A case report of recessive myotonia congenita and early onset cognitive impairment

Is it a causal or casual link?

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Abstract

Rationale: Myotonia congenita (MC) is a non-dystrophic myotonia inherited either in dominant (Thomsen) or recessive (Becker) form. MC is due to an abnormal functioning of skeletal muscle voltage-gated chloride channel (CLCN1), but the genotype/phenotype correlation remains unclear.

Patient concerns: A 48-year-old man, from consanguineous parents, presented with a fixed muscle weakness, muscle atrophy, and a cognitive impairment. Notably, his brother presented the same mutation but with a different phenotype, mainly involving cognitive function.

Interventions: The patient was submitted to cognitive assessment, needle electromyography, brain and muscle MRI, and genetic analysis.

Outcomes: The Milan Overall Dementia Assessment showed short-term memory, verbal fluency and verbal intelligence impairment. His genetic analysis showed a recessive splice-site mutation in the CLCN1 gene (IVS19+2T->A). Muscle MRI revealed a symmetric and bilateral fat infiltration of the tensor of fascia lata, gluteus medius, and gluteus maximus muscles, associated to mild atrophy.

Diagnosis: Recessive myotonia congenita was diagnosed.

Lessons: Further studies should establish if and to which extent the CLCN1 mutation is responsible for this c MC phenotype, taking into account a gene–gene and/or a gene–environment.

Abbreviations: ALS = amyotrophic lateral sclerosis, CI = cognitive impairment, CLCN1 = voltage-gated chloride, CNBP = nucleic acid-binding protein, DMPK = myotonic dystrophy protein kinase, DMs = dystrophic myotonias, EMG = needle electromyography, IBM-PD-FTD = inclusion body myopathy with Paget disease of bone and frontotemporal dementia, IQ = intelligence quotient, MC = myotonia congenita, MODA = Milan Overall Dementia Assessment, NDMs = nondystrophic myotonias, NGS = next generation sequencing, VCP = Valosine Containing Protein gene.

Keywords: CLCN1, cognitive impairment, myotonia congenita, splicing mutation

1. Introduction

An abnormal delay in muscle relaxation after a strong voluntary or evoked muscle contraction is the essence of the myotonic phenomenon, which is the main clinical feature of dystrophic (DMs) and nondystrophic myotonias (NDMs).[1] The former is related to mutations in the myotonic dystrophy protein kinase (DMPK) gene and nucleic acid-binding protein (CNBP) gene (previously known as zinc finger 9 gene, ZNF9), respectively, DMPK or ZNF9 genes, whilst the latter to mutations in voltage-gated chloride (CLCN1) and sodium channels.[1] Specifically, Myotonia congenita (MC), which can be inherited in either dominant or recessive form, is due to an abnormal functioning of skeletal muscle CLCN1, located on chromosome 7q35.[1] Although most recessive CLCN1 mutations produce a channel loss-of-function, and the most dominant CLCN1 mutations produce a channel gain-of-function, yet the genotype/phenotype correlation remains poor. Functional studies on each mutation may be useful to predict phenotype, confirm pathogenicity for novel mutations, and evaluate the treatment response and therapeutic options for NDMs.[2] However, splicing mutations, that is, insertions, deletions or changes of a number of nucleotides in the specific site at which splicing takes place, may lead to the
production of abnormal proteins.\textsuperscript{13} MC is a slowly progressive autosomal disorder, usually manifesting between 4 and 14 years of age, characterized by the presence of painless myotonia starting from lower limbs and spreading to the arms, neck, and facial muscles, and a generalized muscle hypertrophy that gives rise to the peculiar athletic appearance of such patients.\textsuperscript{1,4} The clinical phenotype severity is related to the dominant (Thomsen) or recessive form (Becker), being the latter more severe and more widespread than the former.\textsuperscript{11} Moreover, transient weakness after rest is a common feature of Becker MC.\textsuperscript{1}

To date, a central nervous system involvement has been reported only in DM\textsubscript{2} \textsuperscript{15,16} even though a casual association of MC and Multiple Sclerosis has been shown in some NDM\textsubscript{1}\textsuperscript{7–9}.

Although cognitive impairment (CI) has been associated to DMs, no data have been reported indeed on the presence of CI in NDM\textsubscript{1}\textsuperscript{10}. Herein, we report on a patient affected by recessive MC and early onset familial CI. While investigating the patient, the same diagnosis was performed to his older brother, even though presented a different phenotype. The Local Ethics Committee of our Institute approved the study and the patient and his brother gave their written informed consent to study publication.

2. Clinical report

A 48-year-old man, with consanguineous parents, was referred to our institute because of a marked generalized stiffness and diffuse muscle weakness, mainly involving the axial muscles. Family history was apparently negative for neuromuscular diseases. His 54-year-old brother and his mother (deceased) suffered from early onset CI (Fig. 1).

