all food pureed.

History: Through the Family History no chronic neurological and psychotic disorders such as LD, Epilepsy, MR, ASD, ADHD, neural tube defects, Down's syndrome, defects of the extremities were observed.

- *Clinical observation and developmental history:* common psychiatric examination in all the developmental sections using clinical interview, observation of child's behavior and stimulus responses were applied. The case occurred psychomotor retardation in all areas with possible pervasive developmental disorder. In regard to the speech and language development and academic performance, the case presented a delay in his speech. He displayed inability to speak and to communicate even with meanings. In regard to the social integration and interaction he had developed a social smile, keeping the eye contact; he was usually pleased and he was laughing when someone spoke to him without displaying attachment to his mother as he spontaneously hugged others. He had developed permanence of the object trying to find the concealed object, even though he would not dwell too long if he did not find it. Gradually, he began to mimic movements, such as clapping or to participate in fun game "kou kou - cha." However, K. did not participate in pretend play or imitate other adult movements (taking off his tongue, showing his eyes, nose, etc.). Furthermore, he was not able to put a round object in a round slot unassisted. With regard to the keeping, K. up to 2.6 years used to throw away after a few seconds any object he was clutching, while now he has managed to hold an object for a longer period, to put it into a socket as well as to put plastic cups one inside another, without throwing them. The kind of his participation in an interactive game was limited to pushing a toy car or throwing a ball. He used to turn pages of hard musical children's books and press-in random-buttons in sounds games. In regard to the visual perception, he was following with his eyes the movement of an object. As for the motor coordination and fine motor, a small volatility was observed in his walking, a slight slope of his head to the left side, a great sensitivity to tactile stimuli, and repetitive movements with his hands. Finally, K. has not yet acquired sphincter control.

### 3. Discussion

#### 3.1 Interpreting the data

As it is well documented (Buxbaum and Hof, 2013), the heterogeneity of ASD makes difficult to draw comprehensive, definite clinical profiles.

Taking this argument into account, the accomplishment of targeting a definite diagnosis for the case's disorders to be established, was sought through the analysis of genetic, neuroimaging, medical, and phenotyping measures.

To prove the above, all the findings emerged from each evaluation, were analyzed and interpreted, as following:

I. The findings of the cytogenetic analysis about the alterations of the karyotype regarding the composition of XY sex chromosomes and the inclusion of 47 chromosomes rather than 46, were consistent with results supporting that similar expressions of karyotype are more likely to appear in boys rather than in girls, who are at risk to develop autism (Bonilha et al., 2008; Donna & Geschwind 2013; Halladay et al., 2015).

In line with the above, the finding that the supernumerary chromosome proceeded from the chromosome 15 as observed a doubling in genomic region 15q11.1q13.2, is associated with phenotypes of psychomotor delay, and neurodevelopmental/ASD (Marini, Kitsiou- Tzeli, 2012).

Similar expressions were reported by Coriell Institute referring to two cases ([https://catalog.coriell.org/0/Sections/Search/Sample\\_Detail.aspx?Ref=GM20562](https://catalog.coriell.org/0/Sections/Search/Sample_Detail.aspx?Ref=GM20562)):

i) a 18-year-old Caucasian girl with a phenotype of moderate cognitive impairment, seizures, autism and doubling with native origins (Tang, 2013; Wang, 2004). The girl was subjected to karyotype analysis, through which a karyotype 47 XX was found as well as a doubling in genomic regions 15q11.1q13.2 and 15q13.2q13.3, ii) a 2-year-old girl from the US and ethnicity from Japan, Germany and Ireland. Through molecular karyotype analysis karyotype 45 XX was found as well alterations in genomic regions 15q11.1q13.2 and 15q14. The girl was clinically affected by Prader-Willi syndrome which was associated with autism, due to a non-balanced translocation including the chromosomal regions 10p and 15q. Symptoms began at birth and she was diagnosed at the age of week one since birth. She faced up feeding difficulties and she was fed by means of gastronomy tube. There were even early onset kyphoscoliosis, hypotonia of the trunk, soft thick saliva, right occipital plagiocephaly, seizures and developmental delay.

