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LETTER TO THE EDITOR

Autism Spectrum Disorder and Psychiatric Comorbidity in a Patient with Myhre Syndrome

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Abstract
Myhre syndrome (MS) is a connective tissue disorder with multisystem involvement with or without intellectual disability. In most cases SMAD4 mutations are reported. To date, 55 individuals have been molecularly confirmed. Autism has been proposed among associate clinical features of MS but no standardized diagnosis was available in previous cases. We report a case of a 25-year-old man with a pathogenic heterozygous SMAD4 missense mutation affecting residue Arg^{496} (SMAD4:p.Arg496Cys). Clinical findings are consistent with MS, commorbid with affective disorder and High Functioning Autism Spectrum Disorder confirmed by a standardized assessment procedure. The thorough clinical assessment of cases with syndromes such as MS can extend our knowledge on both the phenotypic characteristics of the syndrome and the genetic basis of autism.

Keywords Myhre syndrome · SMAD4 mutation · High functioning autism spectrum disorder · Affective disorder

Myhre et al. (1981) were the first to report two unrelated males with mental retardation, facial dysmorphism, short stature, brachydactyly, muscle hypertrophy, decreased joint mobility, mixed hearing loss, and cleft lip and palate in one of them. Facial dysmorphism included short palpebral fissures, maxillary hypoplasia, prognathism, short philtrum, and small mouth. Le Goff et al. (2012) identified missense SMAD4 heterozygous mutations, affecting the conserved Ile^{500}residue as a cause in 11 individuals with Myhre syndrome (MS). Shortly after Caputo et al. (2012) reported another eight MS cases with similar SMAD4 mutations.

To date, 55 individuals have been molecularly confirmed with MS (Starr et al. 2017). The syndrome is considered a connective tissue disorder with multisystem involvement, progressive and proliferative fibrosis that may occur spontaneously or following trauma or surgery, mild-to-moderate intellectual disability, and in some instances, autistic-like behaviors. Organ systems that are primarily affected include cardiovascular, respiratory, gastrointestinal and skin. Additional findings include distinctive craniofacial features and skeletal involvement such as intrauterine growth restriction, short stature and limited mobility of joints (Lin et al. 2016).

Behavioral disturbances may be considered as associated symptoms of MS. Titomanlio et al. (2001) reported a case diagnosed with autism in a 14 year-old boy while Burglen et al. (2003) described one of the patients' behavioral disturbances as "autistic-like conditions". Michot et al. (2014) registered behavioral disturbances such as hyperactivity, stubbornness, aggressiveness, frustration intolerance, poor communication skills, autistic features and polyphagia in 18 out of the 32 cases they reviewed. Lin et al. (2016) reported that among the 54 cases described in the literature 46 (85%) had intellectual disability, learning disability or developmental delay, seven (13%) of whom had an autism spectrum disorder. Psychiatric comorbidity has not been mentioned in any of the reported cases. Further observations of the abnormal behavioral features of MS are needed in order to

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identify if autistic or other behavioral disturbances are core features of the syndrome.

We report a new case of MS in a 25-year-old man and describe detailed clinical and molecular findings. Apart from the typical features of the syndrome he exhibits psychiatric comorbidity and Autism Spectrum Disorder (ASD) as assessed with standardized diagnostic instruments.

Clinical Data and Developmental History

Mr M.Y, a 25 y.o. male, was referred to our University Psychiatry Department because of a resistant to treatment psychiatric condition. He was admitted to the Adult Neurodevelopmental Disorders Unit in order to be assessed for his characteristic appearance (Figs. 1, 2, 3) and peculiar behavior.

He is of short height (1.64 m), overweight (100 kg) with characteristic unusual facies namely short palpebral fissure, right eyelid ptosis, mid-face hypoplasia with short philtrum, prognathism, narrow mouth, thin upper lip. Other clinical features included small ears, brachydactyly, muscular hypertrophy, thickened skin at hands and feet and limited range of motion of the ankle joint. Severe myopia and prognathism

Fig. 1 Unusual facies and muscular hypertrophy

Fig. 2 Mid-face hypoplasia, prognathism, small ear

were partially restored by surgical interventions in the past. None of his family members had an appearance similar to that of the patient.

At 22 years of age he reported delusional ideas of persecution and visual paresthesias. At that time he was a student living independently in a town away from his family but was unable to complete his studies. He moved back to his family home and received antipsychotic medication with no substantial improvement. During that period, he was diagnosed with Graves Disease resistant to treatment, complicated with exopthalmos and mild glaucoma. He underwent thyroidectomy and since then he has been administered substitute thyroid hormones. After thyroid surgery paresthesias and delusional ideas gradually disappeared. Soon after, he developed severe agoraphobic behavior and depressed mood. Antidepressant medication was added to his treatment with minimal response. When admitted to the hospital

