Clinical Reasoning:

A 35-year-old woman with hyperstartling, stiffness, and accidental falls

A startling diagnosis

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SECTION 1

A 35-year-old woman presented with a history of accidental falls since age 14. These typically occurred in response to unexpected and sudden stimuli (e.g., noises, unexpected encounters at turnarounds). The attacks were heralded by stiffness in both legs, with the patient fully conscious. On one occasion, she had a sudden and vigorous head retraction because of eyedrop administration at an eye clinic, resulting in head trauma. As a result of the accidental falls and the inability to adequately protect herself, the patient had various emergency department admissions for trauma, including mild concussion. In response, she adopted a toddling gait, walking near walls to curtail falls. Symptoms were worse in cold weather and disappeared during sleep.

The patient's medical history was notable for reports of generalized transient hypertonia during the first years of life, mild delay in motor developmental milestones, and left patellar dislocation at age 8.

The patient was born to unrelated parents, none displaying similar symptoms. She has a healthy brother. Her 3-year-old son has a congenital wedging

of T12 and L1 vertebrae, surgically corrected inguinal hernia, and had mild hypertonia at birth. She works in business and the accidents were interfering with her professional life and the need for frequent travel.

A neurologic examination showed mild hypertonia in all 4 extremities, mostly on the left side, and a positive head retraction reflex. This is a sudden and violent backward jerking of the head after tapping on the root of the nose. A sudden and loud clap evoked the exaggerated startle response, namely forceful contraction of the orbicularis oculi and generalized flexion and stiffening of upper and lower limbs. All these maneuvers were performed in a supervised manner to prevent injury. The patient had a wide-based gait, with a toddling quality. Deep tendon reflexes were brisk on all 4 limbs, except the left knee (1/4), where surgery had been performed. The rest of the examination was normal.

Questions for consideration:

1. Based on the clinical presentation, which is the main neurologic system involved in this patient?
2. What is the differential diagnosis?

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SECTION 2

This patient displayed an abnormal startle reflex. The startle reflex is a physiologic defensive response to sudden or unexpected stimuli, especially of auditory nature. It is characterized by a specific progression of stereotyped and bilaterally synchronous movements in a proximal-to-distal fashion. The nucleus reticularis pontis caudalis (RPC), located in the paramedian bulbopontine reticular formation, has been identified as the probable startle-response generator. In healthy individuals, the startle reflex is subject to swift habituation, being extinguished after 4–6 repeated stimuli.^{1,2} An abnormal startle response is part of many conditions.

Startle-induced epilepsy can be excluded by preserved consciousness during attacks as well as lack of major developmental delays.

Stiff-person syndrome (SPS) is an autoimmune condition characterized by lower body and paraspinal muscle stiffness and startle-induced muscle spasms and rigidity. In SPS, the stiffness is prolonged, disappearing only during sleep and general anesthesia. Anti-glutamic acid decarboxylase autoantibodies (AntiGADAb) and anti-amphiphysin antibodies have been associated with this syndrome.³ Progressive encephalomyelitis with rigidity and myoclonus (PERM), a variant of SPS, has been associated with anti-glycine receptor (GlyR) antibodies.⁴

Abnormal startling responses, startle-induced tics, echolalia, coprolalia, and behavioral abnormalities are found in patients with neuropsychiatric disorders and

in some cultural groups (e.g., Jumping Frenchmen of Maine, Latah in Malaysia and Indonesia).²

Finally, hyperekplexia (from the Greek, “to startle excessively”) is a genetic disorder that involves an isolated dysregulation of the startle response. It was first described in 1958.⁵ The major form presents with transient generalized stiffness and life-threatening apneic spells in the first few years after birth, provoked by handling and abolished by sleep. Additional criteria include excessive startle to unexpected stimuli and brief generalized stiffness following the startle reflex. This abnormal response will often cause the patient to fall forward, without any loss of consciousness. Patients are often described as stumbling or falling like a log. As a reaction, they typically assume a wide-based, cautious gait. Additional supporting features include inguinal, umbilical, or epigastric hernias, congenital dislocation of the hip, periodic sleep limb movements and hypnagogic myoclonus, and normal intellectual ability in most patients.

Hyperekplexia is caused by inherited or sporadic mutations in GlyR. This is an inhibitory ligand-gated chloride pentameric channel, made of a combination of α -1, α -2, and β subunits, as well as clustering proteins collybistin and gephyrin. GlyR are mostly expressed in caudal nuclei of the brainstem and in the spinal cord, and they cause hyperpolarization. They are particularly richly expressed in the nucleus RPC, as shown in the figure.

