

Clinical report: a rare co-occurrence of tuberous sclerosis complex and Rett syndrome in a girl with mental retardation, epilepsy and autism

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SUMMARY

Introduction. There are some genetic disorders with combination of mental retardation, epilepsy and autism in which the abnormal mammalian Target of Rapamycin (m-TOR) signaling is implicated. The most important of them is tuberous sclerosis complex (TSC), but the disturbances of the m-TOR pathway can also be detected in Rett syndrome (RS), Fragile X syndrome and Down syndrome. We describe the rare case of co-occurrence of TSC and RS.

Case study. The female child was born at term by normal delivery after a non-complicated pregnancy. Family history was negative for epilepsy and mental retardation. The neonatal period was uneventful and psychomotor development was normal before the child became 1.5 years old. At the age of 18 months the girl developed hand-wringing stereotypes, facial hypotonia, ataxia and gait apraxia. She lost eye-to-eye contact and verbal contact with relatives, and became indifferent to the surrounding environment. When she was 2 years old, focal adverse seizures started which were readily controlled with carbamazepine. Cerebral cortical and subcortical tubers, cerebral white-matter radial migration lines and subependymal nodules on brain MRI together with hypomelanotic macules suggested the presence of TSC. Diagnosis was confirmed at age of 3 years by a heterozygous mutation c.5161-2A>G in *TSC2* gene on chromosome 16p13. But the rude regression of psychomotor development and speech, autistic features alongside with characteristic hand-wringing stereotypes were unexplained until at age of 4.5 years RS was diagnosed by finding a heterozygous missense mutation in exon 4 of the *MECP2* gene c.455C>T, resulting in a P152R substitution in the methyl-binding domain of the protein. At age of 5 the patient is not able to walk independently and has no expressive speech, she is autistic, has ataxia, limb rigidity, hyperreflexia, lack of purposeful hand movements, verbal and motor stereotypes.

Discussion. The presence of two mutations (one characteristic for *TSC2* and one – characteristic for RS) significantly worsened the developmental and motor delay and autistic features in our patient. Dysregulation of m-TOR way is well established in TSC and recently described in RS, Down syndrome and Fragile X syndrome.

Keywords: Tuberous sclerosis complex · Rett syndrome · co-occurrence · m-TOR signaling

INTRODUCTION

Some well-known genetic disorders have common phenotypes including mental retardation, epilepsy and autism, among them are tuberous sclerosis complex (TSC)

and Rett syndrome (RS). 80–85% of TSC patients have a mutation in either *TSC1* or *TSC2* genes, which leads to constitutive mTOR (mammalian Target Of Rapamycin-

cin) activation (Curatolo et al., 2008). The mTOR pathway plays a critical role in regulating cell growth, proliferation, metabolism, and orientation and migration, as well as in angiogenesis (Krueger and Northrup, 2013). Rett syndrome is caused by mutations in *MECP2*, which binds methylated cytosine-phosphate-guanine dinucleotide (CpG) a chromatin-associated protein that can both activate and repress transcription. It is required for maturation of neurons. Similar clinical features are suggesting common mechanisms of developmental delay (Gadalla et al., 2011). But the co-occurrence of two diseases is very rare. Indeed only two cases has been described in the literature with the author pointing out that "...studying unusual clinical combinations is more likely to shed light on the underlying etiology than focusing on procrustean syndrome definitions" (Philippart, 1993).

CASE REPORT

A girl who is now 5 years old was born at term by normal delivery after a non-complicated pregnancy. Parents were not consanguineous. Family history is negative for epilepsy and mental retardation. Neonatal period was uneventful. Psychomotor development was normal before the child became 1.5 years old – at that age she ran stiffly, walked without support, spoke several words and was feeding herself. Gradually she developed ataxia, poor truncal and gait coordination. Her face became expressionless, she was hypersensitive to sounds and was indifferent to the surrounding environment. She lost eye-to-eye contact, purposeful use of her hands and language, became more agitated and her sleep was disturbed. In addition to loss of previously acquired skills, the girl developed stereotypic hand movements – they can be described like "wringing or washing" and mouthing of the hands. At the age of 2 years focal adverse seizures started, but they were readily controlled with carbamazepine (CBZ); seizures stopped for 1 year. When mother decreased the dose of CBZ, secondarily generalized seizures resumed with a frequency of 3–4 per day and later on they ceased on combination of CBZ and valproic acid (VPA). No definite diagnosis was made until she was 3 years old and the pediatric neurologist saw four hypomelanotic macules. Cerebral cortical and subcortical tubers, cerebral white-matter radial migration lines and subependymal nodules on brain MRI (Figure 1) together with 4 hypomelanotic macules made the certain diagnosis of TSC.