However, the literature indicates that duplication of the 15q11.1q13.2 genomic region on chromosome 15 being associated with autism is almost negligible although



short genomic regions have been associated with autism (Finucane et al., 2016; Urraca et al., 2013).

Interestingly, it was reported that there is a contiguous gene syndrome in duplication of chromosome 15q11-q13 region (Kalsner and Chamberlain, 2015). The area 15q11- q13 is also implicated in Angelman syndrome and Prader-Willi syndrome. The characteristics of the chromosomal duplication syndrome in 15q11-q13 region include autism, mental retardation, ataxia, seizures, developmental delays and behavioral problems (Bundey et al., 1994; Burnside et al., 2011).

Furthermore, Baker et al. (1994) reported two patients with autistic disorder associated with doubling in the region 15q11-q13. Wolpert et al. (2000) reviewing previous reports of people with autism and abnormalities of 15q region, estimated that there may be additional findings in these patients, including hypotonia, seizures, delay in motor milestones and mental retardation.

Filipek et al. (2003) reported two cases of children with autism who had inverted duplication of the genomic region 15q11-q13. Both children had normal perinatal course, normal EEG and MRI scans, moderate kinetic retardation, severe hypotonia and moderate lactic acidosis. A number of applied evaluations and tests in both children confirmed that the candidate gene locus for autism in the critical region on chromosome 15 can affect pathways that in turn affect mitochondrial function.

In addition, Thomas et al. (2003) reported three families with an intermediate duplication (15q11-q13), two of which demonstrated maternal inheritance. Affected individuals had minor defects and developmental delay and 4 out of 5 children tested or meet the criteria for a diagnosis of autism or were in "autistic spectrum".

On the other hand, Miller et al. (2009) examining five patients, including two brothers with micro-duplication on chromosome 15q13.2-q13.3, identified a series of comparative genomic hybridization (CGH). Four of the five patients were diagnosed with autism. The fifth showed repetitive behaviors and expressive language delay. Two other patients also presented severe delays in expressive language. Three patients, including two siblings, inherited one copy from a seemingly unaffected mother.

Additionally, Orrico et al. (2009) reported a 33-year-old woman with severe mental retardation and hypotonia, poor motor skills, stereotyped movements, irregular breathing, speech absence and severe seizures associated with micro-duplication in the genomic region 15q11-q13. Although the early growth and development in general were normal at the age of 2.5 years, she showed developmental delay, progressive cognitive and behavioral discount. Learning and communication difficulties proceeded to aphasia, poor motor coordination, reduction in social interaction as well as repetitive stereotyped hand movements. She was diagnosed with pervasive developmental

disorder, although a variant form of Rett syndrome was suspected. Often, she had bouts of suffocation followed by apnea. At the age of 13, the patient could no longer speak and motor while communication skills were further reduced. She had mild dysmorphic features including palpebral fissures, broad nasal bridge, Mongolian aspects eyelid and wide mouth with full lips. The MRI showed hypoplasia of the corpus callosum and moderate cortical atrophy. The comparative genomic hybridization array-CGH detected a 4-Mb duplication of 15q11.2-q13.1 region.

Also, Bonati et al. (2005) not only reported a doubling in the chromosome 15q11-q13 but they, also, presented evidence pointing to a more distal region of 15q that had a role in autism: in the case of a male child with autistic disorder, postnatal overgrowth, and a slight malformation of the brain, the analyses of karyotyping and FISH test showed the presence of an extra copy of the distal portion of 15q.

It is notable that the remaining areas of micro-deletions and micro-duplications identified through the cytogenetic analysis of the case, include polymorphic copy number sequences (CNPs) that are even observed in normal population or they are not associated with internationally pathological phenotype so far (Vermeesch et al., 2007).

**II.** An essential finding that could positively explain the autistic characteristics of the child is the cyst detected by the imaging resonance imaging (MRI) on the inner surface of the left temporal lobe.

