Exclusive from USA

Fragile X-Associated Tremor/Ataxia Syndrome (FXTAS)

Urednik članka

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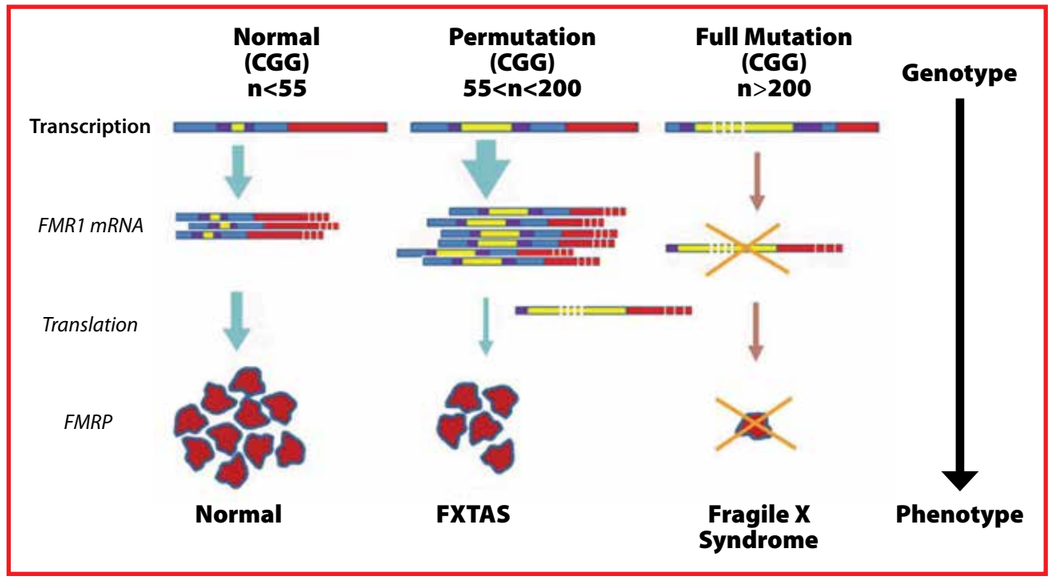
Sa posebnim zadovoljstvom vam predstavljamo tekst koji sledi. Tekst je nastao u saradnji sa najeminentnijim stručnjacima u oblasti Fragilnog X.

Do sada smo pisali o Fragilnom X sindromu koji nastaje kao posledica pune mutacije *FMR1* gena i koji predstavlja najčešći uzrok intelektualne zaostalosti i najčešći uzrok autizma koji nastaje mutacijom jednog gena. Neurodegenerativno oboljenje FXTAS, koje je detaljno opisano u ovom tekstu, i koje ima simptome u potpunosti različite od Fragilnog X sindroma, nastaje kao posledica premutacije istog gena. Od velike je važnosti pravilna dijagnoza ovog oboljenja, prevencija razvoja simptoma, ali i sprečavanje prenosa mutiranog gena na sledeće generacije. Najčešće se iz premutacije *FMR1* gena razvija puna mutacija gena u sledećoj generaciji sa simptomima Fragilnog X sindroma. Ovo ukazuje na posebnu važnost identifikacije premutacije *FMR1* gena, odnosno na pravilnu dijagnozu oboljenja do kojeg dovodi premutacija *FMR1* gena. Detalji slede...



Adopted: Berman, Robert F., et al. "Mouse models of the fragile X premutation and fragile X-associated tremor/ataxia syndrome." *Journal of neurodevelopmental disorders* 6.1 (2014): 25.

Fragile X-associated tremor/ataxia syndrome (FXTAS) is a late-onset neurodegenerative disorder that typically affects adults over 50 years old and is characterized by problems with movement and thinking ability (cognition). It was discovered in 2001 after clinicians found a pattern of neurological symptoms in older people carrying Fragile X syndrome history in the family. FXTAS is caused by a genetic change in the *FMR1* gene that is responsible for making Fragile X Mental Retardation Protein (FMRP). FMRP is an RNA binding protein and plays an important role in the development of synapses, which are critical for the connections between nerve cells. In FXTAS the CGG repeat in 5' Untranslated region of *FMR1* gene that is 5-44 in normal people expanded to 55-200 and called *FMR1* premutation allele. It is different from full mutation allele in which CGG repeats are more than 200 and leads to the development of Fragile X Syndrome that is a most common form of intellectual disability. The higher number of CGG repeats at *FMR1* gene locus leads to the overproduction of abnormal *FMR1* mRNA cause the molecular toxicity. Scientist proposed that this high level of mRNA decrease the amount of FMRP protein by sequestering important proteins involved in the process.

