Movement Disorders
CLINICAL PRACTICE
CASE REPORT

Cockayne syndrome type 3 with dystonia-ataxia and clicking blinks

Özge Berna Gültekin-Zaim, MD,[1,*] Gül Yalçın-Çakmaklı, MD, PhD,[1] Ayşe İlksen Çolpak, MD,[1] Pelin Özlem Şimşek-Kiper, MD, PhD,[2] Gülen Eda Utine, MD, PhD,[2] and Bülent Elibol, MD, PhD[1]

Cockayne Syndrome (CS), a rare autosomal recessive progressive neurodegenerative disease, was first described by Edward Cockayne in 1936.[1] CS is caused by ERCC8 (OMIM# 609412) and ERCC6 (OMIM# 609413) biallelic mutations leading to Cockayne syndrome type A (CSA, OMIM# 216400) and type B (CSB, OMIM# 133540), respectively.[1] *ERCC6* and *ERCC8* are responsible in the transcription coupled DNA repair pathway.[1] Moreover, ERCC gene family especially ERCC3 is associated with pathogenesis of xeroderma pigmentosum, another transcription-coupled nucleotide excision repair disorder.[2] CS has different phenotypes; type 1 (classic), type 2 (severe), type 3 (mild) and cerebro-oculo-facio-skeletal syndrome.[3] CS clinically presents with microcephaly, growth retardation, short stature, sensorineural deafness, cataract, retinal degeneration, cognitive impairment, dermal photosensitivity, premature aging, characteristic dysmorphic findings, progressive multisystem and neurological degeneration.[1,4] Neurologically, patients may present with seizures, loss of developmental milestones and movement disorders such as tremor, ataxia, myoclonus, choreoathetosis and dystonia.[4–8] These are progressive and mostly refractory to medical therapy,[4,8] although there are some cases reported to benefit from deep brain stimulation (DBS).[5–7] Characteristic neuroimaging findings include basal ganglia, diffuse cortical and cerebellar calcifications on computed tomography (CT) and diffuse white matter hypomyelination, cerebral/cerebellar atrophy, thinning of corpus callosum on magnetic resonance imaging (MRI).[9] Here we report on a rare case of CS with survival into adulthood, presenting with progressive dystonia and ataxia as prominent clinical signs and an interesting and unique finding, clicking blinks.

Case Report

A 34-year-old female presented with the complaints of progressive tremor, gait and speech difficulty. Tremor was first noticed in left hand at 17 years of age, increased in severity and became bilateral next year. Later speech and gait difficulties developed. She did not benefit from clonazepam; botulinum toxin injection to extremities provided partial relief. Additionally, she had a history of photosensitivity, weight loss and growth retardation in the adolescence period. Bilateral sensorineural hearing loss was detected when she was 25. Similarly, her younger brother had bilateral sensorineural hearing loss and their parents were consanguineous (first cousins).

Video 1. Full video from the 2022 Video Challenge discussion of this case. A "click" sound can be heard while the patient is winking, thought to be due to diminished periorbital fat tissue. Left upper extremity dystonic tremor originating from shoulder and bilateral intentional tremor of upper extremities can be seen. Heel-to-shin test is abnormal on both sides. The gait is ataxic and inversion of left foot can be seen while the patient is walking.
Video content can be viewed at https://onlinelibrary.wiley.com/doi/10.1002/mdc3.13778

[1]*Department of Neurology, Hacettepe University Faculty of Medicine, Ankara, Turkey;* [2]*Department of Pediatrics, Pediatric Genetic Disorders Unit, Hacettepe University Faculty of Medicine, Ankara, Turkey*

***Correspondence to:** Özge Berna Gültekin-Zaim, Department of Neurology, Faculty of Medicine, Hacettepe University, Ankara, Turkey; E-mail: obgultekin@gmail.com
Keywords: dystonia, ataxia, Cockayne syndrome type 3, movement disorder, clicking blinks.

