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Phelan-Mcdermid Sydrome (PMS) and Autism Spectrum Disorder (ASD): A Case Report

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Abstract **Case Report**

We report a case of a 4 years old boy, presented for the first time in pedopsychiatric consultation for communication and social interaction disorders with a psychomotor and language delay, associated with an organic symptoms manifested by a left renal hypoplasia, a postural-motor hypotonia and a internal rotation of the right foot, after multiple examinations the diagnosis of AUTISM SPECTRUM DISORDER was made, but further investigations revealed a PHELAN MCDERMID SYNDROME as well, so Are these psychiatric manifestations related to Phelan-McDermid syndrome or is it a comorbidity between this to pathologies?

Keywords: pedopsychiatric consultation, psychomotor, psychiatric manifestations, Phelan-McDermid syndrome.

1. INTRODUCTION

The Phelan-McDermid syndrome (PMS), also known as 22q13.3 or 22qter microdeletion syndrome, was described in the medical literature in 1985 by Dr Katy Phelan.

It is a rare disease of mainly neurodevelopmental expression whose incidence is poorly known. It is estimated that the rate of 22q13.3 deletions is about 0.27% of patients with neurodevelopmental disorders [1].

In cohorts of patients with autism spectrum disorder (ASD), the rate of 22q13.3 deletions is reported to be 0.18%, that of SHANK3 mutations 0.51% [1].

The syndrome affects both girls and boys. The heterogeneous phenotype associates a marked hypotonia, a shift in psychomotor acquisitions most often revealing an intellectual deficiency of variable severity. In addition to that, disorders in the acquisition of oral language is frequently observed ranging from a more or less severe shift to a total absence of language. An ASD is present in a large majority of patients [2].

Other disorders may be associated, in particular epilepsy, digestive disorders (gastroesophageal reflux disease (GERD), transit disorders), but also ophthalmological, renal, cardiac, endocrine, orthopedic or vascular disorders. There is no pathognomonic clinical sign of the syndrome and despite the evocative picture, It is hard to make a diagnosis on clinical elements alone [3].

Therefore, our work proposes to corroborate these reported cases by presenting a clinical case of Autism Spectrum Disorder revealing Phelan-McDermid syndrome in a child.

2. CLINICAL CASE

S. M is a 4 years old boy, only son, from an unrelated marriage. The interview reveals a personal history of neonatal jaundice at 24 hours of life for 5 days, regressed spontaneously without recourse to phototherapy with the notion of unilateral left renal hypoplasia revealed on ultrasound at 28 SA; no other surgical history, nor similar case in the family.

SM's pregnancy and delivery were uncomplicated. The psychomotor development is characterized by a delay in the acquisition of walking until the age of 22 months, yet unstable following the persistence of a postural-motor hypotonia associated with a right foot in internal rotation.

Concerning the development of language; it's often limited to a few sound vocalizations. As for cleanliness, both daytime and nighttime are not yet acquired. SM also had facial dysmorphia.

S. M entered the kindergarten at the age of 3, but stopped after 2 months due to his psychomotor instability. S. M first consulted a child psychiatrist at the age of 4 years for a communication and social interaction disorder.

The history of the disorder goes back to early childhood with an overexposure to screens (TV) from the age of 4 months at a frequency of 4 hours/day, until the age of 8 months.

The parents first concerns were around the age of 18 months, the child did not respond to the call of his first name and did not maintain eye contact as well as a total absence of language (S.M. was not able to verbalize any words).

S.M consulted a speech therapist for the first time at the age of 2 years, where he had benefited from a few speech therapy sessions. In view of the non-improvement of the clinical picture, the patient was referred to the child psychiatry department for specialized care, from where a hospitalization was indicated for diagnostic evaluation.

During his hospitalization, which had lasted 4 months in total, the patient had been evaluated individually and also in the presence of the parents; which highlighted a separation anxiety during the first 2 weeks of hospitalization, lasting 10 to 15 min; consolable by the nursing team.

The child was restless with moderate psychomotor instability and was not standing still, with an apparent gait disorder.

The verbal communication is characterized by an absence of language with the presence of vocalizations. Impaired social interaction and non-verbal communication. S.M did not return calls, or stare, respond to requests neither share his desires or interests with peers. but he understood simple instructions.

The stereotyped behaviors were mainly manifested by jumping on the spot, hand flapping and spinning on himself.

Concerning the observation of S.M in free play and directed activities and therapeutic workshop; S.M was playing alone, he had no concept of sharing, symbolic and functional games were not acquired.

During meals: S.M always needed help, didn't hold the spoon correctly, he didn't have food selectivity but had difficulty chewing and swallowing.

The patient also benefited from the use of various standardized scales such as the Autism Diagnostic Interview Revised (ADI) where the child scored in all 3 domains: Communication, Social Interaction, and Repetitive Behaviors and Stereotypic Patterns as well as the Childhood Autism Rating Scale (CARS) where the child rated between moderately and severely autistic. The child had also benefited from a speech and psychomotor assessment and rehabilitation.

