

Clinical Problem Solving: A Tobacco Merchant Who Can't Spit

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ABSTRACT: A 47 year old man presented with a combination of dry mouth and lightheadedness while standing. His medical background was unremarkable except for cigarette smoking and hyperlipidemia. Sjögren's syndrome was ruled out, and he was referred for evaluation of orthostatic hypotension, which by then included syncopal episodes and injuries. Additional symptoms included dry eyes, constipation, reduced sweating, and erectile dysfunction. After excluding medications and structural cardiac abnormalities as causes of orthostatic hypotension, a clinical autonomic evaluation was performed. The pattern of beat-to-beat blood pressure associated with performance of the Valsalva maneuver, and a low plasma norepinephrine level that did not increase in response to standing, established that the orthostatic hypotension was neurogenic. Treatment with an alpha-adrenoceptor agonist and fludrocortisone yielded partial improvement. After systemic diseases involving autonomic failure were excluded, cardiac sympathetic neuroimaging was performed by ¹²³I-metaliodobenzylguanidine (MIBG) scanning. The normal uptake seen in the heart indicated intact post ganglionic sympathetic innervation. There were no signs of central neurodegeneration or peripheral neuropathy. Because of symptoms and signs of both parasympathetic and sympathetic failure without denervation, an autonomic ganglionopathy was considered. A high titer of antibody to the neuronal nicotinic receptor, which mediates ganglionic neurotransmission, was obtained. The diagnosis of autoimmune autonomic ganglionopathy (AAG) was made, and the management strategy shifted to first lowering the antibody burden by plasma exchanges and then instituting chronic anti-autoimmune treatment with rituximab and a low dose of corticosteroid. The patient showed remarkable improvement.

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sensation of the mouth, difficulty speaking, and difficulty chewing dry foods. He had no fever, arthralgia, or rash, and no ocular complaints. His medical history was remarkable for heavy tobacco use and hyperlipidemia, as well as treatment with statins (atorvastatin 40 mg/d) and aspirin.

Xerostomia is a common complaint and can be induced by drugs, dehydration, smoking, infections, diseases of the salivary glands, autoimmune disorders, or irradiation. This patient's medications have not been associated with xerostomia. He was a heavy smoker; but did not suffer from xerostomia in the 39 years prior and cessation of smoking did not improve his symptoms.

On physical examination he had no swelling of the salivary or parotid glands, and no palpable cervical lymph nodes, yet dry and chapped lips with tissue atrophy and lack of saliva were apparent. His physical examination was notable only for skin dryness. His blood pressure was 114/68 mmHg, and his heart rate was 65 beats per minute. Standard blood tests revealed no abnormality and no sign of dehydration or diabetes mellitus. Chest X-ray showed mild interstitial changes in both lungs, suggested to be early chronic lung disease. Sialometry showed no saliva at rest and 0.03 ml/min under stimulation (normal values 0.5–1.5 ml/min) but with no salivary gland pathology apparent upon salivary gland scanning. His eye examination was suggestive of sicca syndrome, as the Schirmer test was pathologic in the left eye at 2.5 mm/5 minutes (abnormal under ≤ 5 mm/5 minutes). Consequently, the patient was sent to a rheumatology clinic with suspicion of Sjögren's syndrome.

Sjögren's syndrome is characterized by sicca symptoms such as xerophthalmia (dry eyes), xerostomia (dry mouth), and xeroderma (dry skin). Notably, parotid gland enlargement as well as extra-glandular features such as arthralgia, arthritis, Raynaud's phenomenon, anemia, leukopenia, and lymphadenopathy may also be observed. Objective parameters are also required for the diagnosis of Sjögren's syndrome. Of those, the presence of autoantibodies such as anti-RO/SSA, anti-LA/SSB, abnormal Schirmer test, ocular staining score ≥ 3, and the presence of focal lymphocytic sialoadenitis (with focus score ≥ 1 focus/4 mm² in labial salivary gland biopsies) are most commonly used [1,2].