Gestation and delivery were uneventful. His early development progressed normally, apart from leg muscle hypertrophy, until the age of 17 years, when he presented a single episode of marked and generalized muscle stiffness, also involving the tongue and the jaw, with difficulty to move and speak, lasting about 6 hours, with a spontaneous recovery. Since then, these episodes became more frequent over the years, so that stiffness was persistent all day long, with transient dysphagia, easy fatigability, and tendency to fall. However, he usually recovered spontaneously and improved with exercise. Rest, but not cold, worsened his stiffness.

General examination showed some dysmorphisms, including high-arched palate, short neck, small extremities and sharp nose. Neurological examination showed marked lumbar hyperlordosis, generalized muscle hypertrophy, especially at the lower limbs, and a slight bilateral ankle tendon retraction. The patient presented difficulty to raise from a chair, from the ground and from the supine position, with a marked neck flexor muscles weakness. He also showed a slight waddling gait with difficulty to walk on heels and toes, jaw and eyelid myotonia (which partially improved with repeated exercise, that is, warm-up phenomenon), but not percussion and handgrip myotonia (Video 1, http://links.lww.com/MD/C255). Notably, during the neurological examination he used to repeatedly make the same comments, he had some difficulties in language fluency, in making decisions, and in recalling some words during speech. For this reason and considering patient’s family history for early onset CI, the patient was administered the Milan Overall Dementia Assessment (MODA), showing short-term memory, verbal fluency and verbal intelligence impairment (Table 1). A depressed mood with anxiety was also detected. Cardiac evaluation showed signs of high blood pressure, properly treated with ACE-inhibitors. Neither other signs of cardiovascular involvement nor hemodynamically significant carotid artery stenosis were detected. Extensive laboratory tests did not disclose any abnormality, apart from a slight increase of CK levels (300–400 U/L). Needle electromyography (EMG) revealed membrane hyperexcitability (myotonic discharges) in each of the muscles tested (biceps brachii, first dorsal interosseous, paraspinous, vastus laterals, and tibialis anterior muscles). Voluntary activity was quantitatively and qualitatively normal. Evidence of membrane disinhibition belonging to a Fournier pattern II was also found.\textsuperscript{11,12}

Taking into account the severity of the clinical phenotype, the muscle weakness mainly involving axial muscles, the diffuse myotonic discharges, and the CI, a biceps muscle biopsy was performed. We observed a mildly abnormal variation in fiber size and a significant decrease of type IIIB fibers at pH 4.6 ATPase staining. Therefore, a molecular study for DMPK and CNBP genes was performed, showing no alteration supporting DMs. Then, a direct nucleotide sequence analysis of PCR products revealed the IVS19+2T>A mutation in the CLCN1 gene. Although the genomic DNA of the patient’s parents was not available, considering the clinical phenotype, the findings indicated that the patient was most likely to be homozygous, and a Becker MC diagnosis was thus reached.

A brain and muscle MRI were also performed. The former showed the presence of numerous postischemic gliotic lesions, hyperintense on T2-weighted images, in the bilateral frontal subcortical and peri-trigonal white matter, and a diffuse enlargement of the Virchow–Robin perivascular spaces.

Table 1

|                  | Milan Overall Dementia Assessment (MODA) | Subscale scores |
|------------------|----------------------------------------|-----------------|
|                  | Proband | Brother |
| Orientation      | Temporal orientation | 8/10 | 7/10 |
|                  | Spatial orientation | 3/3 | 2/3 |
|                  | Personal orientation | 8/10 | 6/10 |
|                  | Familial orientation | 12/12 | 9/12 |
| Daily autonomy   | Autonomy scale | 12/15 | 10/15 |
|                  | Reversal learning | 5/5 | 3/5 |
|                  | Attention test | 9/10 | 6/10 |
|                  | Verbal intelligence | 2/6 | 2/6 |
|                  | Little story | 4.4/8 | 3/8 |
| Neuropsychological tests | Word production test | 1/5 | 1/5 |
|                  | Coins’ test | 5/5 | 3/5 |
|                  | Digital agnosia | 5/5 | 5/5 |
|                  | Construction apraxia | 3/3 | 2/3 |
|                  | Street’s completion test | 2/3 | 2/3 |
(Fig. 2). The latter revealed a symmetric and bilateral fat infiltration of the tensor of fascia lata, gluteus medius, and gluteus maximus muscles, associated to mild atrophy (Fig. 3).

Mexiletine, at the dosage of 800 mg/daily, was then prescribed, with a marked myotonia improvement.

Given that the patient’s older brother had also an early onset CI, we submitted him to an electromyographic examination, which showed diffuse myotonic discharges, even though clinical examination did not show any sign of myotonia. His genetic analysis disclosed the IVS19+2T>A in CLCN1 gene, confirming the well-known intrafamilial heterogeneity of NDMs. Because of the muscular clinical variability and the common CI, both siblings underwent a gene specific panel analysis for familiar CI by means of next generation sequencing (NGS). The analysis showed in both siblings 2 homozygous mutations in the Valosine Containing Protein (VCP) gene: the c.1695+8A>G and the c.811+3G>A, which explained their early onset CI.