This cystic formation had the same characteristics of an arachnoid cyst. The arachnoid cyst is a benign membrane around the brain and sometimes this membrane is folded and forms a cyst containing cerebrospinal fluid (Logan et al., 2016; Mondal, 1995)

As recorded in the MRI evaluation, this cystic formation had the same intensity as the cerebrospinal fluid which is justified by the existence of cerebrospinal fluid within the arachnoid cyst and similar features with the arachnoid cyst. Also, the arachnoid cyst occurs mainly in the temporal lobe, just as in our case (Helland and Wester, 2007).

In some cases, large arachnoid cyst causes headache, dizziness, epileptic episodes and other neurological problems like weakness in the arm or leg and difficulty in speaking (Proimos et al., 2014; Raeder et al., 2005; Wester and Hugdahl, 2003). In the current case, the severe motor problems observed in the speech therapy evaluation and related to the autistic symptoms, may visibly be attributed to the arachnoid cyst that causes neurological problems such as difficulty in verbal communication. Although problems in the movement have been found to be caused due to spinal muscular atrophy (Lunn and Wang, 2008; D'Amico et al., 2011), in this case of K. the disabled

movement was not reflected from spinal muscular atrophy as the conducted examination of molecular control eliminated the possibility for SMA Carrier.

The arachnoid cyst detected in the left hemisphere, seems to be responsible for the language development, strengthen the relation of the above findings with autism: the case's speech delay and inability to communicate with gestures, are in accordance with the DSM -IV diagnostic criteria of autism. Of note, Tunguay (2011) has documented damages localized in the left hemisphere of the brain of children with autism, explaining the language disorder and speech delay. It therefore seems that the views of Tunguay are consistent with the results of other studies, which have found that most children in the autism spectrum had impaired left hemisphere (Catani et al., 2016; Perkins et al., 2014; Rojas et al., 2002).

Most specifically, a remarkable observation is the location of the cyst in the left temporal lobe, which is considered (Kiernan, 2012; Mizuno and Takeda, 2009; Pertzov et al., 2013; Squire et al., 2004) as responsible for mood, motivation, decision processing, hearing, vision, memory, comprehension, and receptive language (Zilbovicius, 2006). The receptive language is associated with the Wernicke area, located at the upper temporal region (Bigler et al., 2007; Jou et al, 2010). In a series of studies (Bachevalier, 1994; Bauman & Kemper, 2004; Koyama, 2005), autism was associated with structural abnormalities in the Wernicke area, superior temporal gyrus and hippocampus (Nielsen et al., 2014; Williams, 2007).

Consequently, the damages to the left temporal lobe could potentially be linked with the inability of the case to perceive auditory instructions and not respond to the sound of his name (Dinstein et al., 2010)

As it becomes obvious, these findings meet the diagnostic criteria of ASD (DSM-IV) (see Supplementary Table 1) (APA, 2000).

Additionally, the MRI showed that the bladder caused slight pressure in the parahippocampalis propeller. The limbic system consists of a set of cortical and para cortical brain structures with main functions emotions, autonomic responses and long-term memory (Swenson, 2015; Rajmohan and Mohandas 2007). Among the structures are the amygdala, the hippocampus, the parahippocampalis propeller, the cingulate gyrus, the chamber, the hypothalamus and the nucleus accumbens. In several studies, the limbic structures of amygdala and hippocampus were associated with autism (Aylward et al., 1999).

Similarly, to the above statements, it became obvious that the finding of the pressure which exerts the bladder to parahippocampalis propeller could be typically implicated in ASD.

Moreover, in his survey, Courschense (2004), using MRI in individuals with autism, he identified structural abnormalities in the cerebellar, leading to the assumption of a possible relation between cerebellar and ASD.

Interestingly, in the case of K., the MRI illustrated the cerebellum without any alterations in size or any abnormalities in its morphology. A finding that seems to contribute rather to a more general understanding of the variety of structural abnormalities that are related to autism than to confirm or exclude any abnormalities in specified brain regions related to autism (Adolphs, 2003; Hadjikhani et al., 2005; Gendry Meresse et al., 2005; Levitt et al., 2003; Ohnishi et al., 2000; Zilbovicius et al., 2000).

