Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Benign Hereditary Chorea as a Manifestation of HPCA Mutation

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Biallelic pathogenic variants in the *HPCA* gene encoding hippocalcin have been recently identified as causative of autosomal recessive (AR) isolated dystonia (MIM 224500). The first reported family consisted of three siblings presenting in the first decade of life with dystonia that progressively became generalized, with a more severe involvement of the upper limbs and craniocervical district. Pathogenic variants in *HPCA* were also identified in an unrelated subject affected by sporadic isolated dystonia.[1] The pathogenic role of *HPCA* in causing AR dystonia was confirmed by the identification of truncating mutations in two unrelated individuals from two consanguineous Turkish families, displaying generalized dystonia with prominent bulbar involvement, febrile seizures, and neurodevelopmental delay.[2] Yet, subsequent studies failed to identify additional pathogenic variants in patients with early onset isolated dystonia, suggesting *HPCA* variants are a rare cause of AR-dystonia.[3,4] Recently, a novel HPCA missense variant was also found in a pediatric patient and two affected relatives with dystonia and intellectual disability.[5]

HPCA encodes for a neuronal calcium sensor protein involved in sensing cytosolic calcium levels and regulating activity of voltage-dependent calcium and potassium channels.[6–8] The gene is almost exclusively expressed in the brain with highest expression levels in the cortex, striatum, cerebellum, and hippocampus,[6,7] the latest implicated in memory formation.[1] Hippocalcin has been intensely studied in relation to its role in dendritic maturation and synaptic plasticity of striatal neurons, where it is hypothesized to play a role in dystonia-onset. Recent functional work suggests an overall loss-of-function mechanism for dystonia-linked variants.[9]

We report a case of an 8-year-old girl with a generalized chorea, homozygous for a novel *HPCA* variant.

Case Report

The patient is an 8-year-old girl, first-born child from healthy consanguineous parents (first cousins) from Pakistan. Clinical and neurological examinations of her two siblings and parents were normal. Delivery and neonatal period were uneventful. Head and trunk control were reported on time, independent gait was at 26 months with later normal motor achievements. Parents reported mild language delay in mother tongue. She has learned Italian on admission in the nursery school, and now she can speak Urdu and Italian regularly from a lexical and syntactical point of view. On indication of preschool teachers, the child was referred to the Child Neurology and Psychiatry Unit of Spedali Civili of Brescia at the age of 6 years for "learning difficulties"; the neurological evaluation revealed nonrhythmic, unsustained, and non-suppressible involuntary movements of upper and lower limbs and the orofacial district (Video 1). These movements were reported by parents as being present since age 2 starting from the face and increasing in intensity over time. They presented at rest, but were induced by intention and manifested as mild dysarthria, facial grimacing, and choreiform jerking of the trunk and limbs (Videos 2 and 3). Nevertheless, the girl's quality of life (QoL) did not seem to be affected by this movement disorder. She could write and draw well; she could also run and kick the ball without falling over and objects did not drop from her hands.

To exclude secondary causes of chorea, a complete routine blood tests including antistreptolysin O titer (ASO), erythrocyte sedimentation rate (ESR), C-reactive protein, iron metabolism, α-fetoprotein, and prolactin level were performed with unremarkable results. Pharyngeal swab and a complete cardiological examination were normal. Additional investigations including ophthalmological and audiological examinations, electroencephalography, and brain magnetic resonance imaging (MRI) (conventional 1,5 Tesla) were found to be normal. Electromyographic (EMG) studies (polygraphy with EMG video recording) failed to identify a dystonic pattern. Neuro-ophthalmological examination revealed mild oculomotor dyspraxia characterized by impaired smooth pursuit and hypometric saccadic gaze movements, sometimes associated with compensatory movements of the head or blinking.

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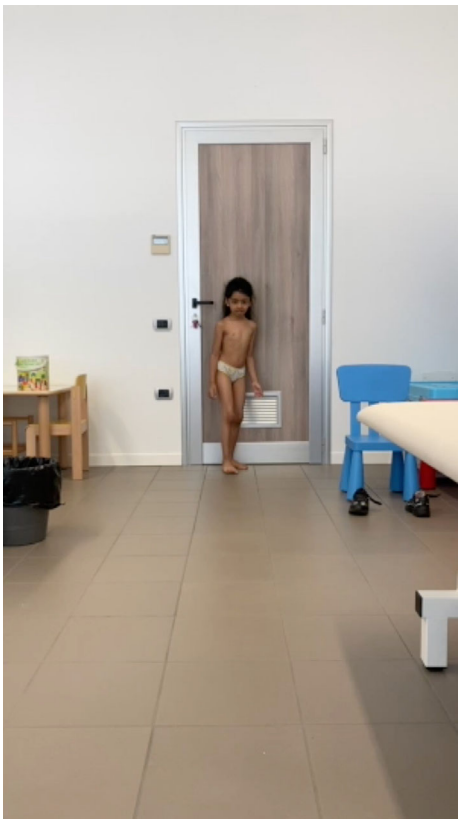
Video 1. The child is filmed doing Mingazzini's arm test. Involuntary, irregularly timed, non-repetitive and purposeless movements of the arms and face's muscles are evident. Recording videos demonstrate the poor pharmacological response to different treatment approaches: 1: no treatment; 2: pimozide 4 mg/die; 3: levodopa 75 mg/die; 4: carbamazepine 400 mg/die; 5: trihexyphenidyl 10 mg/die; 6: tetrabenazine 25 mg/die.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13572