Received 11 December 2022; revised 11 April 2023; accepted 13 April 2023.
Published online 00 Month 2023 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mdc3.13778

Neurological examination revealed cerebellar dysarthria, bilateral intentional and dystonic tremor of the hands, bilaterally abnormal heel-to-shin test, dystonia of the left hand and abnormal gait due to dystonia and ataxia (Video 1). Mini-mental status exam score was 23/30. Physical examination showed cachexia, short stature and dysmorphic features such as widow's peak, prominent nasal bridge, long columella, malar hypoplasia, retrognathia, helix folding anomaly of ears, diminished periorbital fat tissue, deeply located eyes, multiple lentigines on the face, multiple nevi on the chest and the arms, rigid metacarpophalangeal joints. Ophthalmological evaluation was normal. Optical coherence tomography showed retinal nerve fiber layer (RNFL) thinning of the nasal and temporal parts of the right and nasal and central parts of the left optic nerve. Interestingly each time she blinked either spontaneously or voluntarily, a strange "click" sound was audible. The patient and her family mentioned that the "click" sound was present for many years independent from any factors. After further evaluation, ophthalmology and otorhinolaryngology departments concluded that the "click" on the blink was due to loss of periorbital fat tissue.

Liver enzymes were elevated on routine laboratory tests. Serum ceruloplasmin level, 24 h urine copper excretion, serum lactate and pyruvate levels were normal excluding Wilson's disease and mitochondrial cytopathies. Previously performed liver biopsy showed minimal fibrosis. Bilateral calcifications of the globus pallida were detected on CT. MRI showed prominent thickening and sclerosis of calvarium, diffuse cerebral, brainstem and cerebellar atrophy, periventricular non-specific T2 hyperintensities (Fig. 1).

Altogether these symptoms and findings suggested the diagnosis of CS. Whole exome sequencing analysis revealed a novel homozygous missense variant, NM_000082.3: c.321G > C, p.(Trp107Cys) in *ERCC8*, also confirmed by Sanger sequencing. The parents were heterozygous for the same variant confirming the homozygosity in the patient. This change was classified as "variant of unknown significance" according to ACMG guidelines. According to disease progression rate, symptom severity and occurrence age, the patient was considered as CS type 3.