Equally positive were the findings related to the brainstem, as no abnormalities or changes in overall size were recorded. Also, no other pathology was found in regard to vital activities controlled by brainstem system, like metabolism, blood oxygenation, heart rate, respiration, pulse, breathing, consciousness, and sleep (Bujnakova, 2016; Porges and Furman, 2011; Goodwin et al., 2006; Jou et al., 2013)

Over the last decade, it becomes widely accepted that abnormalities in the brainstem cause significantly impaired sensory modulation, emotion/behavior regulation, under reactivity and/or over reactivity to sensory stimuli that are occurred in autism (Bauman & Kemper, 2005; Delafield-Butt & Trevarthen, 2017; Panksepp, 2005; Rodier, 1996; Tucker, Luu and Derryberry, 2005; Welsh, Ahn, and Placantonakis, 2005).

However, the brainstem images do not seem to confirm that the impairments of motor coordination or autonomous manual and oral movements that the case meets are caused by the brainstem. In essence, this finding becomes in line with reported (Jou et al., 2013) arguments about the brainstem's relationship to autism pathophysiology (see Supplementary Table 2).

**III.** A noteworthy finding pointed out through the history and clinical observation of K., is the consistent series of impairments in language development that were initially attributed to SLI rather than ASD (Bishop, 2006; Bishop and Norbury, 2002). The most common features of SLI that K. meets, are the following: early speech delay up to 2 years (Ullman & Pierpont, 2005); poor symbolic play and social imitation (Kent, 2004); impaired auditory perception (Henry et al, 2011); non language problems such as movement disorders, included in the phenotypic characteristics of SLI (Ullman et al, 2005). However, it is wide believed that SLI is not accompanied by other disorders, such as mental retardation, hearing loss, autism, motor dysfunctions and neurological or psychological disorders (Bernstein and Tiegerman-Farber, 2009; Livaniou, 2004).

Is it therefore, a strong evidence of a coexistence between SLI and ASD or a wide range of phenotypic characteristics of ASD? The relationship between autism and SLI is ultimately closer than we thought a few years ago and requires an in-depth evaluation

in order to arrive at a more accurate diagnosis (Taylor & Whitehouse, 2016; Tomblin, 2011).

### **3.2 Defining the case's clinical profile**

The analysis and the translation of the findings as they were emerged in the areas of neurobiological development (including genetic components, structural alterations with relative dysfunctions), cognitive, communication and interrelatedness, mood, language and behavior, mainly reflect the diagnostic criteria for ASD (Buxbaum and Hof, 2013; Coleman and Gillberg, 2012).

An additional issue raised to be explored in the current case, was the coexisting of ASD with language impairments; the core questions have been stated were with regard to the definition of the phenotype both of the two impairments, their relative causal factors, and the use of language in social communication and interaction (Miniscalco et al., 2006; Tager-Flusberg, 2003). In essence, we tried to test the hypothesis whether these language impairments constitute the distinct profile of SLI or be structural features of ASD.

Through the detailed evaluation of the etiology and the descriptions of the case's impairments, it was concluded that ASD phenotype was the dominant one, while the language impairments were rather considered as an included affected area in ASD, than a display of SLI as a coexistent disorder to ASD.

## **4. Conclusions**

In line with the current literature (Carlsson et al., 2013; Fernell et al., 2013; Gillberg et al., 2013) the findings of the current case study interestingly established the following significant observations:

- i. The co-evaluation of the omissions occurred in several developmental domains and functions affected in ASD is considered as fundamental for a definite diagnosis and effectiveness intervention of ASD
- ii. Both the complexity and the variety of phenotypic descriptions of ASD indicate that multidisciplinary as well as multifactorial assessments and measures are needed
- iii. The multi-variations of the phenotypic characteristics of ASD mirror high peaks of abnormalities in different endophenotypic areas
- iv. The above diversity usually becomes the reason for the dominating impairment not to be clear or the core symptoms to be misinterpreted and/or to be concealed

- v. Several disorders overlap to a large extent or coexist with ASD, specifically in their early onset. As a result, a deep and continuous analysis of phenotypic descriptions is demanded.