3. Discussion

We report on 2 siblings affected by Becker MC harboring the IVS19+2T>A pathogenic variant in the CLCN1 gene, associated
to the c.1695+8A>G and the c.811+3G>A in the VCP gene, presenting a severe generalized MC phenotype with a familial early onset CI.

The 2 siblings presented a marked clinical variability for both diseases, MC and CI, in keeping with the intrafamilial variabilty of NDMs and VCP-related FT.

In fact, the proband was more severely affected by MC, whereas his brother by CI. The severe involvement of muscle system was confirmed by the MRI we performed. To date, literature data on MRI imaging in MC are discordant. In fact, Maggi et al. reported on MRI findings in a cohort of patients affected by NDMs, including 2 patients affected by Thomsen and Becker MC, demonstrating a marked T1w changes in medial gastrocnemius, sartorius, gracilis and semitendinosus, and a sparing of rectus and vastus lateralis, without specific distribution pattern.[13] On the contrary, a study investigating 3 patients with recessive MC through whole body MRI did not demonstrate any abnormality.[14] No data are, however, available on muscle atrophy in NDMs. Indeed, our patient showed a symmetric and bilateral fat infiltration of proximal muscles (i.e., tensor of fascia lata, gluteus medius, and gluteus maximus), associated to a mild atrophy, being this the first description of atrophy at MRI scans in MC.

CI is defined as “a significantly reduced ability to understand new or complex information, to learn new skills, . . . with a reduced ability to cope independently . . . which started before adulthood, with a lasting effect on development.”[15] Among the different forms of CI, the milder ones are considered the lower part of a normal intelligence quotient (IQ) distribution and the result from the interplay of many genetic and epigenetic factors. Considering such genetic complexity, little is still known about the genetic factors underlying a CI. Moreover, the difficulty to unambiguously distinguish normal and mildly affected family members could be considered another factor complicating genetic research of this field. However, not all forms of CI are multifactorial, since some segregate in families as Mendelian traits,[16] as it occurs, for example, in DMS (for myotonic dystrophy, ~1/8000 cases).[1]

From the molecular point of view, the IVS19+2T>A in the CLCN1 has not been clearly described in its clinical phenotype. Its location in the CLCN1 gene is considered to be implied in causing recessive MC in Italian and Russian patients.[17] Recently, Liu et al. reported on another mutation, the IVS19+2T>C, which is located in the same intron 19 and CBS2 domain of CLCN1. This site (IVS19+2T>C) showed that it probably has an impact on splicing, as the partial removal of the CBS domains of CLCN1 (that are known to interact and form intra-molecular dimeric complexes), can cause either loss-of-function, or alterations in channel gating or subcellular distribution.[17,18]

Given that these mutations share the same splice site, even for the IVS19+2T>A pathogenic variant, the splicing effects could be similar.

However, to date, the IVS19+2T>A has been reported as harbored together with other CLCN1 variants (R894X and A493G), although only one individual was confirmed to harbor variants on both CLCN1 alleles, as parental testing was not performed in the other 2 cases.[17,18] Moreover, it is worthwhile to note that no other CLCN1 mutations were reported in our patient, who was homozygous for IVS19+2T>A.

Regarding the CI mutations in the VCP gene were detected in both siblings. VCP gene encodes a member of the AAA ATPase family of proteins,[19] playing different important roles, that is, intracellular membrane fusion, DNA repair and replication, regulation of the cell cycle, protein degradation, and activation of the NF-kappa B pathway.[20,21] VCP mutations alter the ubiquitin-binding,[22,23] thus causing different diseases, such as Inclusion Body Myopathy with Paget Disease of bone and Frontotemporal Dementia (IBM-PD-FTD), amyotrophic lateral sclerosis (ALS) and Charcot-Marie-Tooth disease, and dementia, mainly of the FTD.[22,23]

FTD often begins when the patient is in the fifth to seventh decades, and includes a group of progressive degenerative disorders presenting with progressive behavioral change, executive dysfunction, and language difficulties.[24] Hereditary FTD forms account for the 40% of cases[25] and VCP, located on chromosome 9p13.3, is one of the rare genes involved in such disease.[22,26] Even though our siblings presented a mild form of CI, but having demonstrated the homozygosity for VCP mutations, they are closely monitored in order to evaluate the development of a more compromised CI.

To date, the NGS technologies provide faster and more cost-effective sequencing strategies that allow an entire genome to be sequenced in <1 day. NGS technology has important implications in understanding the basis of many Mendelian neurological conditions and complex neurological diseases that have enabled the identification of rare disease variants, including unmasking small mutations.

To have an autosomal recessive form of MC and CI within the same family members, let us speculate that in small villages or in populations with a high degree of parental consanguinity, some of these gene defects may interact.

Thus, a gene–gene and/or a gene–environment interaction may account for such particular phenotype in the 2 brothers.

Further studies should be performed in order to identify more patients harboring these mutations and looking for an early onset CI in other individuals harboring the IVS19+2T>A, suggesting a genetic predisposition induced by one of the 2 genes alterations.

Author contributions

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