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REVIEW ARTICLE

The Multiple Faces of Spinocerebellar Ataxia type 2

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Abstract

Spinocerebellar ataxia type 2 (SCA2) is among the most common forms of autosomal dominant ataxias, accounting for 15% of the total families. Occurrence is higher in specific populations such as the Cuban and Southern Italian. The disease is caused by a CAG expansion in *ATXN2* gene, leading to abnormal accumulation of the mutant protein, ataxin-2, in intracellular inclusions. The clinical picture is mainly dominated by cerebellar ataxia, although a number of other neurological signs have been described, ranging from parkinsonism to motor neuron involvement, making the diagnosis frequently challenging for neurologists, particularly when information about the family history is not available. Although the functions of ataxin-2 have not been completely elucidated, the protein is involved in mRNA processing and control of translation. Recently, it has also been shown that the size of the CAG repeat in normal alleles represents a risk factor for ALS, suggesting that ataxin-2 plays a fundamental role in maintenance of neuronal homeostasis.

Epidemiology

More than 40 different forms of dominant ataxias, also called spinocerebellar ataxias (SCAs), associated with mutations in over 20 genes, have been described, with a global prevalence of 1:35,000 individuals.[1] Within this family of diseases, SCAs caused by a CAG expansion encoding a polyglutamine tract (polyQ) in the mutant protein represent the large majority. SCA2 is the most prevalent of the polyQ ataxias in Cuba, India, Mexico, and Southern Italy, and the second most prevalent worldwide, after SCA3, accounting for 15% of all cases.

Genetics

SCA2 is caused by a CAG repeat expansion in the *ATXN2* gene.[2–4] In most control individuals, the N-terminal region of the gene harbors the repetitive trinucleotide sequence (CAG)8(CAA)1(CAG)4(CAA)1(CAG)8, encoding for consecutive glutamine residues. Despite still encoding for glutamine residues, the CAA interruptions are believed to play a critical role in conferring stability to the CAG repeat expansion[5] and to affect the secondary RNA structure,[6] therefore possibly contributing to the phenotype variability. Normal alleles have 31 or fewer CAG repeats, with the 22 repeat allele being present in >90% of normal individuals worldwide, followed by the 23 and the 27 repeat alleles.[7] Alleles with a CAG triplet repeat number >31 are present in patients with SCA2. A more variable phenotype with parkinsonism or ALS features has been associated with an interrupted sequence (see below). Alleles with 32 and 33 repeat are considered extremely rare and have been associated with very late onset ataxia. The most common disease-causing alleles have 37–39 repeats. Extreme CAG repeat expansions (>200) have been also reported and have been associated with severe, multi-systemic forms with infantile onset.

Expanded alleles are unstable in intergenerational transmissions. In a personal series of 27 parent–child pairs, there was a variation of repeat size in 70% of transmissions, with 56% increasing in size and 11% contracting. Higher variability in repeat length was present in the paternal transmission compared with the maternal one. Expansions were larger in father–child pairs, than in mother–child pairs. Intergenerational instability of the expanded alleles is the biological substrate of the phenomenon of anticipation that is an earlier onset and more severe phenotype in recent generations. In a personal series of 33 parent–child pairs

anticipation of disease onset was in average 15.0 years (±14.1 SD). The number of triplets inversely correlates with age at onset and explains 76% of its variance.[8] Among other factors accounting for the residual variance are CAG repeats in *CACNA1A* (SCA6),[9] *ATX7 (SCA7)*[10] and *RAI1*[11] genes and a polymorphic variant of the mitochondrial complex 1 gene.[12]

Protein and its function

Ataxin-2 has 1312 residues and a molecular mass of about ~140 KDa. Ataxin-2 is a highly basic protein except for one acidic region (aminoacids 254–475) containing 46 acidic aminoacids. This region is predicted to consist of two domains named Lsm (Like-Sm, aminoacids 254-345), and LsmAD (Lsm-Associated Domain, aminoacids 353-475). The LsmAD of ataxin-2 contains both a clathrin-mediated trans-Golgi signal and an endoplasmic reticulum exit signal. The N-terminal tail (aminoacids 166-187) contains the polyQ region. At the C-terminus, there is the putative PABP (poly(A)-binding protein) interacting motif, PAM2, (aminoacids 908-925).[13]

