**The first two-year follow-up in a patient with isolated sensory neuronopathy due to biallelic expansion in *RFC1* gene.**

Stefano Tozza,[1*] Riccardo Currò,[2,3] Daniele Severi,[1] Vincenzo Marcelli,[4] Carlo Cavaliere,[5] Gabriella Esposito,[6,7] Rosa Iodice,[1] Andrea Cortese[2,8] and Fiore Manganelli.[1]

[1] Department of Neurosciences, Reproductive and Odontostomatological Sciences, University of Naples "Federico II", Naples, Italy;

[2] Department of Brain and Behavioral Sciences, University of Pavia, Pavia, Italy;

[3] IRCCS Mondino Foundation, Pavia, Italy;

[4] ASL Napoli1 Centro, Ospedale del Mare, Naples, Italy;

[5] IRCCS SYNLAB SDN, Naples, Italy;

[6] Department of Molecular Medicine and Medical Biotechnologies, University of Naples "Federico II", Naples, Italy;

[7] CEINGE-Advanced Biotechnologies s.c. a r.l., Naples, Italy;

[8] Department of Neuromuscular Diseases, UCL Queen Square Institute of Neurology, London, UK.

*Corresponding author:
Stefano Tozza, MD
Univeristy of Naples "Federico II"
Via Sergio Pansini, 5
80131 - Naples - Italy
+39 081 746 4579
ste.tozza@gmail.com

**Keywords** RFC1-related sensory neuropathy; CANVAS; vestibular areflexia; vestibular test.

Dear Editor,

biallelic expansion in *RFC1* gene is the genetic alteration underlying Cerebellar Ataxia, Neuropathy and Vestibular Areflexia syndrome (CANVAS) [1]. Recently, this genetic alteration in *RFC1* gene was found in 34-50% of patients labelled as having isolated chronic idiopathic axonal polyneuropathy (CIAP) with pure involvement of sensory nerves [2,3]. In patients carrying *RFC1* biallelic expansion, sensory neuropathy seems to be the first and constant system involved, while vestibular and/or cerebellar dysfunction is less commonly complained and/or appears later in the natural history of RFC1-related disorder [4].

We report the first two-year follow-up of a male patient carrying a biallelic expansion in *RFC1* gene that presented as isolated sensory neuropathy.

A 54-year-old man was evaluated in our tertiary neuromuscular disease center for tingling sensation at both hands in the past few months. Past medical history was unremarkable with exception of chronic cough, which was attributed to smoking habit. Neurological examination was unremarkable with normal strength, no sensory deficit and sign of sensory ataxia (he could walk with closed eyes, Romberg test was negative). Deep tendon reflexes were overall present. No signs of cerebellar involvement were present. In the suspicion of carpal tunnel syndrome, patient underwent neurophysiological test that revealed total absence of sensory action potentials at upper and lower limbs whereas motor nerve conduction study was normal. A diagnosis of sensory ganglionopathy was made. In the suspicion of CANVAS [5], the evaluation of vestibular function through bedside Head Impulse Test (b-HIT) and video Head Impulse Test (v-HIT) using ICS-impulse® equipment (GN Otometrics, 99 Taastrup, Denmark) appeared normal (Figure 1A).

Meanwhile, common acquired causes for sensory neuronopathy (autoimmune, paraneoplastic, deficiency, toxic) were excluded. In the suspicion of hereditary sensory neuropathy, a targeted next generation sequencing panel including about 140 genes associated with isolate and syndromic inherited neuropathies did not show any significant pathogenetic variants. Therefore, neuropathy was labelled as idiopathic sensory axonal ganglionopathy.
After the biallelic RFC1 expansion has been associated with the isolated sensory neuro(no)pathy [2,3], we therefore considered the hypothesis of the RFC1-related neuropathy. Molecular analysis by Southern blot sized an AAGGG expansions of 800 and 1150 repeats. The concluding diagnosis was *RFC1*-related isolated sensory neuronopathy. No family history was present, the neurological examination and nerve conduction study of the two siblings were completely unremarkable.

Two years later, patient did not report any significant clinical changes. A new neurological assessment confirmed normal sensory, motor and cerebellar examination. However, B-HIT showed abnormal catch-up saccades at the rapid rotation of the head, confirmed through v-HIT that showed a bilateral vestibular horizontal canal hypofunction with a reduced vestibulo-oculomotor reflex (VOR) gain for both lateral semi-circular canal (right= 0.52; left=0.65). The function of anterior (right=0.82; left= 0.9) and posterior (right= 0.87; left=0.7) canals appeared otherwise normal (Figure 1B).

To detect any subclinical involvement of cerebellum, patients performed 3T brain MRI with volumetric structural sequences. Brain imaging did not show any focal/diffuse cerebellar atrophy and signal alterations neither enlargement of liquoral pericerebellar spaces (Figure 2).

In conclusion, we would like that clinician pay attention on patients with sensory neuropathy. In fact, these patients, regardless the involvement of other systems (vestibular and cerebellar), should be tested for RFC1 gene since this alteration can explain up to 50% of them [3].