PATIENT DESCRIPTION

A 47 year old tobacco merchant presented following 12 months of progressive dryness of mouth accompanied by a burning

Our patient underwent serologic investigations for anti-nuclear antibodies (ANA), rheumatoid factor (RF), ANTI-Ro/SSA, and Anti-LA/SSB, which were negative. Moreover, biopsy of salivary glands demonstrated fibrosis, fatty infiltration, acinar atrophy, and some sialectasia but no histopathologic signs of Sjögren's syndrome. Hence Sjögren's syndrome was excluded. Further investigations ruled out endocrinology conditions, salivary gland disease and infections (e.g., hepatitis C).

Six months after appearance of the first symptoms, he started to suffer from dizziness when standing up. After the second episode of syncope, he was admitted to the internal medicine department. The patient denied vomiting or diarrhea. He denied urinary incontinence during loss of consciousness. At admission, he was afebrile (36.6°C) with a heart rate of 72 beats per minutes (bpm), blood pressure of 104/59 mmHg and normal oxygen saturation in ambient air. His physical examination was unremarkable. Digital rectal examination was normal. There were no interim changes in his chest X-ray. A computed tomography (CT) scan of his brain showed only a subcutaneous hematoma at the left eyebrow. Blood tests showed mild anemia (13 g/dl). There were no electrolyte disturbances, troponin was negative and renal function was normal. Blood pressure when supine was 133/82 mmHg and after 3 minutes of standing was 77/44 mmHg.

This patient has recurrent syncope after 6 months of prodromal symptoms, with severe xerostomia. The patient did not meet diagnostic criteria for Sjögren's syndrome. It does not seem that the origin of the syncope is cardiogenic, since heart auscultation was normal (no murmur), and there was no sign of coronary symptoms (no chest pain, negative troponin, normal electrocardiogram). There does not seem to be a neurologic origin (no involuntary movements, no urinary incompetence, and nothing suggestive of post-ictal state). The cause does not seem to be metabolic according to the blood tests, nor due to pulmonary embolism (no tachypnea, no tachycardia). Orthostatism needs to be evaluated.

In addition to his presenting symptoms, the patient complained of combined upper and lower gastrointestinal symptoms. His complaints consisted of new constipation that developed during the past year, with spontaneous bowel movement once in 10 days, abdominal bloating, post-prandial fullness, nausea, and several episodes of vomiting. The patient had lost 8 kg over the past year. He also had urinary voiding dysfunction and erectile failure. He had a sensation of incomplete bladder emptying and straining to urinate, accompanied by a feeling of pre-syncope. His standing intolerance worsened and he had as many as a few syncopal episodes in a day. He felt eye dryness and intolerance to bright light. His general and neurological examination otherwise remained normal.

The patient suffers from sub-acute generalized autonomic dysfunction, which includes both sympathetic failure (orthostatism) and parasympathetic failure (dryness of mouth and skin, urinary retention, constipation). The autonomic system controls various important body functions and all of this patient's symptoms are due to failure of his autonomic system. Infectious, metabolic, and rheumatologic processes have been excluded. The origin of the dysfunction can be either degenerative or autoimmune. The persistent, primary orthostatism requires that the patient have autonomic function testing.

The patient had autonomic function testing. A deep breathing test showed no heart rate variability, indicating parasympathetic dysfunction. Valsalva maneuver [Figure 1] was abnormal (no increase in the second part of phase II and no overshoot in phase IV), which suggested sympathetic failure. Supine blood pressure was 156/86 mmHg with heart rate 72 bpm. Upright blood pressure was 113/56 mmHg with heart rate 63 bpm. The patient was not able to tolerate more than 1 minute upright on a tilt table. Plasma noradrenaline was undetectable both lying down and during tilt.