Ataxin-2 is a ubiquitously expressed protein in normal human brain, especially in Purkinje neurons, midbrain, medulla, large neurons in substantia nigra and trochlear neurons. The wild-type ataxin-2 is localized in cytoplasm. Subcellulary most ataxin-2 was observed at the Golgi apparatus/endoplasmic reticulum in cell lines and brain.[14–17] Nonubiquinated intracytoplasmic inclusions were observed in SCA2 brains. The expression pattern of ataxin-2 was identical in brain of normal individuals and those affected with SCA2.[18]

Ataxin-2 function is still unknown. Ataxin-2 knock-out mice are viable and only show increased weight gain on a fat-enriched diet, overall suggesting that ataxin-2, although widely expressed, is not essential in development.[19] There are several evidences that it plays a role in RNA processing, in regulating the calcium release from the endoplasmic reticulum, in the assembly of stress granules and endocytic trafficking of epidermal growth factor receptor. The CAG expansion in the *ATXN2* gives rise to an abnormal polyglutamine sequence in the ataxin-2 protein, which results in a gain of a toxic function that could lead to oligomerization in vulnerable neurons.[20,21]

Ataxin-2 aggregation

The CAG-triplet expansion in the *ATXN2* gene encodes an abnormal polyglutamine sequence in the ataxin-2 protein, which results in accumulation of the mutant protein in mostly cytoplasmic neuronal inclusions. Dysfunction and death of specific neuronal population, such as Purkinje cells, striated pontine nuclei, anterior shaft motor neurons of the spinal cord and cranial-nerve motor nuclei is believed to occur via a mechanism of toxic gain of function. Selective cellular environment and specific protein–protein interactions could lead to oligomerization in vulnerable neurons. The degree of neuronal degeneration is related to the length of the polyglutamine expansion.[22]

Ataxin-2 and RNA metabolism

The Lsm domain proteins are involved in a variety of RNA processing events, including RNA modification, pre-mRNA splicing, and mRNA decapping and degradation. The PAM2 domain is known to bind RNA. Ataxin-2 has been observed to interact with A2BP1 (ataxin-2-binding protein 1), which might regulate RNA tissue-specific alternative splicing.[23] In addition, ataxin-2 shows significant homology to the yeast protein Pbp1 (Pab1/PABP-binding protein 1) that is involved in mRNA polyadenilation. Based on these observations, ataxin-2 seems to be capable of binding RNA and could participate in regulation of polyadenilation of mRNA.[13] McCann et al. showed that ataxin-2 is required for miRNA-mediated repression of several translational reporters in vivo and plays a central role in RNA silencing processing.[24]

Ataxin-2 and calcium-mediated signaling

Recent evidence suggests an alteration of the intracellular calcium signaling in SCA2. In Purkinje cells, mutant ataxin-2, but not wild-type, interacts with the C-terminal region of the type 1 receptor for the inositol triphosphate (ITPR1), an intracellular calcium release channel. ITPR1 is highly expressed in Purkinje cells and is involved in calcium handling by regulating calcium release from the endoplasmic reticulum. Mutant ataxin-2 caused an exaggerated calcium release from endoplasmic reticulum with increased cell death in Purkinje cells isolated from mutant ataxin-2 transgenic mice,[25] a model expressing full length polyglutamine-expanded ataxin-2 (Q58) targeted to Purkinje cells.[18]

Other mechanisms of ataxin-2 function include the interference of assembly of stress granules,[26] and endocytic trafficking of epidermal growth factor receptor (EGFR).[27]

Pathology

SCA2 stands out among other SCAs by the rarity of neuronal inclusion bodies, which seem to be completely absent in Purkinje neurons and rare in inferior olives, while they are usually detected in pontine neurons. Protein microaggregates were found throughout brains in the neuronal cytoplasm.[28] The olivopontocerebellar atrophy (OPCA) pattern usually found in SCA2 is the most severe among the SCAs. In addition, the OPCA pattern appears quite early in