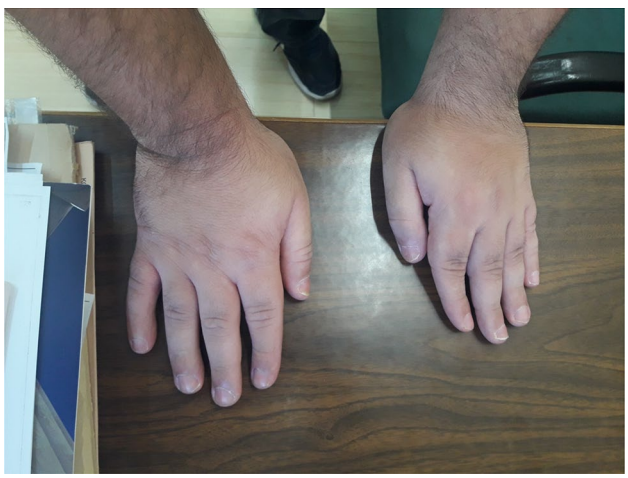

Fig. 3 Brachydactyly

his main complaints were agoraphobia along with anxious and depressed symptomatology. He had no insight into his past psychotic phenomena. Lamotrigine was added and he received behavior therapy with a poor outcome. Agoraphobic avoidance behavior and anxious and depressed mood still remain. There is no psychiatric history in the family.

M.Y. is the younger of two siblings in the family. Parental age at birth was 41 years for the father and 31 years for the mother. No perinatal complications were recorded. According to his developmental history the first symptoms to arouse parental concern at the age of three were his limited social interaction with children of the same age, some stereotyped movements, stuttering, and his intense fear of the sea and darkness.

M.Y. walked at 13 months and has always been toe walking. He acquainted bladder control during nighttime at 12 years of age. He put words together before the age of two. He started stuttering at the age of 30 months and stopped gradually during school years. His language comprehension has always been good but he could not understand metaphors and humor. He has always enjoyed inventing new words. No echolalia was noted but his speech was repetitive. Social chat has always been limited and when younger he found difficult to build a conversation with strangers. His eye contact has always been good with parents but inconsistent with other people. When younger both his social responses to unfamiliar people and his approaches to children were limited. He has always been enjoying listening to music rather than being with other people. He is socially naïve and in the past he was often teased by his classmates. Nevertheless, he had three friends at school and is still in touch with them.

When young his imagination and pretend play were rather poor. As a toddler he had a strong interest in the vacuum cleaner although he was sensitive to its noise. He is very resistant to pain and has a strong memory for dates. Occasionally, when excited, he still beats his chest and flaps his hands although less than in the past.

At the age of 6 years he was given the diagnosis of mild developmental delay, motor coordination disorder and stuttering. At that time he spent an extra year in nursery before entering the primary school. At school he was good in language, but had difficulties in science, mathematics and particularly in geometry.

During his clinical assessment with ADOS2 (Module 4), M. Y.' speech had little variation in tone while facial expression and the use of gestures were limited. Eye contact was poorly used to regulate social interaction. He was good at offering information and reporting of events but did not express interest in the examiner's ideas and experiences. Identification and communication of emotions was somewhat limited and social overtures were restricted to personal demands. He showed examples of insight into typical social situations but he did not indicate responsibility for his own actions appropriate for his age. Imagination and creativity were poor. Brief hand mannerisms were noted.

Taking into consideration our clinical assessment as well as the scores of ADOS2 and ADI-R (Le Couteur et al. 2003; Lord et al. 2012; Papanikolaou et al. 2009) M.Y. received the diagnosis of Autism Spectrum Disorder, severity level 1 (APA 2013).

The current WAIS psychometric assessment showed a significant difference between verbal and performance IQ (VIQ: 94, PIQ: 71). At the age of six, scores in WISC III were similar (VIQ: 95 and PIQ: 75).

Molecular Findings

The Whole Exome next-generation Sequence analysis (WES), showed a major finding that is a pathogenic heterozygous SMAD4:c,1486C>T variant in exon 12 of the SMAD4 gene (ref seq NM_005359.3). The variant has been confirmed by Sanger sequencing. This is a missense variant predicted to result in the substitution of an arginine by a cysteine (SMAD4:p.Arg496Cys). The SMAD4 gene encodes a protein involved in signal transduction of the transforming growth factor-beta superfamily (TGFB) and bone morphogenic proteins (BMP) by mediating transcriptional activation of target genes. SMAD4 is the common SMAD protein required for most transcriptional responses to TGFB and BMP signaling. Apart from dysmorphic facial features, skeletal anomalies and congenital heart disease, autosomal dominant variants of the SMAD4 gene are involved in juvenile polyposis syndrome and polyposis/hereditary hemorrhagic telangiectasia syndrome.

An incidental finding that is a heterozygous TNNT2:c.862C>T variant with unknown significance (VUS) was identified in exon 17 of the TNNT2 gene (ref seq NM_001276345.1). It is a missense variant predicted to result in the substitution of an arginine by a cysteine (TNNT2:p.Arg288Cys). The TNNT2 gene encodes cardiac muscle troponin T, the tropomyosin-binding subunit of the troponine complex that regulates muscle contraction in response to alterations in intracellular calcium ion concentration. The variant has previously been described in patients with hypertrophic cardiomyopathy (Watkins et al. 1995) and with dilated cardiomyopathy (Millat et al. 2011).