Video 2. The child is filmed while walking. Gait is characterized by instability because of foot strike dysmetria and the presence of generalized chorea. Segments compare distinct treatment approaches: 7: pimozide 4 mg/die; 8: carbamazepine 400 mg/die; 9: Deltacortene (1 month trial); 10: trihexyphenidyl 10 mg/die; 11: tetrabenazine 25 mg/die.
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Neuropsychological assessment (Table 1) showed a profile of global intellectual functioning[10] and adaptive functioning[11] within the normal range (only speed of execution was found to be weak) associated with difficulties in visual-constructive and visual attentive tasks.[12–14] Verbal and visual memory[15] assessment did not detect any impairment. As concerned academic skills,[16,17] a mild reading and writing disorder was found. Formal language skills[18] (lexical and syntactic comprehension/production) were in the normal range. A moderate deficit in speech[19] also appeared in rapid naming, reading tasks, or repeating sentences.

After obtaining informed consent, whole-exome sequencing (WES) was performed on genomic DNA and relevant variants were validated by Sanger sequencing. WES analysis revealed a novel homozygous missense variant (c.248G>A, p. Arg83Gln) in the *HPCA* gene, classified as likely pathogenic based on current American College of Medical Genetics and Genomics guidelines. Both parents were heterozygous carriers of the variant. The variant has never been reported before and is not present in the gnomAD population database; it affects a highly conserved amino acid and is consistently predicted as damaging by several bioinformatic tools.

Therapeutic attempts with pimozide, levodopa, carbamazepine, corticosteroid, and trihexyphenidyl failed to reduce her movement disorder. Parents reported slight improvements (such as a better accuracy in precision tasks, eg, use of the knife) only with tetrabenazine 25 mg/day, which is still ongoing. After 2 years of follow up, the clinical course is stable.

Video segments were extracted from the regular neurological examination. Segments are organized in three sections (Videos 1, 2, and 3). We present videos of the child performing specific tasks during the neurological examination to illustrate the evolution of the movement disorder and to document the treatment's efficacy.

Video 3. The child is filmed while doing precision tasks with the upper limbs. 12: the child is writing. She can write slowly, but in a formally correct way. 13 and 14: the child performs an Archimedes spiral and another precision task with minimal instability of the graphic line.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13572

Discussion

Pathogenic variants of hippocalcin have been reported to date only in few patients with childhood-onset generalized dystonia and adolescence-onset segmental dystonia.[1,2,5] To the best of our knowledge, this is the first clinical report proving a choreiform phenotype in association to *HPCA* gene mutations.

Previously, "choreatic movements" have been described only in the proband's father of Siegert et al[5] when he was a child. The proband described here showed a hyperkinetic movement disorder with subtle onset in the first years of life, which progressively evolved into generalized writhing movements more prevalent in the orofacial and upper limb districts, and absent during sleep. However, this movement disorder had a low functional impact on daily life activities, and the patient only came to our attention at age of 6 years old. Additional neurological features were mild neurodevelopmental delay, moderately dysarthria, mild oculomotor dyspraxia, and some learning difficulties, with a minor impact on QoL and academic success.