the course of the disease[29] and it is similar to that found in MSA.[30] Inspection shows marked atrophy of the cerebellum, pons, and frontal lobe. In a series of 11 Cuban autopsies, cerebellum weight was decreased to about 50%, and Purkinje cells number to about 80%; whereas dentate nucleus and efferent fibers were relatively spared. Weight of the brainstem was decreased (60%) with a marked loss of inferior olivary (80%), pontocerebellar (80%) and of substantia nigra neurons (70%).[29] Neuronal loss of the subthalamic nucleus is constant and more severe in dorsolateral motor territory.[31] Atrophy of thalamic nuclei is severe in late stages.[32] Brainstem nuclei as well as several nuclei of the oculomotor system (oculomotor, trochlear, and abducens nuclei; rostral interstitial nucleus of the medial longitudinal fascicle reticulo-tegmental nucleus of the pons; raphe interpositus nucleus; prepositus hypoglossal nucleus) are affected. Degeneration occurs in giant Betz cells of the primary motor cortex and spinal motor neurons, particularly at cervical level. Neurons of dorsal root ganglia and Clarke columns are reduced in number. There is degeneration of posterior funiculi and dorsal spinocerebellar tracts.[33,34] Sural nerve biopsy shows a loss of myelinated fibers even in the absence of clinical signs of peripheral neuropathy.[35]

Clinical features

Even though the unequivocal diagnosis of SCA2 depends on the molecular test, the combination of early saccade slowing, hyporeflexia, tremor that is sometimes severe (action or resting, and truncal titubation), and myoclonus is very suggestive of the clinical diagnosis.[35] Onset occurs in the fourth decade with a wide range from the first to the eighth decade. A quarter of the patients has a juvenile onset (10–25 years), which is associated with larger CAG repeat size. Peculiar phenotypes have been associated with infantile onset (see below). In the full-blown disease cerebellar signs (gait ataxia, dysarthria, dysmetria, and action tremor) are constant and very frequently associated with abnormal eye movements (slow saccades and supranuclear ophthalmoplegia) and clinical signs of peripheral neuropathy (decreased/absent ankle and knee jerks associated with decreased vibration sense). Signs of cortical spinal impairment (Babinski signs and increased tone) affect about one-fourth of the patients. Head tremor, perioral fasciculations, and cramps are not uncommon. Dysphagia and sphincter disturbances are prominent in late stages of the disease. Overt dystonia and marked cognitive impairment are present in a minority of patients. Bulbar and autonomic signs correlate with the disease duration, pyramidal signs with the CAG size, while the cerebellar features and peripheral neuropathy with both.[8,22,36,37]

Autonomic dysfunctions are also common and include postural hypotension, gastrointestinal alterations, sexual dysfunction, increased salivation, sweating and lacrimation. A cardiovascular neurophysiologic examination revealed vagal or sympathetic abnormalities in most patients.[38] A cardiac sympathetic dysfunction is also present, and similar but less marked than that found in Parkinson disease.[39]

The disease progresses relentlessly to the use of the cane, walker, and wheelchair that occurs 12–25 years on average after disease onset. The mean progression rate is 1.49 ($\pm$0.07 SE) per year at the Scale for Assessment and Rating of Ataxia (SARA),[40] with earlier age at onset being associated with faster progression.[41]

A survival analysis conducted on Cuban patients showed an overall survival-years from birth to death of 52 years ($\pm$17.7 SD), and survival-years from onset to death of 21.8 years ($\pm$9.3 SD). The life expectancy of contemporaneous of SCA2 patients in general population was 77.97 years of age in Cuba.[42]

Imaging

Morphometric magnetic resonance imaging (MRI) shows a severe olivopontocerebellar atrophy (OPCA) pattern in the majority of SCA2 patients.[43] It is associated in a quarter of the patients with degeneration of the transverse pontine fibers and the middle part of the reticular formation, with sparing of the corticospinal tracts that results in the 'hot-cross bun' signs, a T2-weighted imaging hyperintensity in the axial slices of the pons.[44] These radiological signs are not specific since they may be present in other forms of sporadic ataxias, such as multiple system atrophy, or other SCAs. The pattern of atrophy has been better defined by voxel-based morphometry. Significant volume loss was observed not only in the subtentorial structure, including cerebellar hemispheres, vermis, pons, mesencephalon and thalamus but also in the supratentorial structures, including right orbitofrontal cortex, right temporomesial cortex, and primary sensory motor cortex.[45] Diffusion-weighted imaging (DWI), a sensitive method used to study structural regional brain changes in early stage of the disease and to monitor disease progression, showed increase in the apparent diffusion coefficient in subtentorial structures, including cerebellar white matter, pons, medulla, transverse pontine fibers, superior, and middle cerebellar peduncles.[46,47] More recent DWI studies also showed microstructural changes in supratentorial regions as cerebral hemispheres and corticospinal tracts at the level of centrum semiovale.[48,49] Proton magnetic resonance spectrometry showed a decreased of NAA in the pons and cerebellar hemispheres.[50,51] Finally, a resting state functional magnetic resonance imaging study, corrected for atrophy, showed, besides disruption of the cerebellar component of the major resting state networks,