Moreover, the 2-year follow-up in this patient with initial isolated sensory neuronopathy revealed a subclinical vestibular dysfunction. We firstly demonstrated the notion of a spatial progression in CANVAS. In fact, the disease seems to early involve sensory neurons and later vestibular system and/or cerebellum [4]. In patients with isolated sensory neuropathy related to RFC1 expansion, in addition to a neurological assessment, we suggest a periodic follow-up through vestibular test and brain MRI is needed, in order to early detect the subclinical involvement of vestibular and/or cerebellar systems. Only a multidisciplinary evaluation, indeed, can be able to define the appropriate management of these patients and to elucidate the natural history of RFC1-related disorder.

**Disclosure of potential conflicts of interest** The authors declare no competing interests.

**Ethics approval** Ethical approval was waived by the local Ethics Committee in view of the retrospective nature of the study and all the procedures being performed were part of the routine care.

**Informed consent** Informed consent for publication was collected from patient.

**Figure 1. Video head impulse test**

Vestibular function, analysed through ICS-impulse® equipment, showed a normal dynamic VOR gain of anterior (right=1,02; left= 1,08), lateral (right= 0.93; left=0.97) and posterior (right= 0,91; left=1,02) canals at first evaluation (1A). After two-year follow-up, v-HIT showed a reduced dynamic VOR gain of both lateral canals (right= 0.52; left=0.65), while anterior (right=0,82; left= 0,9) and posterior (right= 0,87; left=0,7) canals appeared normal (1B).

**Figure 2. Brain MRI**

Brain MRI (midsagittal view) showed normal cerebellar findings.

**REFERENCES**


1. Cortese A, Simone R, Sullivan R, Vandrovcova J, Tariq H, Yau WY, Humphrey J, Jaunmuktane Z, Sivakumar P, Polke J, Ilyas M, Tribollet E, Tomaselli PJ, Devigili G, Callegari I, Versino M, Salpietro V, Efthymiou S, Kaski D, Wood NW, Andrade NS, Buglo E, Rebelo A, Rossor AM, Bronstein A, Fratta P, Marques WJ, Züchner S, Reilly MM, Houlden H. Biallelic expansion of an intronic repeat in RFC1 is a common cause of late-onset ataxia. Nat Genet. 2019 Apr;51(4):649-658. doi: 10.1038/s41588-019-0372-4. Epub 2019 Mar 29. Erratum in: Nat Genet. 2019 May;51(5):920. PMID: 30926972; PMCID: PMC6709527.
2. Currò R, Salvalaggio A, Tozza S, Gemelli C, Dominik N, Galassi Deforie V, Magrinelli F, Castellani F, Vegezzi E, Businaro P, Callegari I, Pichiecchio A, Cosentino G, Alfonsi E,

Marchioni E, Colnaghi S, Gana S, Valente EM, Tassorelli C, Efthymiou S, Facchini S, Carr A, Laura M, Rossor AM, Manji H, Lunn MP, Pegoraro E, Santoro L, Grandis M, Bellone E, Beauchamp NJ, Hadjivassiliou M, Kaski D, Bronstein AM, Houlden H, Reilly MM, Mandich P, Schenone A, Manganelli F, Briani C, Cortese A. RFC1 expansions are a common cause of idiopathic sensory neuropathy. Brain. 2021 Jun 22;144(5):1542-1550. doi: 10.1093/brain/awab072. PMID: 33969391; PMCID: PMC8262986.

3. Tagliapietra M, Cardellini D, Ferrarini M, Testi S, Ferrari S, Monaco S, Cavallaro T, Fabrizi GM. RFC1 AAGGG repeat expansion masquerading as Chronic Idiopathic Axonal Polyneuropathy. J Neurol. 2021 Nov;268(11):4280-4290. doi: 10.1007/s00415-021-10552-3. Epub 2021 Apr 21. PMID: 33884451; PMCID: PMC8505379.

4. Cortese A, Tozza S, Yau WY, Rossi S, Beecroft SJ, Jaunmuktane Z, Dyer Z, Ravenscroft G, Lamont PJ, Mossman S, Chancellor A, Maisonobe T, Pereon Y, Cauquil C, Colnaghi S, Mallucci G, Curro R, Tomaselli PJ, Thomas-Black G, Sullivan R, Efthymiou S, Rossor AM, Laurá M, Pipis M, Horga A, Polke J, Kaski D, Horvath R, Chinnery PF, Marques W, Tassorelli C, Devigili G, Leonardis L, Wood NW, Bronstein A, Giunti P, Züchner S, Stojkovic T, Laing N, Roxburgh RH, Houlden H, Reilly MM. Cerebellar ataxia, neuropathy, vestibular areflexia syndrome due to RFC1 repeat expansion. Brain. 2020 Feb 1;143(2):480-490. doi: 10.1093/brain/awz418. PMID: 32040566; PMCID: PMC7009469.

5. Tozza S, Cortese A, Iovino A, Esposito M, Dominik N, Iodice R, Manganelli F. Bedside Head Impulse Test: A Useful Tool for Patients With Sensory Ataxia. Neurol Genet. 2020 Dec 21;7(1):e541. doi: 10.1212/NXG.0000000000000541. PMID: 33728375; PMCID: PMC7879339.