TABLE 1 *Neuropsychological profile*

Neuropsychological assessment		Clinical range
Intelligence indexes		
Verbal comprehension[10]		
Visual perceptual reasoning[10]	115[a]	Normal
Working memory[10]	94[a]	Normal
Processing speed[10]	59[a]	Deficit
General ability[10]	115[a]	normal
Academic skills		
Reading speed[16]	−1.39[b]	Borderline
Reading accuracy[16]	0.18[b]	Normal
Writing accuracy[17]	−1.45[b]	Borderline
Language skills		
Viking speech scale[19]	Level II	Mild deficit
Lexical production[18]	−1–0[b]	Normal
Lexical comprehension[18]	0–1[b]	Normal
Syntactic production[18]	−2[b]	Deficit
Syntactic comprehension[18]	−1–0[b]	Normal
Memory skills		
Verbal recall[15]	9[c]	Borderline
Delayed verbal record[15]	50[c]	Normal
Visual spatial record[15]	16[c]	Normal
Delayed visual spatial record[15]	25[c]	Normal
Executive functions		
Selective visual attention[14]	−1.57[b]	Borderline
Sustained visual attention[14]	−1.87[b]	Borderline
Verbal working memory[24]	−1.52[b]	Borderline
Shifting[24]	−1.13[b]	Borderline
Visual spatial and visual motor skills		
Visual integration skills[12]	6[c]	Borderline
Movement ABC2[13]	0.1[c]	Deficit
Adaptive functions		
Vineland adaptive behavior scales[11]		
Communication	79[a]	Borderline
Socialization	104[a]	Normal
Daily living	98[a]	Normal

[a]Performance expressed in standard scores (mean, 100; SD, 15; normal range, 85 and higher; borderline range, 84–71; pathological range, 70 and lower).
[b]Performance expressed in z scores (mean, 0; sd 1; normal range, −0.99 and higher; borderline range, −1.0–1.99; pathological range, −2 and lower).
[c]Performance expressed in centiles (normal range, 16 and higher; borderline range, 5–15; pathological range, 5 and lower). II level at Viking speech scale: speech is imprecise, but usually understandable to unfamiliar listeners.

From a movement disorder perspective, hyperkinetic movements in children are associated with dysfunction of the basal ganglia, cerebral cortex, cerebellum, and other motor pathways because of static or progressive injury.[20] Such movements are commonly seen in the dyskinetic form of cerebral palsy, the main differential diagnosis to rule out, but they also are important features of congenital, acquired, and degenerative diseases[20] (such as ataxia telangiectasia, Sydenham's chorea, neurotransmitter disorders, and Wilson's disease).

As previously reported,[21] some phenotype–genotype correlations emerged for HPCA, with truncating variants being associated to a more severe degree of cognitive dysfunction.[21] The present patient would confirm this observation, because the milder cognitive phenotype might correlate with the presence of a missense variant. Regarding the distribution of the movement disorder, an orofacial involvement seems to be a common feature in all forms of HPCA mutation.[21]

Based on studies in knockout mice models, hippocalcin has been also implicated in hippocampus' synaptic plasticity where it is hypothesized to play a role in memory formation.[22] However, memory impairments were not reported by any of the individuals with identified HPCA mutation.[1,2]

Neuropsychological assessment in our patient showed mild learning difficulties and low performance in some neuropsychological tests involving visual-constructive and visual attentive tasks, possibly influenced by the neuro-ophthalmological impairment exhibited by our patient. Difficulties in encoding verbal and visual information were previously reported in two members of an index family by Charlesworth et al[1] and in one member of Atasu et al.[2] More studies are needed to explain if oculomotor dyspraxia is a mutation-related sign or an incidental finding.

In conclusion, we expand the spectrum of movement disorders associated to HPCA dysfunction to include a spectrum of extrapyramidal movement disorders including chorea. These usually present generalized distribution, with a more marked upper limb and craniocervical involvement and with a relatively benign clinical course. From a neuropsychological point of view, a low performance in verbal fluency and visuospatial abilities seems to be a common feature of HPCA-related conditions. Based on these considerations, this case adds another genetic cause to the syndrome of benign hereditary chorea (BHC) (OMIM 118700), which is defined as "onset of chorea in infancy or early youth, relatively poor clinical progression, and absence of other major neurological deficits, particularly prominent cognitive decline".[23] HPCA should not be included only in dystonia gene panels, but sequencing of the gene should be recommended in patients with early onset hyperkinetic movement disorders, especially when combined with cognitive or neuropsychological under functioning.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript: A. Writing of the First Draft, B. Review and Critique.

S.B.: 1A, 1B, 1C, 2C, 3A, 3B
S.M.: 1A, 1C, 2A, 2B, 2C, 3B
P.I.: 2B, 2C, 3B
E.M.V.: 2B, 2C, 3B
E.F.: 1A, 2C, 3B

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Written informed consent was obtained by the child's parents. Informed consent was also obtained to publish identifying images in an online open-access publication. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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References

1. Charlesworth G, Angelova PR, Bartolome-Robledo F, et al. Mutations in HPCA cause autosomal-recessive primary isolated dystonia. *Am J Hum Genet* 2015;96:657–665.
2. Atasu B, Hanagasi H, Bilgic B, et al. HPCA confirmed as a genetic cause of DYT2- like dystonia phenotype. *Mov Disord* 2018;33:1354–1358.