supratentorial involvement for the default-mode network.[52] Dopaminergic transmission studied by beta-CIT, a presynaptic dopamine reuptake site ligand, and iodobenzamide (IBZM), a postsynaptic dopamine D2 receptor ligand, was found to be abnormal even in patients without parkinsonian features.[53,54] Rarity of parkinsonism despite severe degeneration of the substantia nigra and dopaminergic pathways has been explained by the lesion of the motor territory of the subthalamic nucleus in postmortem studies.[31] FDG-PET in 2 patients showed hypomethabolism in cerebellum and pons.[55] Transcranial sonography showed hyperechogenicity of the substantia nigra in 4 patients out of 6, similar to that found in PD but in absence of parkinsonian features.[56]

Neurophysiology

Peripheral nerve conduction study is abnormal in 63–100% of the patients. The peripheral neuropathy is usually sensory-motor and of axonal type, with sensory potential amplitude more severely affected than the amplitude of motor potentials.[57,58] Evidence of neuronopathy has been pointed out in a very small group of patients.[59] Sensory action potential amplitude of sural nerve correlated with disease duration and disease severity as measured by the International Cooperative Ataxia Rating Scale (ICARS) scores,[60] and presence of neuropathy was associated with early onset and more severe ataxia at the SARA[58] without effect of CAG repeats. Motor-evoked potentials showed a prolonged central conduction time more marked at lower limbs.[57] The cortical silent period is prolonged.[61] Somatosensory-evoked potentials are constantly abnormal at lower limbs. Brainstem and visual-evoked potential are also frequently abnormal.[57]

Cognition

Cognitive defects occur in about one quarter of the patients.[62,63] Cognitive deficits in moderate stage of the disease are broad and concern several domains, including executive function, fluid intelligence, verbal memory, visuo-spatial abilities.[62,64–67]

Burk et al. suggested that the performances at neuropsychological tests are related to the disease duration but not to the size of the expanded allele.[68] On the other hand, infantile forms that are characterized by larger expansions have marked cognitive impairment. Lack of association between motor dysfunction and cognitive impairment has been reported.[43,67,69]

The pattern of alteration in executive functions can be attributed to the disconnection syndrome in fronto-ponto-cerebello-thalamo-cortical pathways. The study of psychiatric features demonstrated a prevalence of major depression syndrome in about 20% of the patients and anxiety in about 15%.[63]

Infantile forms

Infantile forms of SCA2 are an uncommon occurrence and are associated with extremely large CAG expansions (range 100–200 repeats). The most frequent signs reported are developmental delay, visual impairment usually dependent on retinitis pigmentosa or optic atrophy, hypotonia, seizures with infantile spasms or myoclonic seizures, facial dysmorphism, and dystonic features. Death occurs early. Brain MRI showed extreme cerebellar and brainstem atrophy, but also different degrees of supratentorial atrophy and ventricular enlargement, and white matter signal abnormalities likely attributable to dysmyelination and/or delayed myelination.[70–73]