Cardiovascular autonomic function testing determines whether autonomic function is normal or abnormal, assesses the degree and site of the dysfunction, and provides information about the underlying pathophysiological processes. In this case, autonomic function is clearly and profoundly abnormal, and both sympathetic and parasympathetic function are affected. The abnormal Valsalva maneuver confirms the neurogenic nature of the orthostatism. The next step for diagnosing the origin of neurogenic orthostatism is performing a cardiac iodine-123-meta-iodobenzylguanidine (¹²³I-MIBG) scan, which was found to be normal.

The cardiac 123I-MIBG scan was found to be normal [Figure 2]

MIBG is an analog of guanethidine, an adrenergic blocking agent. It is actively taken up by the post-ganglionic nerve endings of the sympathetic noradrenergic nervous system. Labeled with the radioactive isotope iodine-123 (¹²³I), the uptake of MIBG

Figure 1. Valsalva maneuver

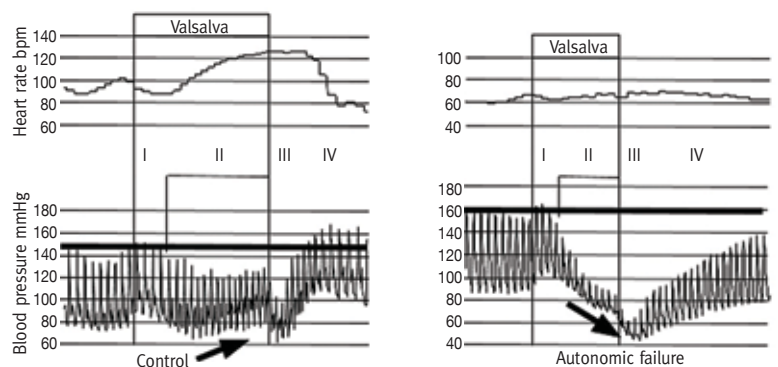
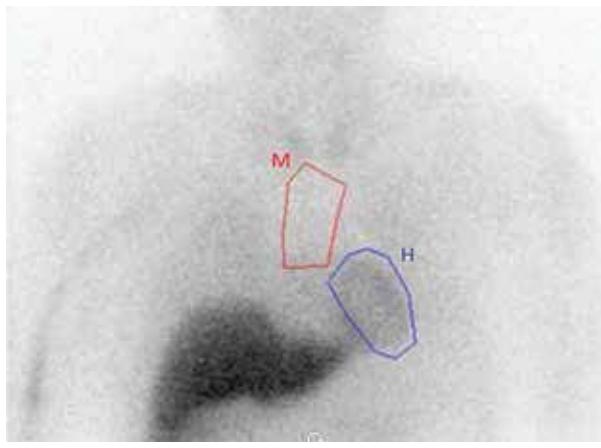


Figure 2. A cardiac iodine-123-meta-iodobenzylguanidine (^{123}I -MIBG) scan uptake is assessed using the heart-to-mediastinum (H/M) activity ratio



is imaged and evaluated semi-quantitatively by calculating the heart to mediastinum uptake ratio. Cardiac ^{123}I -MIBG uptake mainly reflects the density of myocardial sympathetic nerve endings. Abnormally decreased cardiac uptake is noted in pure autonomic failure as it is a slowly degenerative disease that affects mainly sympathetic noradrenergic nerves. However, ^{123}I -MIBG cardiac scanning is normal in autoimmune autonomic ganglionopathy (AAG) as it is a functional autonomic deficiency and there is no nerve degeneration. In this case, results indicated intact cardiac sympathetic innervation [Figure 2].

The differential diagnosis of neurogenic orthostatism includes neurological diseases such as multiple systemic atrophy or Parkinson's disease, pure autonomic failure, systemic diseases such as amyloidosis, or autoimmune diseases such as AAG. Autonomic dysfunction may precede motor symptoms in both Parkinson's disease and multiple system atrophy for months and even years; however, since the motor and sensory examinations of this patient are completely normal, a neurological disease appears less likely. There is no evidence for systemic disease such as amyloidosis. In this case, with evidence of intact cardiac sympathetic innervation as demonstrated by normal ^{123}I -MIBG uptake, the most likely diagnosis is AAG. As such, the next step is checking anti-ganglionic acetylcholine receptor anti-bodies.