Figure Visual representation of *GLRA1* expression throughout the CNS

(A) Selection of representative MRI axial (left), coronal (middle), and cortical reconstruction (right) with superimposed representation of high expression (red dots) mainly in the caudal brainstem and lower expression (green dots) in the brain. The red cross indicates the right nucleus reticularis pontis caudalis. The scale on the right shows the range of expression. (B) Complete microarray analysis of *GLRA1* expression. Note the cranial-to-caudal expression gradient. CbCx = cerebellar cortex; CgG = cingulate gyrus; DT = dorsal tegmentum; FL = frontal lobe; HiF = hippocampal formation; MES = mesencephalon; MNI = Montreal Neurological Institute; MY = myelencephalon; OL = occipital lobe; PTg = pontine tegmentum; Str = striatum; TL = temporal lobe. Image credit: Allen Institute. © 2015 Allen Institute for Brain Science. Allen Human Brain Atlas. Available at: human.brain-map.org. The original image and additional tools can be obtained from the Allen Brain Atlas permalink at goo.gl/dMzdXw.

One of the first mutations associated with the disease was in the *GLRA1* gene, and it was originally described by Shiang et al.⁶ The group described substitution of arginine to glutamine in position 271 of the mature protein (Arg271Gln). This is also known as p.Arg299Gln on the precursor protein, according to the revised Human Genome Variation Society Guidelines on nomenclature. This mutation causes loss of a positive charge on the extracellular end of transmembrane domain 2 at the α -1 subunit. As a result, there is reduced glycine binding and reduced concentration of chloride at the channel pore. Loss of inhibitory control over motor neurons causes

powerful muscle contractions. Partial protection is obtained via potentiation of GABAergic pathways. This compensatory response, however, is not satisfactory during sudden stimuli, hence the hyperstartling and secondary stiffness.⁷ Since 1993, over 60 mutations have been described. Most are autosomal dominant and involve the α -1 subunit (OMIM #149400).

Questions for consideration:

1. What are the next steps in the management of the patient?
2. Which treatment has been demonstrated to be most effective?

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SECTION 3

Contrast-enhanced MRI of the brain and spinal cord showed congenital, low-lying cerebellar tonsils, without full criteria for Arnold-Chiari malformation, and was otherwise unremarkable. Basal and sleep-deprivation EEG and routine laboratory tests, including AntiGADAb, were all normal.

Amplification and direct sequencing of genomic coding DNA and splicing regions, using DNA from the patient's peripheral blood, confirmed the presence of the Arg271Gln mutation in heterozygosity. The patient's family was also tested for the same mutation: both her parents and her brother tested negative, hence configuring a *de novo* mutation in the proband. Her 3-year-old son, who presented mild hypertonia after birth, an inguinal hernia, and vertebral malformations, has been confirmed to be heterozygous for the same maternal mutation. A diagnosis of sporadic hyperekplexia was established, with vertical transmission to offspring.

The patient was started on clonazepam, 0.625 mg per day, slowly increased to 1.25 mg per day. Physical therapy was also initiated, to improve stability of the torso and limbs. At 2 and 4 months after the diagnosis, the patient reported notable improvement, detailing how once intolerable sudden stimuli are much more bearable. On follow-up examination, the head retraction reflex is absent. The patient's quality of life has notably improved and she has been able to return to her highly demanding job. Her child is receiving pediatric neurology assessments.

DISCUSSION This patient's presentation posed some challenges due to absence of family history and apparently no reported hyperstartling between early childhood and adolescence.

As Bakker et al.² suggest, extensive history taking and detailed neurologic examination are needed in order to correctly identify a hyperstartling disorder. Particular attention should be devoted to the neonatal and pediatric history. Family history and pedigree should also be detailed, including any cases of sudden infant death syndrome.

Tonic neonatal cyanosis, most commonly found in sporadic hyperekplexia cases, can be interrupted with the Vigevano maneuver, consisting of forced flexion of head and legs towards the trunk.

Laboratory examinations, MRI, and EEG are generally normal in patients with hyperekplexia. Of importance, paraneoplastic etiology should always be carefully excluded, as tumors may produce antibodies against components of both GABAergic and glutamatergic systems. EMG can help in the differential diagnosis with SPS and PERM, as constant muscle activity will be detected in these 2 conditions.

Therapy with benzodiazepines, specifically clonazepam, is advocated as it potentiates the compensating

GABAergic pathway of the brainstem, increasing protection during a startle. The initial dose is 0.5 mg QD, and this is gradually increased, up to a maximum of 6 mg QD, divided in 3 doses. This therapy also controls life-threatening neonatal apneic crises. All patients need physical therapy in order to increase agility and tone, hence protecting from falls. Regular follow-ups are aimed at dose adjustments.⁸ Isolated case reports have described benefit with fluoxetine, valproate, carbamazepine, and phenytoin, but none have the same level of evidence as clonazepam.⁹ Propofol has been shown to bind to the mutant human glycine receptor specifically and increase its conductivity in mice, without causing excessive somnolence.¹⁰ This finding paves the way for future development of agonists targeted specifically at the mutant glycine receptors.

AUTHOR CONTRIBUTIONS

Dr. Russo: drafting/revising the manuscript for content, including medical writing for content, study concept and design. Dr. Fossati: analysis or interpretation of data, acquisition of data. Dr. Toffetti: analysis or interpretation of data, acquisition of data. Dr. Lanzone: analysis or interpretation of data, acquisition of data. Dr. Cardani: analysis or interpretation of data, acquisition of data. Prof. Meola: study concept and design, revising the manuscript for content, study supervision or coordination.

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