The speech and language assessment revealed a language delay with vocalizations as well as the absence of use of words or sentences.

And in the psychomotor assessment, r an overall delay in psychomotor development that is expressed in several areas: gross motor skills; fine motor skills; interaction and communication; body schema; graphism; visuo-constructive ability and imitation ability, was revealed.

In addition to that, a paraclinical assessments for diagnostic and therapeutic purposes was requested, consisting of: Complete biological workup (CBC, thyroid workup and a BHE) with no abnormalities; an electrocardiogram along with a normal cardiac consultation, a brain MRI showing no abnormalities, a normal electroencephalogram and an electroneuromyogram revealed normal as well as a normal auditory evoked potential (PEA) (threshold at 20db).

The patient was then referred to the genetics department for diagnostic exploration and management, the patient had undergone several checkups: Standard karyotype with normal income (46 XY) in adition to a Postnatal constitutional karyotype: DNA ANALYSIS shows a terminal deletion at 22q13.31q13.33 carrying the SHANK 3 gene: this type of deletion is associated with Phelan-McDermid syndrome. A Genetic counseling and parental investigation were planned afterward.

S.M was also referred to the otolaryngology department for follow-up and management of his swallowing disorder as well as the orthopedic departement to check his internal rotation of the right foot.

The psychiatric follow-up as well as the speech and psychomotor rehabilitation were regular, the patient always attended the appointments.

The evolution was marked by an improvement of the non-verbal communication: returns to the call of his first name by moment, fixes the glance as well as a light improvement of his psychomotor instability.

3. DISCUSSION

The child S.M**.** presented for the first time in consultation for communication and social interaction disorders with a psychomotor and language delay (criteria A: 1, 2, 3, and B 1 of the DSM-V of ASD).

The diagnostic workup in front of this clinical picture revealed a Phelan-McDermid syndrome (PMS**)** associated with an ASD picture.

Faced with this case, two questions arose: is it a comorbidity or is it a child psychiatric symptomatology secondary to PMS?

3.1 Genetic Generalities:

Phelan-McDermid syndrome (PMS) is most commonly linked to a deletion of the terminal part of the long arm of chromosome 22, 22qter or 22q13.3 covering the SHANK3 gene. Since the advent of high-throughout sequencing techniques, structural variants of the SHANK3 gene are increasingly reported. The relationship between the genetic anomaly itself and the phenotype of the patients is not yet clearly established but several data seem to be supported by different studies.

The 22q13.3 Deletion:

a. Isolated Deletion:

Their size is variable (without recurrent breakpoint) ranging from a few kilobases to several megabases. They may involve only the SHANK3 gene, in part or in whole. Depending on their size, the number of genes involved in the deletion increases. Large deletions are associated with a more severe phenotype, including the more frequent presence of associated disorders. In particular, severe language disorders are linked to the deletion of a region located upstream of SHANK3 [4].

b. Deletion Associated With A Duplicated Segment Of Another Chromosome

These alterations occur as part of de novo translocations or as a result of mis-segregation of a balanced parental translocation. The duplicated segment can modulate the phenotype depending on the genes involved.

c. Deletion Associated With An Adjacent Duplicated Segment On Chromosome 22

This more complex chromosomal abnormality may also be correlated with a more severe phenotype. The mechanism of occurrence of this anomaly is essential to determine as it may guide family genetic counseling.

3.2 Initial assessment and search for associated disorders:

Due to the clinical heterogeneity of the syndrome, many presentations are possible. The initial clinical examination by a geneticist, a child psychiatrist and/or a neuropediatrician must first detail the anamnesis and the family context. It must detail the physical examination (morphological, neuromotor, osteoarticular...) as well as the search for dysmorphic elements. As well as an evaluation of cognitive functioning, interactions and language to help clarify the diagnosis.

In the literature, apart from visceral, cerebral (MRI) and neurological manifestations (such as epilepsy, which occurs in 17 to 70% of cases), other neuropsychiatric disorders have been reported in these children, such as neurodevelopmental disorders;

3.2.1 Autism Spectrum Disorder (ASD):

In the DSM-5, ASD is defined by two domains: Persistent deficits in social communication and social interaction and restricted and repetitive aspects of behaviors, interests, or activities that may include, in particular, hyper- or hypo-reactivity to sensory stimuli or unusual interest in sensory aspects of the environment.

The notion of spectrum takes in consideration the diversity of clinical forms, variousness of affected persons and the gradation of signs. All domains can be affected with heterogeneity of expression according to the persons and according to the stages of development.

According to the HAS recommendations, the diagnosis of ASD is a medical process. It cannot be reduced to the result of a diagnostic scale. The approach includes a history supported by parental observations and clinical observation of the child (direct and indirect). It can be structured using standardized tools that most professionals specifically trained in neurodevelopmental disorders can administer: ADI, and clinical observations using ADOS, CARS, ECA-R or SRS. It will be essential to combine this with a measurement of language level, intellectual functioning and sensory processes using adapted tools.