3. Dobričić V, Kresojević N, Marjanović A, Tomić A, Svetel M, Novaković I, Kostić VS. HPCA-related dystonia: Too rare to be found? *Mov Disord* 2016;31:1071.
4. Carecchio M, Reale C, Invernizzi F, et al. DYT2 screening in early-onset isolated dystonia. *Eur J Paediatr Neurol* 2017;21:269–271.
5. Siegert S, Schmidt WM, Pletschko T, Bittner RE, Gobara S, Freilinger M. Specific cognitive changes due to Hippocalcin alterations? A novel familial homozygous Hippocalcin variant associated with inherited dystonia and altered cognition. *Neuropediatrics* 2021;52(5): 377–382.
6. Kim KS, Kobayashi M, Takamatsu K, Tzingounis AV. Hippocalcin and KCNQ channels contribute to the kinetics of the slow after hyperpolarization. *Biophys J* 2012;103:2446–2454.
7. Tzingounis AV, Kobayashi M, Takamatsu K, Nicoll RA. Hippocalcin gates the calcium activation of the slow after hyper-polarization in hippocampal pyramidal cells. *Neuron* 2007;53:487–493.
8. Helassa N, Antonyuk SV, Lian LY, Haynes LP, Burgoyne RD. Biophysical and functional characterization of hippocalcin mu-tants responsible for human dystonia. *Hum Mol Genet* 2017;26:2426–2435.
9. Osypenko DS, Dovgan AV, Kononenko NI, et al. Perturbed ca(2+)-dependent signaling of DYT2 hippocalcin mutant as mechanism of autosomal recessive dystonia. *Neurobiol Dis* 2019;132:104529.
10. Wechsler D. *WISC–IV Wechsler Intelligence Scale for Children Quarta Edizione. Manuale di somministrazione e scoring*. Firenze: Giunti OS; 2012.
11. Sparrow SS, Cicchetti DV, DA B. *Vineland-II Vineland Adaptive Behavior Scales-II – Second Edition – Survey Interview Form*. Italia version adapted by Balboni G, Belacchi C, Bonichini S, Coscarelli A. Firenze: Giunti Psychometrics; 2016.
12. Beery KE. *Beery VMI: The Beery-Buktenica Developmental Test of Visual-Motor Integration*. Minneapolis, MN: Pearson; 2004.
13. Henderson SE, Sugden D, Barnett AL. *Movement Assessment Battery for Children-2 Second Edition (Movement ABC-2)*. London: The Psychological Corporation; 2007.
14. Biancardi A, Stoppa E. Il test delle Campanelle modificato: una proposta per lo studio dell'attenzione in età evolutiva. *Psichiatria dell'Infanzia e dell'Adolescenza* 1997;64:73–84.
15. Reynolds CR, Bigler ED. *TEMA Test*. Trento: Test di memoria e apprendimento, Erickson; 1995.
16. Cornoldi C, Cerretti B. *Prove MT −3 Clinica*. Firenze: Giunti Psychometrics; 2017.
17. Cornoldi C, Re AM, Tressoldi PE. *BVSCO-2 Valutazione della Scrittura e della Competenza Ortografica. Batteria per la Valutazione della Scrittura e della Competenza Ortografica – 2*. Firenze: Giunti Edu; 2013.
18. Marini A. *BVL 4–12 Batteria per la Valutazione del Linguaggio in Bambini dai 4 ai 12 anni*. Firenze: Giunti Psychometrics; 2015.
19. Pennington L, Virella D, Mjøen T, et al. Development of the Viking speech scale to classify the speech of children with cerebral palsy. *Res Dev Disabil* 2013;34:3202–3210.
20. Sanger TD, Chen D, Fehlings DL, et al. Definition and classification of hyperkinetic movements in childhood. *Mov Disord* 2010;25:1538–1549.
21. Balint B, Charlesworth G, Erro R, Wood NW, Bhatia KP. Delineating the phenotype of autosomal-recessive HPCA mutations: Not only isolated dystonia! *Mov Disord* 2019;34:589–592.
22. Kobayashi M, Masaki T, Hori K, et al. Hippocalcin-deficient mice display a defect in cAMP response element-binding protein activation associated with impaired spatial and associative memory. *Neuroscience* 2005;133:471–484.
23. Kleiner-Fisman G, Lang AE. Benign hereditary chorea revisited: A journey to understanding. *Mov Disord* 2007;22:2297–2305.
24. Korkman M, Kirk U, Kemp S. *NEPSY-II*. Firenze: Giunty Psychometrics; 2011.