To confirm the diagnosis, resequencing of coding

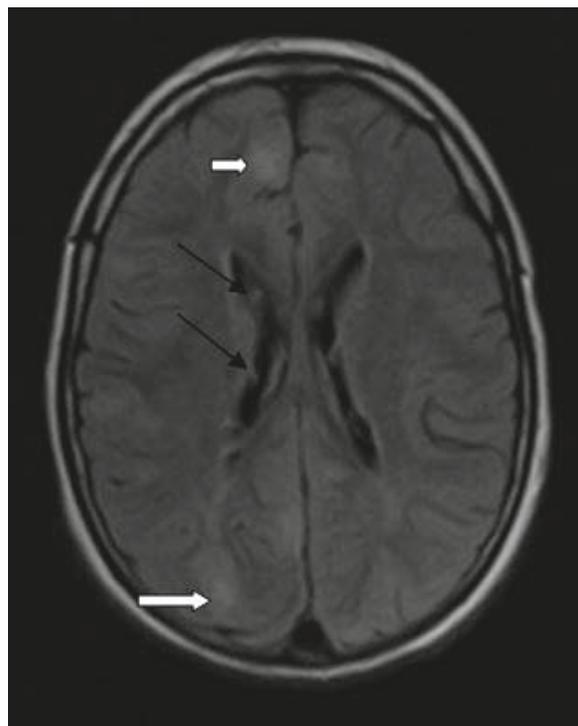


Figure 1. Brain MRI: Cortical and subcortical tubers (dark arrows), cerebral white-matter radial migration lines and subependymal nodules (white arrows).

exons and exon-intron borders of the *TSC1* and *TSC2* genes has been made on Ion Torrent platform using Ion AmpliSeq Inherited Disease panel. The 5 genomic variants found included 1 in *TSC1* gene and 4 in *TSC2* gene. Population frequency filtration has showed that 4 of them are common polymorphisms (>1% frequency according to the 1000 Genomes project data) whereas only one has been found in neither 1000 genomes project nor the NHLBI Exome Sequencing Project data or other publically available databases. The latter is a splice site mutation c.5161-2A>G in *TSC2* (adjacent to the 41st exon of the NM_000548 transcript) gene on chromosome 16p13 in heterozygous state, pathogenicity of which we suggest. The site is evolutionary conservative (GERP++ score 4.21, Davydov et al., 2010). Our hypothesis is also supported by the *in silico* modeling (MutationTaster2 tool, Schwarz et al., 2014).

The girl was hospitalized at our department when she was 5 years old. At time of hospitalization she was severely mentally retarded (unable to participate in formal standardized testing) and autistic; she had lost mobility and was wheelchair-bound and had no expressive speech. Restlessness, overactivity and aggres-



Figure 2. Hypomelanotic macules on the skin of the patient.

sive outbursts were evident. There was a lack of purposeful hand movements and verbal and motor stereotypes. She had mild dysmorphic features: frontal bossing, low-set ears, and irregular teeth placement. 4 hypopigmented, oval macules are seen over the trunk and limbs (Figure 2). No other skin manifestations (shagreen patches, connective tissue hamartomas, etc.) were noted. She had ataxia, limb rigidity and hyperreflexia. The patient's vital functions were normal and there were no pathological changes in her inner organs.

Interictal EEG registered epileptiform spike and wave discharges in left frontal and right occipital regions.

Abdomen MRI showed the absence of angiomyolipomas and glomerular filtration rate was normal.

Echocardiography revealed no rhabdomyomas and the electrocardiogram showed no conduction defects.

Ophthalmologic evaluation – no retinal lesions were found.

The patient was receiving VPA 21 mg/kg/day in combination with CBZ 10.5 mg/kg/day, and had seizure remission during the previous 2 years on these drugs' combination.