Autism Spectrum Disorder affects 50-90% of PMS patients, the rate varies from study to study depending on the diagnostic criteria used [5].

In a study by Denayer *et al*., of seven individuals (3 children, 4 adults) with PMS, all participants had characteristics of ASD and one of the children was diagnosed with ADHD [6].

ASD symptoms were also described in another study of 40 children and adolescents with this syndrome, according to DSM criteria [7].

Socio-communicative disorders were present in 90% (36/40) of the participants in this study, while restrictive and repetitive behaviors were present in 55% (22/40) [7].

The phenotype could significantly differ in deletion carriers versus sequence variant carriers of SHANK3 [8]. Regarding individuals with autism, Serret *et al*., report two individuals diagnosed with autism spectrum disorder in childhood who exhibited regression, catatonic features and disruptive behavior problems after a stressful event during adolescence [9].

3.2.2 Intellectual disability:

The intellectual developmental disorder is constant, with patients showing severe to profound intellectual disability in about 77% of cases [10]. It constitutes a major prognostic issue both for the functional prognosis and for the adaptation of the patient's management.

The examination of adaptive capacities must systematically accompany the assessment of intellectual functioning. The evaluation must be done on the basis of updated and scientifically validated tools in order to avoid erroneous or incomplete diagnoses that could lead to a wrong orientation of the persons and the implementation of adapted educational projects. These objective evaluation tests must therefore be systematically carried out by an experienced psychologist and adapted to the age and supposed abilities of the patient. Several quality instruments are currently available for the evaluation of IQ: Wechsler scales, the most widely used in France and abroad: WPPSI IV, WISC I, WAIS IV, KABC-II, and more recently, the NEMI-2.

The identification and orientation of the diagnosis will allow for the earliest possible intervention, the implementation and coordination of the diagnostic process in view of a global strategy of early individualized and adapted care calling for the cooperation of different actors.

3.2.3 Motor Disorders:

Delayed psychomotor acquisition is almost constant in patients with PMS but of variable severity. The acquisition of walking is delayed with an average of 22 months [11]. In the context of postural-motor hypotonia already described, walking is often unstable with low muscle tone, which can lead to secondary and non- specific balance disorders. Global and fine motor disorders are also reported. These range from a simple delay to a coordination acquisition disorder (CAD). Later, it manifests itself by a delay in motor acquisitions in everyday life with clumsiness, slowness, motor learning difficulties (impaired postural control and balance, visuomotor difficulties, failing manual dexterity, ...) and at school (difficulties with graphing, geometry, physical education, ...).

3.2.4 Language Acquisition Disorder:

Language disorders in PMS are consistent, with a spectrum of expression and severity ranging from delayed acquisition to no language at all. The severity of the disorders could be related to the size of the 22q13 deletion [12, 13]. In patients with mutations in the SHANK3 gene, language impairment may be less severe [8]. These impairments can affect all domains such as articulation (individual sounds), phonology (the assembly of sounds), lexicon (vocabulary), syntax (grammar) and pragmatics (the general meaning of social use and communication). Its exploration has two sides: Receptive (comprehension) and Expressive (production).

3.2.5 Sensory impairments

Nearly 80% of patients with PMS have sensory disorders, which may involve hearing, vision, touch or pain sensitivity (especially hyposensitivity). These sensory particularities are sometimes difficult to determine and evaluate because of children's intellectual level and language abilities.

3.2.6 Neuropsychiatric disorders:

A recent study [14] of 38 people in psychiatry department found that the onset of psychiatric disorders occurred early in childhood with a second peak at the passage to adulthood. The disorders reported in this study meet the criteria of a manic episode, a depressive episode or a brief psychotic episode. Anxiety disorder often occur with the thymic episodes in the majority of these patients. In general, studies seem to report more mood disorders and schizophrenic spectrum disorders [15] compared to general population. However, longitudinal data related to PMS patients are still rare. Regular follow-up is important in order to prevent the psychiatric manifestations often seenqin childhood, adulthood and at the transitional phases from one age to another.

4. CONCLUSION

The coexistence of neurodevelopmental disorders in children with Phelan-McDermid syndrome (PMS) has been reported. Are these psychiatric manifestations related to Phelan-McDermid syndrome or a comorbidity?

Regular monitoring by a child psychiatrist should be proposed to detect the onset of these psychiatric disorders frequently associated in childhood for early multidisciplinary management, as well as follow-up in adulthood and in the transition phases from one age to the next.

5. RECOMMENDATIONS

As the end of this work, we recommend for ASD patient with organic manifestations to think about the phelan-McDermid syndrome because of the frequency of psychiatric disorders, even if it remains rare.

Conflicts of Interest: There is no conflict of interests regarding the publication of this paper.

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