EPIDEMOLOGY OF FXTAS

Premutation alleles have a prevalence among the general population of ~1 in 110–260 females and ~1 in 400–850 males; however, the prevalence can vary depending on ethnicity being the highest in Colombia and Israel. About 40% of male carriers over the age of 50 develop FXTAS. However, the risk of FXTAS is influenced by CGG repeat size, age, and sex of an individual. As 75% of men ≥80 years of age are affected. Approximately 8% of female carriers develop FXTAS however, they present with similar but less severe symptoms likely due to the presence of the second X chromosome carrying a normal allele. Secondly, in women, there are the phenomena called X-inactivation by which one of the two X chromosomes is permanently inactivated in somatic cells (cells other than egg and sperm cells). It makes ensure that like males in females there is only one active copy of the X chromosome. This distribution of active and inactive X chromosomes could also help determine the severity of FXTAS in females or whether they develop signs and symptoms of the condition.

SYMPTOMS OF FXTAS

The main clinical features of fragile X-associated tremor/ataxia syndrome (FXTAS) include the presence of intentional tremor which is trembling or shaking of a limb when trying to perform a voluntary movement such as reaching for an object and ataxia that is problems with coordination and balance. Patients may also suffer from neurological symptoms such as parkinsonism, while tremor is the most frequent symptom seen in 80% of patients, cerebellar ataxia in 50% and parkinsonism in 30%. Many FXTAS patients experience autonomic dysfunction that is a condition in which the autonomic nervous system (ANS) does not work properly which ultimately affects the functioning of the heart, bladder, intestines, sweat glands, pupils, and blood vessels. In addition, the weakness, numbness, and pain from nerve damage usually in the hands and feet is also observed in patients. FXTAS patients also showed cognitive decline, ranging from memory deficits to global dementia disabilities. It includes the short-term memory loss to loss of executive function, that is the ability of strategic planning and self-monitoring. Anxiety, depression, moodiness, or irritability is common among the patients and thyroid problems are also reported in women.

DIAGNOSIS OF FXTAS

FXTAS at the present is likely still underdiagnosed. Some of the reasons can be attributed to the fact that, as FXTAS is a newly discovered disorder, many physicians are not yet familiar with the disorder. Addition only 4% of subjects affected by FXTAS are seen by a movement disorders neurologist. Finally, the symptoms of the FXTAS often involve the combination of tremor, ataxia, and dementia, which are common in the elderly and in some cases the disorder can be difficult to recognize due to its heterogeneous nature, which facilitates misdiagnosis, especially in the earlier stages. Although the accurate diagnosis is required for target treatment,

DIAGNOSTIC CRITERIA		
Definite	**Probable**	**Possible**
One clinical major + (one radiological or pathological major)	Two clinical major or (one clinical minor + one radiological major)	One clinical major + one radiological minor
MOLECULAR		
Required	*FMR1* mutation including the premutation and the gray zone	
CLINICAL		
Major	Intention tremor, Cerebellar galt ataxia	
Minor	Perkinsonism, Neuropathy, Executive function deficit, > Moderate generalized brain atrophy	
Neuropathology		
Major	Ubiquitin-positive intranuclear inclusions	
Radiological		
Major	MRI white matter lesions, in MCPs or brainstem	
Minor	MRI cerebral white matter lesions, > Moderate generalized brain atrophy	

Table: Diagnostic Criteria of FXTAS

some people are reluctant to genetic testing so the permission of some of the patients and family members is really important

For the diagnostic criteria of FXTAS tremor and ataxia are considered the main clinical features for a definite diagnosis of FXTAS. At the molecular level, the presence of an expanded premutation allele is required for the diagnosis of FXTAS. It accomplished by using the combination of two molecular techniques polymerase chain reaction (PCR) and Southern blot analyses. Three categories, termed as "definite", "probable" and "possible" are used in the diagnosis of FXTAS. "Definite" indicates the presence of one major radiological sign plus one major clinical symptom. "Probable" indicates the presence of either one major radiology sign plus one minor clinical symptom or two major clinical symptoms. "Possible" indicates the presence of one minor radiology sign plus one major clinical.