Presymptomatic carriers

Preclinical SCA2 carriers were mainly studied in two cohorts: the European cross-sectional RISCA (individuals at risk for spinocerebellar ataxia) study group and the Cuban cohort. The RISCA study showed that SCA2 mutation carriers had subtle coordination deficits that started in preclinical stage, and gradually increased before the onset of clinically manifested ataxia. Cramps appeared to be more frequent in SCA2 carriers than in noncarriers.[74] In the prospective Cuban cohort study, signs of peripheral nervous system involvement such as muscle cramps (4–12 years before ataxia), and sensory abnormalities (1–8 years before ataxia) occurred very early. Other signs included hyperreflexia followed by hyporeflexia, abnormal tandem gait (1–2 years before clinical diagnosis), oculomotor disturbances, executive dysfunction, impairment of visual memory, and a variety of autonomic symptoms. Altogether, these signs reflect subclinical involvement of the peripheral and autonomic nervous system, cerebellum, pons, prefrontal and medial temporal lobe, fronto-ponto-cerebellar and fronto-basal ganglia pathways.[75–77] The amplitude of sensory action potentials was decreased in medial and sural nerves several years before disease onset, and P40 latency of the tibial nerve somatosensory-evoked potentials was prolonged.[75] Saccades were slowed most notably in subjects with the largest CAG expansions. A correlation was present between the decreased of saccade velocity and time to manifestation of symptoms.[78] Eighty-three SCA2 RISCA cohort carriers underwent volumetric analysis that showed reduced brainstem volumes, and brain voxel-based morphometry MRI that showed gray matter loss in lobule V and VI of the cerebellum.[74] Nuclear imaging study have

shown dopaminergic impairment[79] and cerebellar and brainstem hypometabolism in preclinical stage.[55]

Atxn2 and amyotrophic lateral sclerosis (ALS)

SCA2 presenting as motor neuron disease with features of ALS

For alleles of 34 or more repeats, most individuals will develop cerebellar degeneration but some may present with motor neuron disease. At least five patients carrying a CAG expansion in SCA2 gene have been reported with ALS-like phenotype, with a CAG expansion ranging from 33 to 39.[80–84] The allele was interrupted by 1 CAA in the only sequenced case.[81] The disease may start with ataxia or parkinsonism, followed by signs of upper and lower motor neuron involvement. The case described by Van Damme et al. began with lower motor neuron signs and was followed 20 years later by ataxia. MRI varies from normal to severe cerebellar and brain stem atrophy.[83]

ATXN2 repeats as a risk factor for ALS

Based on interaction between ataxin-2 and TDP-43, a protein involved in ALS pathogenesis, Elden et al. investigated ataxin-2 as a risk factor for ALS in North American population.[85] More than twice as many patients with ALS compared to a control population had ataxin-2 polyglutamine repeat length in the high spectrum, within normal range (≥24 glutamines). The ratio was even greater with the repeat length ≥27 glutamines. The association of ALS with ataxin-2 longer normal alleles was confirmed in familial and sporadic ALS in different populations: North American, Dutch-Belgian, Italian, French-Canadian, Chinese, and Turkish. Lee et al. did not find association of ALS with long repeats in other polyglutamine disease genes.[86] In a meta-analysis, which included 7505 controls and 6151 sporadic ALS patients from different geographical and ethnic origins, Neuenschwander et al. found that alleles up to 30 repeats do not increase apparent risk. In fact, alleles of 27 repeats had a slight but significant reduced risk.[87] The risk of ALS was increased with alleles of 31, 32 and 33 repeats. Although these alleles are rare in the population they represent one of the most relevant risk factor for ALS. Chiò et al. in a large study of North Italian population showed that alleles ≥31 polyQ entailed a shorter survival than those <31 repeats by about 1 year.[84] In addition, ALS patient ≥31 CAG had more frequent spinal onset. There was no effect on age at onset. In a large cohort of French patients, larger repeats were also associated with increased risk of frontotemporal dementia-ALS.[88]

Atxn2 and parkinsonism

SCA2 presenting as parkinsonism

Gwinn-Hardy et al. reported a four-generation Chinese-American family with eleven affected members and different phenotypes.[89] Three of the four family members with PD phenotype showed L-Dopa responsiveness and complications of medications (wearing-off and dyskinesias). The trinucleotide repeat number was 35–36. Three further patients showed prominent parkinsonism associated with variable ataxic features. One patient was diagnosed as progressive supranuclear palsy because of the presence of bradykinesia, lack of response to L-Dopa, prominent vertical gaze palsy but not ataxia signs. Several other families with parkinsonian phenotype have been described since then.[90–94] Number of CAG repeats was <40 repeats and the sequence was interrupted by CAA when explored. They usually responded to L-Dopa treatment. It is not known the prevalence of asymptomatic cerebellar atrophy in parkinsonian patients. SCA2 expansions explained 0–2% of familial parkinsonism in Caucasian[94–96] and up to 10% in Asian population.[92,93]