Further Clinical Investigations

Following the molecular confirmation of the syndrome our patient underwent an extended clinical and laboratory work-up, excluding pathological findings in the upper and lower gastrointestinal tract and cardiomyopathy. Cerebral MRI

showed small bilateral enlargement of the occipital pole of the lateral ventricles.

Discussion

This is a new case of MS referred to our department because of a resistant to treatment psychiatric condition and a syndrome-like appearance. Clinical evaluation and laboratory findings confirmed the diagnosis of MS comorbid with ASD, severity level 1 (APA 2013) and Affective Disorder with anxious and depressed mood.

His clinical physical features are in accordance to the ones described in previous reviews (Michot et al. 2014; Lin et al. 2016). His clinical picture though was less severe, which is a possible explanation for the delay in receiving the diagnosis of MS. No long-term physical complications with the exception of myopia were found. In their review Starr et al. (2017) suggest extreme caution to surgical interventions because of the abnormal wound healing due to progressive and markedly abnormal fibroproliferative responses to surgical intervention. Piccolo et al. (2014) have even suggested the use of antihypertensive drug Losartan for the treatment of connective tissue manifestations. Although our case underwent three surgical interventions (prognathism, myopia, thyroidectomy) he showed minor complications.

In terms of behavioral disturbances, mental retardation was first reported by Myhre et al. (1981) and autism and autistic like conditions in a small number of other cases as described in the introduction. Since no standardized assessment was used in previous reports there is a degree of uncertainty regarding the exact rate and the level of severity of ASD in MS. Our case of MS is the first one reported with ASD confirmed through a standardized diagnostic procedure. Also no intellectual disability was noted and M.Y.'s level of functioning was satisfactory, allowing him to live independently as a student. Even if the underlying mechanisms are not known our findings support a possible association of SMAD4 gene mutations not only with MS but also with ASD and add to the evidence for the genetic heterogeneity of autism.

Psychiatric comorbidity of an affective and anxiety disorder has not been described in previous reports (Moss et al. 2015). It is difficult to conclude whether the affective disorder is part of the behavioral disturbances of the clinical phenotype of MS or not. If not, it might be that thyroiditis Gravis played a role in its presentation in adulthood. Also it is well known that ASD has a high comorbidity with anxiety and affective disorders due not only to genetic loading but also to aversive experiences such as teasing at school and failure in studies as already reported by our case. On the other hand, some signs of anxiety were present from his preschool years supporting a predisposition to anxiety and affective disorders. If we consider psychiatric symptomatology as part of the phenotype of MS its absence in previous reports might be explained by the fact that intellectual disability and life threatening physical complications make harder to diagnose psychiatric comorbidity.

The pathogenic heterozygous SMAD4:c,1486C>T variant in exon 12 of the SMAD4 gene (ref seq NM_005359.3) has been previously described in other patients with MS, (Michot et al. 2014; Caputo et al. 2014) and listed as pathogenic (Lelieveld et al. 2017). Geisheker et al. (2017) report that missense mutations of the SMAD4 gene were among the de novo mutations in 200 genes important in neurodevelopmental disorders. The most common SMD4 mutation affects ILe^{500} and is considered to affect either the SMAD heterotrimer function, causing dysregulation of TGF-β-mediated transcriptional control (Le Goff et al. 2012) or proper SMAD4 ubiquitination and defective degradation (Caputo et al. 2012; Le Goff et al. 2012). The p.Arg496Cys substitution found in our case is reported to affect the complex stability by indirectly perturbing the interface structure of the SMAD heterotrimer and/or impair proper ubiquitination, perturbing signal flow as a result of enhanced levels of nonubiquitinated SMAD4 (Caputo et al. 2014).

The Whole Exome next-generation Sequence analysis incidentally found a heterozygous TNNT2:c.862C>T variant with unknown significance (VUS). Since TNNT2 is reported in cardiomyopathy our patient underwent an extensive cardiological assessment and no pathological signs were found. Although TNNT2 has not been related to autism so far we must also consider that an individual's genetic make-up can modify the effect of rare damaging variants explaining why mutations in the same gene often have different symptoms (Niemi et al. 2018).

To conclude, the thorough clinical assessment of cases with syndromes such as the one presented in our report is very important and can extend our knowledge on both the phenotypic characteristics of the syndrome and the genetic basis of autism. Mild clinical manifestations can delay the diagnosis of MS. Also it might be that the rate of ASD in MS is underestimated since no standardized assessment was reported in previous cases and symptoms can go unrecognized because of a more general diagnosis of intellectual disability. On the other hand early detection of the syndrome and its clinical manifestations is essential for dealing with long term physical complications and behavioral disturbances. Especially for ASD early detection is crucial in order to benefit from specific interventions that can result to a better outcome.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Additional informed consent was obtained from the participant for whom identifying information is included in this article.

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