MANAGEMANET & TREATMENT OF FXTAS

Unfortunately, there is no available cure for the FXTAS but certain medications and treatments are proven helpful in a slowdown of progression and alleviating symptoms of tremor, ataxia, mood changes, anxiety, cognitive decline, and dementia. The symptoms of FXTAS differ from person to person, so the treatment should address a person's individual needs. Moreover, health care providers should work together as a team to provide appropriate treatment, such as physical therapy and psychological counseling. There is no clear evidence if the lifestyle choice has some impact on the development and progression of this disorder. However, it has been shown that exercise on regular basis can also be beneficial for psychiatric symptoms in FXTAS. Rehabilitative treatments such as speech and occupational therapy and gait training may also prove helpful in the management of the disorder. It is also very important, as immediate family members may be at risk of having children with FXS (developmental delay, learning disability, autism) or being affected by FXTAS. Thus, the clinician should immediately consider the option of FXTAs if there is a history of a grandchild with a form of developmental delay. Clinical trials of allopregnanolone that are underway slowly progress toward a goal of making meaningful clinical differences for these individuals.

POINT OF CONTACT FOR FXTAS

The National Fragile X Foundation is non- profit organization that unites the fragile X community at one platform to enrich the lives through educational and emotional support, promote public and professional awareness and advance research toward improved treatments and a cure for fragile X and fragile X-Associated syndrome. It can also provide information regarding FXTAS (*800-688-8765 orfragilex.org*). Fragile X Clinical and Research Consortium clinics can also provide information or referral to a Neurologist or other physician with experience in caring for patients with FXTAS (/research/#-1498268491073-e38da661-8aca).

RELATED READING ARTICLES

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Važni skupovi

KONGRES SRPSKE ORTOPEDSKO-TRAUMATOLOŠKE ASOCIJACIJE

Prof. dr Maurilio Marcacci

Prof. dr Kassim Javaid, Oxford

Prof dr Miroslav Milankov

Akademik Marko Bumbaširević

doc. dr Vladimir Harhaji, doc. dr Radmila Matijević

Srpska ortopedija prati svetske trendove

Piše: doc. dr Radmila Matijević,

tehnički sekretar Kongresa

Ovaj skup, šesti po redu, održan je u Novom Sadu u periodu 20–22. septembra 2018. u zajedničkoj organizaciji Klinike za ortopedsku hirurgiju i traumatologiju i Asocijacije za sportsku traumatologiju i artroskopiju Srbije. Skup je održan u Kongresnom centru zgrade Naftne industrije Srbije i privukao je pažnju velikog dela stručne javnosti, bilo je akreditovano više od 400 učesnika iz Srbije i inostranstva.

Predsedavajući Kongresa bio je prof. dr Miroslav Milankov. U svom pozdravnom govoru istakao je:

– Svi mi na Klinici za ortopedsku hirurgiju i traumatologiju Kliničkog centra Vojvodine stvaramo okruženje koje će našim pacijentima pomoći, olakšati im bolove, dati nadu u zdrav život. Imamo i čime da se pohvalimo! U Klinici za ortopedsku hirurgiju i traumatologiju Kliničkog centra Vojvodine svake godine uradi se oko 2.400 operacija, u Poliklinici pregleda 32.000 pacijenata, a naši hirurzi, u dve hirurške sale, svakodnevno urade najmanje 8–10 operacija. Jedina smo ustanova u Vojvodini koja radi traume kičme, sve revizione operacije proteza u Pokrajini, a počeli smo da radimo i transplantacije matičnih ćelija i biomedicinu. Prvi smo uradili operaciju kolena kod hemofiličara i ovakvim pristupom pacijentima sa hemofilijom, te formiranjem tima lekara za takve intervencije, Klinički centar Vojvodine stekao je uslove da bude evropski Centar za sveobuhvatno lečenje hemofilije. Osoblje Klinike se redovno edukuje u okviru domaćih i internacionalnih stručnih skupova, odlazi na stručna usavršavanja u vodeće evropske trauma centre, specijalne bolnice za zbrinjavanje sportskih povreda i zamenu oštećenih zglobova veštačkim. Klinika je i nastavna baza Medicinskog fakulteta Univerziteta u Novom Sadu za Katedru za hirurgiju, za studente medicine, stomatologije, medicinsku rehabilitaciju, specijalne edukacije i rehabilitacije, a istovremeno i nastavna baza lekarima na obaveznom lekarskom stažu i lekarima na specijalizaciji. Organizovanjem Kongresa Srpske ortopedsko-traumatološke asocijacije okupili smo na jednom mestu velik broj onih koji su svojim doprinosom u nauci i medicini uopšte u samom svetskom vrhu, stručnjake koji se respektuju i sa uvažavanjem slušaju. Drago nam je da su svi prisutni na ovom skupu prepoznali inovativni i profesionalni pristup koji je moto našeg dugogodišnjeg rada i očekujemo vas na nekom od narednih skupova.

Predsedavajući Srpske ortopedsko-traumatološke asocijacije akademik prof. dr Marko Bumbaširević zahvalio se organizatorima kongresa na sjajno obavljenom poslu i istakao značaj ovakvih stručnih skupova, na kojima se lekari iz regiona sreću sa stručnjacima svetskog ranga.

Stručni deo konferencije su otvorila plenarna predavanja profesora Maurilia Markačia, profesorke Elizavete Kon i profesora Dragana Savića. On je održao predavanje na temu alotransplantata u ortopedskoj hirurgiji koji se primenjuju u Kliničkom centru Vojvodine.

Kongres je zvanično otvorio pokrajinski sekretar za zdravstvo doc. dr Zoran Gojković. Naučni deo skupa bio je podeljen u nekoliko sesija tokom svakog dana i kroz njih je obrađena zdravstvena problematika iz oblasti artroplastičnih procedura zgloba kuka i kolena, sportskih povreda, artroskopija, regenerativne medicine, traume karličnog prstena, intramedularne fiksacije preloma, osteoporoze i drugih pratećih stanja u ortopediji i traumatologiji.

O rezultatima lečenja pacijenata na Klinici za ortopedsku hirurgiju i traumatologiju različitim metodama i tehnikama, termine za predavanja sa imali prim. dr Veselin Bojat, dr Aleksandar Lažetić, doc. dr Vladimir Harhaji, prof. dr Srđan Ninković, doc. dr Predrag Rašović, dr Vaso Kecojević i dr Oliver Dulić. Svojim znanjem i iskustvom koje su podelili sa ostalim učesnicima, nesumnjiv doprinos su dali i kolege iz drugih ortopedskih centara Srbije, poput Kliničkog centra Srbije, IOH Banjica, KC Niš, KC Kragujevac i Opšte bolnice Subotica.

Veliku zahvalnost dugujemo i kolegama iz inostranstva, pre svega autorima plenarnih predavanja, ali i ostalima koji su učestvovali u radu svake sesije i doprineli kvalitetu stručnog dela programa svojim ekspertskim znanjem prezentovanim u njihovim izlaganjima, kao i aktivnim učešćem u diskusijama.

Održavanje Kongresa su pomogle mnogobrojne ortopedske i farmaceutske kompanije koje su izložile savremena tehnička rešenja koja se koriste u implantacionoj hirurgiji i medikamentoznoj terapiji ortopedskih pacijenata, a pored njih su značajno učešće imali i izdavači medicinskih udžbenika i stručne literature, pre svega Medicinski fakultet Univerziteta u Novom Sadu sa svojom izdavačkom delatnošću.

Verujemo da je većina učesnika otišla zadovoljna onim što su čuli tokom kongresa, kao i lepotama našeg grada i gostoljubivošću ljudi u njemu.