This case study suggests further work using larger samples with ASD in order to clarify and establish all the potential connections between neural mechanisms and behavior domains, translating the prevalence of ASD.

### **Acknowledgements**

Our thanks are due to the infant's family and clinicians, who provided us with all the relative information.

### **Conflict of Interest**

Neither of the authors had no conflicts of interest during the development and publication of this paper.

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## Supplementary Tables

**S. Table 1:** Summary table of the causal factors and the findings in the case study

Tests	Causal factors	Findings
Cytogenetic control	Duplication in the genomic region 15q11.1q13.2	Autism (failure or delay in development, mutual impairment in reciprocal social interaction, qualitative impairment in communication)
MRI	Arachnoid cyst	Unable to move the hands and feet Unable to communicate
MRI	Damage in left hemisphere	Delay in speech Inability to speak. Unable to speak with meanings
MRI	Damage to the temporal lobe	No perception of acoustic instructions
Speech therapist, Occupational therapy and psychological assessment	_____	Stereotypical movements such as flights of  Unable to participate in pretend play  Weakness in mimicking other adults movements  Delay in speech  Inability to speak with meanings  Weakness in chewing, eating all his food pureed  No perception of acoustic instructions  Some instability in walking, slight tilt of the head to the left side  Unable to catch stationery  Salivation
Ultrasound kidney - bladder	_____	It is recommended retesting due to maximum transverse diameter of the pelvis of the left kidney 4mm (in the upper limit of normal)
Molecular control	_____	Shows no likelihood of Carrier SMA
Measurements of thyroid	_____	Normal

hormone		
Echocardiography	_____	Normal
Otoacoustic emissions	_____	Normal
Tympanogram	_____	It is recommended retesting because of presence of liquid in one ear
Blood tests	_____	Does not display a metabolic disease
fMRI	_____	Did not take place
Electroencephalogram (EEG)	_____	Did not take place
Diagnostic tests of Mental Plane	_____	Did not take place

**S. Table 2:** Autism diagnostic criteria according to DSM-IV, ESSENCE and case's phenotypic descriptions

Criteria of DSM-IV	ESSENCE criteria	Findings
Deficiency in the use of multiple nonverbal behaviors such as eye contact, posture, facial expression and gestures to regulate social interaction	Communication problems	Unable to speak with meanings
Failure in the growth of equitable relationships responding to his developmental level	Disturbances in social interaction	There are no findings
Stereotyped and repetitive motor mannerisms (e.g., hitting or bending of the hand or finger, or complex whole-body movements)	_____	Movements of hands
Lack of spontaneous effort to share enjoyment, interests or achievements with other people (e.g. failure to indicate, affix or points of interest issues).	_____	There are no findings
Lack of varied, spontaneous play a role play or social imitative play, responding to his developmental level	_____	Inability to engage in pretend play and to imitate movements of other adults
Delay or total lack of spoken language (not accompanied by replenishment effort through alternative modes of communication such as gestures or imitation)	Problems in language	Unable to speak, delay in speech
Unable to start or continue a conversation with other people (people with speech)	_____	There are no findings
Stereotyped and repetitive use of language or idiosyncratic use of language	_____	There are no findings
Lack of social or emotional reciprocity	Emotional dysfunction	There are no findings
Intense preoccupation with one or more stereotyped and restricted patterns of interest	Behavioral problems including the insistence	There are no findings

that is abnormal either in intensity or in focus	on similarity	
Apparently inflexible adherence to specific, non-functional routine acts or rituals	obsessive-compulsive disorder	There are no findings
Persistent preoccupation with parts of objects	Behavioral problems including insistence on sameness	There are no findings
_____	Coordination of movements	There are no findings
_____	Perception	Weakness in perception on hearing his name, weakness in perception of verbal instructions
_____	Problems related to sleep and / or feeding	Weakness in chewing, he eats all food pureed
_____	Impulsiveness	There are no findings
_____	Attention problems	There are no findings
_____	Disorder in coordination of movements	Small unstable gait, slightly tilted head to the left side, fails to catch stationery



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