Of course in patients with TSC and coexisting epilepsy, speech delay and psychomotor development are common. But rude regression of psychomotor development and speech alongside with characteristic hand-

wringing stereotypes (at age of 1.5–2 years old) in absence of epileptic encephalopathy (her epilepsy was not devastating and was easily controlled) were unexplained until Rett syndrome was diagnosed by finding a heterozygous missense mutation in exon 4 of the *MECP2* gene c.455C>T, resulting in a P152R substitution in the methyl-binding domain of the protein (re-sequencing of the *MECP2* coding exons and exon-intron borders has been made on Ion Torrent platform using Ion AmpliSeq Inherited Disease panel). This mutation has been previously described as pathogenic and in published cases was associated with atypical (milder) presentation of RS–macrocephaly and preserved speech (Cheadle et al., 2000; Sheen et al., 2013)

DISCUSSION

A detailed description of TSC and RS can be found in various publications (Roach and Sparagana, 2004; Curatolo et al., 2008; Dolce et al., 2013). Philippart (1993) has provided the only description of co-occurrence of TSC and RS. Both cases were adults (a male and a female). The male had a history of infantile spasms and the female had a history of Lennox-Gastaut syndrome. Thus, both cases had epileptic encephalopathies that caused the mental retardation. In our case the course of epilepsy was more benign – rare focal seizures well

controlled by combination of two antiepileptic drugs. Thus, why was the outcome in our case so poor? Of course, prognosis of TSC depends upon many factors including the localization of mutations – it's well known that cases with *TSC2* mutations are more severe than those with *TSC1* mutations (Kothare et al., 2014). But we speculate that the presence of two mutations (one characteristic for *TSC2* and one – characteristic for RS) significantly worsened the developmental and motor delay and autistic features in our patient.

Some clinical symptoms of TCS and RS are common, including epilepsy, mental retardation and autism; the same can be said about Down syndrome and Fragile X syndrome. Despite the different genetic background of these diseases there is some evidence that they can have shared underlying mechanisms. The common pathogenic pathway can be the dysregulation of m-TOR activity. In addition to having a role in regulating cell growth, proliferation and migration, this protein kinase is involved in dendrite morphogenesis and synaptic plasticity, modulating both glutamatergic and GABAergic synaptic transmission (Troca-Marín et al., 2014). It is well known that the main pathogenic mechanism in TSC is the m-TOR activation (Krueger and Northrup, 2013). The majority of children with RS have mutations in Methyl-CpG-binding Protein 2 (*MECP2*), a transcriptional regulator – it can both activate and repress transcription and it is required for maturation of neurons (Gadalla et al., 2011; Neul, 2012). It has also been shown that in experimental models of RS, synaptic transmission and plasticity are disrupted (Della Sala and Pizzorusso, 2014). Recently, a reduction in m-TOR signaling in *Mecp2* mutant brains was found by Ricciardi S. et al. (2011), showing that "... cognitive deficits, autism and impaired language and communication might arise from a positive as well as negative unbalance of the same molecular processes". The dysregulation of m-TOR activity occurs in both Down syndrome and Fragile X syndrome (Troca-Marín et al., 2014).

TSC is also considered to be a model disorder to study the development and treatment of autism spectrum disorder (ASD) because of its high frequency and progress in target treatment of TSC (Davis et al., 2015). There are studies that have specifically examined the underlying mechanisms of autism-like behaviors in animals with a TSC mutation, demonstrating complex interaction of mTOR pathway overactivity and the development of ASD-like behaviors and also showing the normalization of decreased social behavior and increased repeti-

tive behaviors in mutant mice after treatment with rapamycin. Some ongoing trials in humans are trying to determine the efficacy of the m-TOR inhibitor, everolimus, in the treatment of autism including Efficacy of RAD001/Everolimus in Autism and NeuroPsychological Deficits in Children With Tuberous Sclerosis Complex (RAPIT) (clinicaltrials.gov: NCT01730209). There is hope that the better understanding and treatment of m-TOR hyperactivation will provide a path for the treatment for ASD in other disorders (Davis et al., 2015).

CONCLUSION

Identification of common pathogenic pathways both of TSC and RS can enhance the understanding of the neurobiology of epilepsy, autism and mental retardation in these progressive neurological diseases (Khawaja and Sahin, 2011).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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