Wang et al. in a large study on patients, both Caucasian or Asian, with idiopathic Parkinson disease has not identified causative mutations or increased risk attributable to long normal alleles.[97]

Symptomatic treatment and rehabilitation

It has been reported that dopaminergic and anticholinergic treatments might decrease tremor, dystonia, and bradykinesia in patients with SCA2, whereas painful muscle contractions can be alleviated by magnesium, quinine, mexiletine or high doses of vitamin B. SCA2 patients with parkinsonism might exhibit beneficial response to levodopa.[98] The use of deep brain stimulation has been reported to improve a severe tremor by stimulation at the thalamic and subthalamic targets in two patients. Piracetam could be considered in the treatment of myoclonus refractory to conventional therapy.[99] Rehabilitation does not stop disease progression but can improve motor performances.

Aids can help the patient to maintain independence. Patients with dysarthria can benefit from speech therapy and the use of electronic devices for communication. Dysphagia may require gelling agents to facilitate the ingestion of liquids. Percutaneous endoscopic gastrostomy (PEG) could be necessary in late stages of disease.

Therapeutic avenues

No treatment is currently available for the disease. Nevertheless, clinical and preclinical work, using in vitro and

in vivo models of the disease have highlighted a number of possible rational therapeutic approaches, which could be summarized into targeting the mutant gene or targeting the pathogenic cascade downstream of ataxin-2.

Targeting the mutant gene

Antisense oligonucleotides (ASOs) represent a promising strategy to effectively downregulate the expression of the polyQ expanded ataxin-2. Once in the cell, ASOs hybridize with the complementary mRNA and forms a DNA-RNA duplex, which is recognized and cleaved by the RNaseH enzyme. Modified ASOs such as 2′-O-dimethoxyethyl-group-gapmer (MOE-gapmer ASO) support RNaseH cleavage. Treatment of a transgenic mouse carrying 127 CAG repeats (Pcp2 ataxin Q127) with ataxin-2-targeting 2′-O-dimethoxyethyl-group-gapmer (MOE) ASO, a chemistry that supports RNaseH cleavage, reduced both endogenous mouse and human transgenic ataxin-2 mRNA, partially reversed Purkinje cells low firing frequency in transgenic animals, and improved the motor phenotype. Work is currently ongoing to modify the properties of antisense molecules, which do not cross the blood–brain barrier and therefore require intrathecal administration to reach neuronal targets.[100] Furthermore, the reduction of ataxin-2 has therapeutic potential for ALS and fronto-temporal dementia. TDP-43 pathology is a component of 7% of ALS cases and nearly 50% of fronto-temporal dementia cases. In *ataxin-2* knockout/*TDP-43* transgenic mice, the decrease in ataxin-2 reduced aggregation of TDP-43 and markedly increased survival. The latter result was also achieved by the administration of ASOs targeting ataxin-2 to the central nervous system of *TDP-43* transgenic mice.[101]

Targeting the pathogenic cascade downstream of ataxin-2

Dantrolene, a ryanodine receptor inhibitor and stabilizer of intracellular calcium, reduces cell death induced by glutamate in Purkinje cells. These results were confirmed in the SCA2 (Q58) murine model, where the administration of dantrolene improves motor coordination and decreases loss of Purkinje cells.[25]

Riluzole is a drug licensed for treatment of amyotrophic lateral sclerosis. The mechanism of action is not yet fully understood, but it has been shown to exert a neuroprotective effect by modulating glutamate neurotransmission and inhibiting voltage-gated sodium channels. It has been used in a 12-month, double-blinded, placebo-controlled trial on 60 patients with heterogeneous forms of hereditary ataxias (Friedreich ataxia or different forms of SCAs). Riluzole was well tolerated and had a positive effect on reducing SARA scores in 50% of treated patients versus 11% in the placebo group.[102]

Lithium might stimulate autophagy, clear protein aggregates, reduce inositol-trisphosphate levels and the subsequent calcium efflux from the ITPR1. A randomized, placebo-controlled trial showed nonsignificant differences at SARA or in MRI brain volume.[103]

Conflict of Interest

Drs. Antonella Antenora, Carlo Rinaldi, Alessandro Roca, Chiara Pane, Maria Lieto, Francesco Saccà, Silvio Peluso, Giuseppe De Michele, Alessandro Filla have nothing to disclose.

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