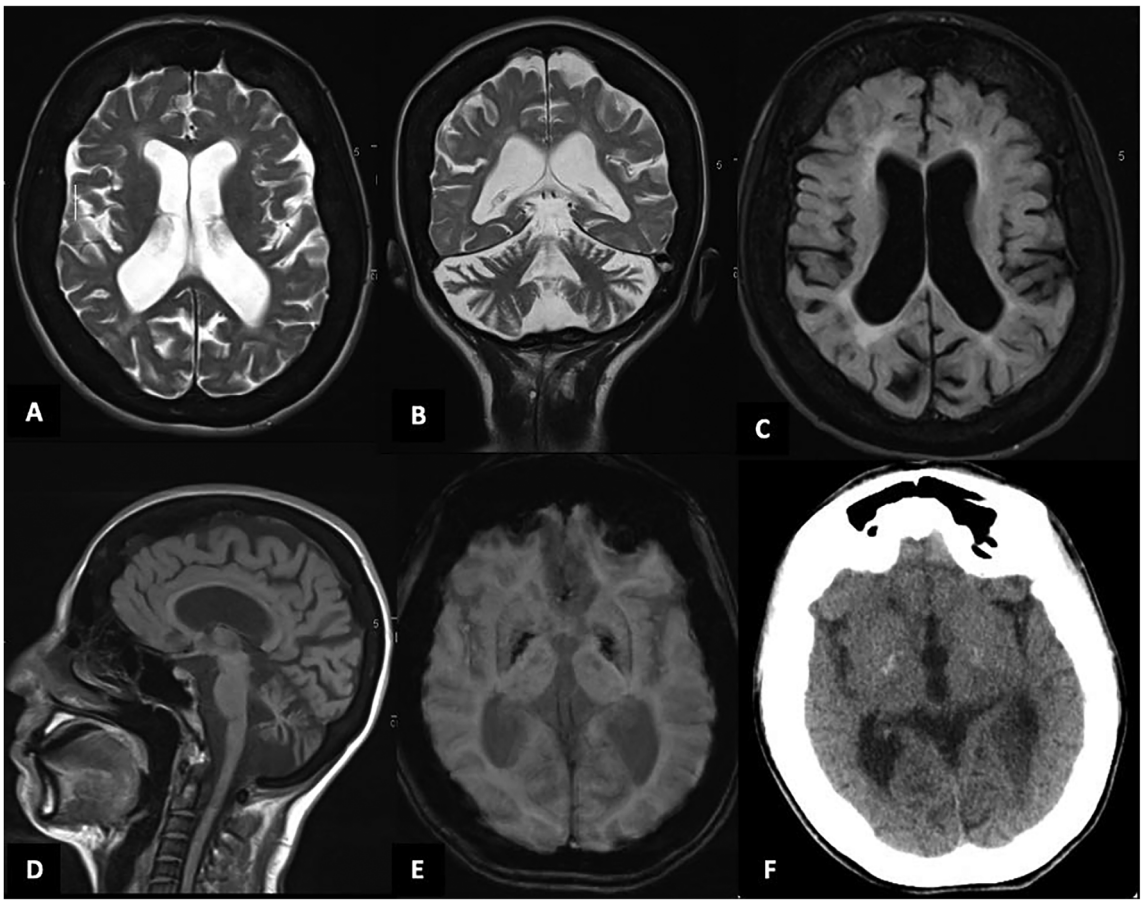

Figure 1. (A–D) Prominent thickening and sclerosis of calvarium, diffuse cerebral and cerebellar atrophy, periventricular non-specific T2 hyperintensities were seen at axial and coronal T2, axial FLAIR and sagittal T1 images. (E) SWI shows bilateral paramagnetic matter deposition at globus pallida. (F) Bilateral calcifications at globus pallida, prominent thickening and sclerosis of calvarium on CT imaging are seen.

Discussion

Cockayne syndrome is caused by the biallelic mutations in the ERCC8 and ERCC6 genes. Protein products of both genes are responsible in DNA repair and other aspects of DNA metabolism.[10] The impaired transcription-coupled nucleotide excision repair in CS causes a progressive multisystem disorder including nervous system.[1] Neurologically, microcephaly and cognitive impairment accompany pyramidal, extrapyramidal, cerebellar and peripheral nervous system involvement.[3,11] The cases with movement disorders mostly had ataxia and tremor.[4,5,12] However, myoclonus, dystonia and choreoathetosis have also been reported.[4,12] Our patient similar to most of the cases reported, had tremor, ataxia and dystonia. The movement disorder spectrum in CS shows phenotypic variability, but the course is typically progressive and medical therapy is mostly ineffective.[4] However, in a study of three CS patients, clinical benefit from levodopa-carbidopa treatment for tremor was documented.[8] DBS of ventral intermediate nucleus of thalamus or globus pallidus interna showed successful improvement of symptoms in selected cases.[5–7] It could, therefore, be considered as a therapeutic option for tremor in slowly progressive cases like CS type 3 as they have a longer life span compared to other types.[5] Moreover, botulinum toxin injection is another symptomatic treatment option as in our patient.

This case was recognized as CS with the help of the physical examination findings and consanguineous marriage history. It shows the importance of noting morphological findings in whole as such they may facilitate the diagnosis of complex diseases. It is the first time we encounter the "click" sound on the blinking in a CS case, possibly due to loss of periorbital fat tissue. Audible clicking blinks have also been scarcely reported in ophthalmology case reports, related to prostaglandin-associated periorbitopathy with sunken eyes and deepened upper eyelid sulci and these reports hypothesized that periorbital fat atrophy caused by prostaglandin medications was responsible from the clicking sound.[13–15] It has not been described before in CS, and therefore does not have a clear diagnostic value but it may help clinicians in future evaluation of adult-onset CS.

