Bethlem myopathy and vascular malformations

Marco Auletta [1], Tommaso Verdolotti [2], Irene Scala [3], Cristina Sancricca [4,5], Guido Primiano [4,7], Costanza Lamperti [6], Serenella Servidei [4,7]

1 Neurology Section, Department of Neuroscience, Università Cattolica del Sacro Cuore, Roma, Italy.
2 UOC Radiologia e Neuroradiologia, Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Roma, Italy.
3 Cerebrovascular Unit, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milano, Italy
4 Neurophysiopathology unit Fondazione Policlinico Universitario A. Gemelli IRCCS, 00168 Roma, Italy.
5 Fondazione UILDM Lazio Onlus, Roma 00167, Italy.
6 Unit of Medical Genetics and Neurogenetic, Fondazione IRCCS Istituto Neurologico Carlo Besta, 20133 Milano, Italy.
7 Dipartimento di Neuroscienze, Università Cattolica del Sacro Cuore, Roma, Italy.

Background

Type 6 collagen (**COL6**) constitutes a key component of the extracellular matrix and serves multiple roles in facilitating cell adhesion, proliferation, migration and survival. COL6 related dystrophies (**COL6-RDs**) are caused by either AD or AR mutations involving ***COL6*** genes *(A1-A3)*. The resulting disruption of the extracellular matrix manifests clinically as two main phenotypes:

- **Bethlem Myopathy:** mild form characterized by the progressive deveolpmente of tendon contractures, joint hyperlaxity and muscle weakness.
- **Ullrich congenital muscular dystrophy:** severe and early onset form with hypotonia and severe joint contractures. Common respiratory involvment.

Case 1

- Woman affected by congenital hip dysplasia, proximal myopathy and tendon contractures.
- Spontaneous subarachnoid emorrhage at 35 y.o.
- **MRI:** Detection of a right subcortical ischemic lesion and multiple intracranial aneurysms: two affecting the right middle cerebral artery (MCA) and two affecting the left MCA (*fig.1 a-d*)→ Succesful coil embolization
- **Muscle MRI:** Diffuse atrophy and fat replacement of pelvic and scapular girdles and lower limbs (*fig.1 e*).
- **Genetic testing**: COL6A3 mutation (G2077D)
- **Family History:** father with elevated CK levels and mild tendon contractures→ detection of the proband ***COL6A3*** mutation and an aneurysm affecting the right MCA. *(fig.2)*

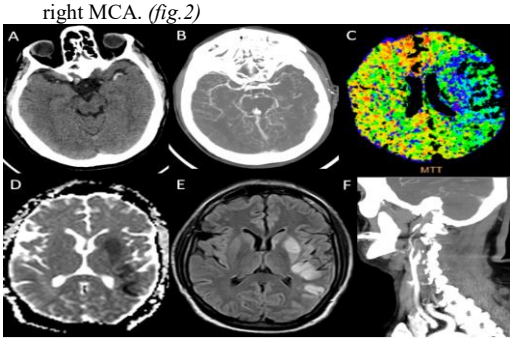

Fig. 3 Case 2 A) Brain CT scan showing hyperdensity in the M1 segment of the left middle cerebral artery (MCA). **B) CTA** confirmed left MCA occlusion and showed a proximal left internal carotid artery (ICA) dissection **(F)**. **(C) CT perfusion** showing an area of increased MTT in the left hemisphere. **(D-E) MRI scans** 2 days after treatment showed areas of FLAIR signal hyperintensity (E) with restricted diffusion (D) in the left deep grey nuclei and in the cortex of insular and temporo-parietal gyri, representing ischemic stroke

Aim

Despite the similarities with other collagen-related diseases (e.g. Ehler Danlos syndrome) it has never been reported the increased occurrence of vascular malformations in COL6-RDs. We report here two cases showing this association.

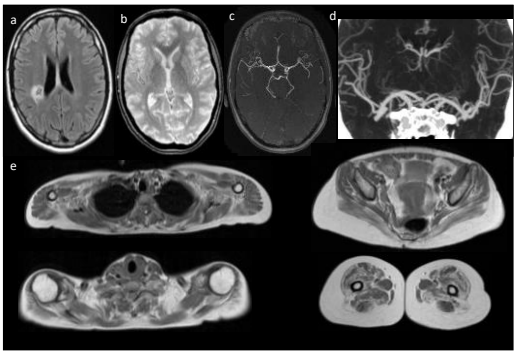

Fig 1. Case 1 Brain MRI FLAIR (a), GRE T2*w c (b) sequences and **Time of flight (TOF) MR angiopraphy, MIP reconstruction (c)** and **CT angiography, MIP reconstruction (d)** showimg a focal area of signal hyperintensity in the right corona radiata **(a)**, representing previous stroke. Linear hemosiderin deposits due to previus subaracnoid hemorrage are located along the right silvian fissure **(b)**. TOF angiography **(c)** and CTA **(d)** showing aneurysms affecting middle cerebral artery, bilaterally.
Proband **whole body muscle MRI** T1w Fast Spin Echo (FSE) image **(e)**. Scans show atrophy of muscles of the shoulder and pelvic girdles and of the lower limbs. There are patchy areas of T1w signal hyperintensity, likely representing fat replacement with bilateral and simmetric distribution.

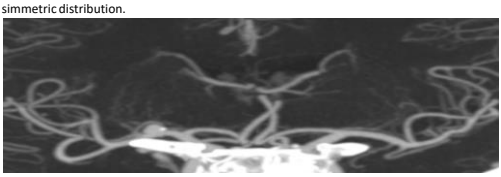

Fig 2 Proband Father CT Angiography of Circle of Willis; MIP reconstruction. Scans show the presence of an unruptured aneurysm of the right middle cerebral artery (M1 segment) along with an eccentric parietal calcification

Case 2

- Man affected by congenital hip dysplasia, flat feet and genu valgum
- Muscle biopsy showing unspecific myopathic changes (not shown)
- Family history unremarkable for neurological diseases
- At the age of 42, sudden onset of global aphasia and right hemiplegia
- **CT angiography**: left internal carotid artery (ICA) dissection, ipsilateral MCA occlusion and right ICA tortuosity→ unsuccesful thrombolysis and mechanical thrombectomy.
- **MRI**: left sided subcortical ischemic lesions→ started on acetilsalicyclic acid

Conclusions

This report suggests that COL6 mutations can pose an increased risk for vascular malformations. After establishing the diagnosis it would be reasonable to include head and neck imaging studyies to allow early detection of vascular malformations. Furthermore, in the setting of early onset sponteanous subarachnoid hemorrhages secondary to aneurysmal rupture, multiple aneurysms, spontaneous vascular dissections and/or familial recurrence, it would be useful to include COL6 genes in the diagnostic work-up

24-28 Ottobre 2025
Padova Congress
55° CONGRESSO SOCIETÀ ITALIANA DI NEUROLOGIA