CS should be kept in mind as a rare cause of dystonia and cerebellar ataxia for adult patients with growth retardation, dysmorphic features, hearing loss and characteristic MRI findings in presence of parental consanguinity.

Author Roles

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

O.B.G-Z.: 3A.

G.Y-C: 3A, 3B.

A.I.C.: 3B.

P.O.S-K.: 3B.

G.E.U.: 3B.

B.E.: 3B.

Disclosures

Ethical Compliance Statement: The authors confirm that the approval of an institutional review board was not required for this work. Informed consent of patient had taken in a written format. 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.

Funding Sources and Conflicts of Interest: No specific funding was received for this work and the authors declare that there are no conflicts of interest relevant to this work.

Financial Disclosures for Previous 12 Months: The authors declare that there are no additional disclosures to report. ■

References

1. Wilson BT, Stark Z, Sutton RE, et al. The Cockayne Syndrome Natural History (CoSyNH) study: clinical findings in 102 individuals and recommendations for care. *Genet Med* 2016;18(5):483–493.
2. Weeda G, van Ham RCA, Vermeulen W, Bootsma D, van der Eb AJ, Hoeijmakers JHJ. A presumed DNA helicase encoded by ERCC-3 is involved in the human repair disorders xeroderma pigmentosum and Cockayne's syndrome. *Cell* 1990;62(4):777–791.
3. Laugel V. Cockayne syndrome: the expanding clinical and mutational spectrum. *Mech Ageing Dev* 2013;134(5–6):161–170.
4. Planas-Ballve A, Morales-Briceño H, Crespo-Cuevas AM, Fung VSC. Movement disorders and spinal cord atrophy in Cockayne syndrome with prolonged survival. *Mov Disord Clin Pract* 2018;5(2):209–211.
5. Domino JS, Gelineau-Morel R, Kaufman C. Deep brain stimulation for Cockayne syndrome-associated movement disorder. *J Mov Disord* 2022;15(1):62–65.
6. Hebb MO, Gaudet P, Mendez I. Deep brain stimulation to treat hyperkinetic symptoms of Cockayne syndrome. *Mov Disord* 2006;21(1):112–115.
7. Hamasaki K, Yamada K, Hamasaki T, Kuratsu JI. GPi-pallidal stimulation to treat generalized dystonia in Cockayne syndrome. *Mov Disord* 2010;25(5):656–658.
8. Neilan EG, Delgado MR, Donovan MA, Kim SY, Jou RL, Wu BL, Kang PB. Response of motor complications in Cockayne syndrome to carbidopa-levodopa. *Arch Neurol* 2008;65(8):1117–1121.
9. Koob M, Laugel V, Durand M, et al. Neuroimaging in Cockayne syndrome. *AJNR Am J Neuroradiol* 2010;31(9):1623–1630.
10. Okur MN, Lee JH, Osmani W, Kimura R, Demarest TG, Croteau DL, Bohr VA. Cockayne syndrome group A and B proteins function in rRNA transcription through nucleolin regulation. *Nucleic Acids Res* 2020;48(5):2473–2485.
11. Karikkineth AC, Scheibye-Knudsen M, Fivenson E, Croteau DL, Bohr VA. Cockayne syndrome: clinical features, model systems and pathways. *Ageing Res Rev* 2017;33:3–17.
12. Cocco A, Calandrella D, Carecchio M, Garavaglia B, Albanese A. Adult diagnosis of Cockayne syndrome. *Neurology* 2019;93(19):854–855.
13. Fong CS, Rajak SN, Pirbhai A, Selva D. Audible blink in prostaglandin-associated periorbitopathy. *Clin Experiment Ophthalmol* 2016;44(7):630–631.
14. Skorin L Jr, Dailey KH. Clicking eyelids: a new finding of prostaglandin-associated periorbitopathy. *Optom Vis Sci* 2016;93(7):779–781.
15. Abedi F, Chappell A, Craig JE. Audible clicking on blinking: an adverse effect of topical prostaglandin analogue medication. *Clin Experiment Ophthalmol* 2017;45(3):304–306.