The serum of the patient was sent for anti-ganglionic acetylcholine receptor antibody testing and results returned highly positive (1691.4 pM). Samples are positive if > 100 pM. Treatment by plasmapheresis was initiated with a dramatic reaction. During the first plasmapheresis the patient reported saliva in the mouth, and even a tear began to flow. In the evening of his first plasmapheresis, he had, for the first time in months, a spontaneous bowel movement. Unfortunately, these effects were quite short lasting.

The diagnosis of autoimmune AAG was confirmed by serologic testing. Treatment of this rare disease was reported in several small studies utilizing various humoral manipulations, such as IVIG or plasmapheresis, in addition to glucocorticoids and B cell depletion therapy. Our patient's antibody titer was exceedingly high, and plasmapheresis was chosen as the initial intervention, with immediate and dramatic results (e.g., saliva production was improved within 48 hours).

Following a course of plasmapheresis for 5 days, symptoms were significantly ameliorated; however, recurrent therapy of 1–2 days monthly was required to maintain the effect. Thus treatment with rituximab was initiated, as well as steroids (10 mg/d). He also received symptomatic treatment. His orthostatism was alleviated by midodrine (70 mg/day) and a mineralocorticoid (fludrocortisone). The patient was advised regarding non-medical measures (elastic socks, large fluid intake, salty food, sleeping with head of the bed elevated, avoidance of prolonged standing, and avoidance of heat). He received symptomatic treatment for erectile dysfunction by sildenafil with a warning not to get up after use because of danger of orthostatism worsening. The patient was sent for a thorough gastrointestinal evaluation consisting of upper and lower endoscopies, bowel transit time exam, gastric emptying scintigraphy, and anorectal manometry. As the decision was to start treatment without delay, only manometry was actually preformed, which displayed anorectal dyssynergy. The patient received high doses of laxatives. He had an ophthalmologic examination that revealed dryness and impaired pupillary constriction to light. The patient was instructed regarding use of artificial tears.

Despite the fact that AAG is a treatable disease, chronic symptoms can remain. The question of monitoring the activity of the disease and adapting the immune-modulatory treatment should be addressed.

About 1 year after starting immune-modulatory treatment, the patient had autonomic function re-testing. All the parameters had returned to normal, including the Valsalva maneuver and plasma norepinephrine levels. But the patient was unable to decrease the dose of the different treatments. When he tried to space out plasmapheresis or rituximab treatment, he was again very symptomatic with recurrence of severe constipation and syncope. However, well controlled by the chronic treatments, the patient was able to function regularly and live a quite normal life.

COMMENT

Dysautonomia, a general term used to describe a failure of the autonomic nervous system, has been known since 1969 [3], although only recently specific antibodies directed against nicotinic acetylcholine receptors in autonomic ganglia (ganglionic receptors) have been found to be linked with this disorder [4,5].

Following the discovery of these antibodies, the term of AAG was adopted.

AAG is characterized by sub-acute onset (less than 3 months). Patients are young to middle-aged adults and are more likely to be female than male (ratio 2:1). The clinical features of AAG reflect involvement of the parasympathetic, sympathetic, and enteric nervous system. There is generally no evidence of somatic peripheral neuropathy. In more than 70% of patients, the presenting symptoms are orthostatic hypotension and gastrointestinal dysfunction [6]. Symptoms due to parasympathetic failure include photophobia due to mydriasis (large pupils that react poorly to light and accommodation), dry eyes and dry mouth, and disturbances of bladder and bowel function. There are mainly lower gastrointestinal tract complaints (e.g., constipation), although upper gastrointestinal tract complaints (e.g., anorexia, early satiety, and heartburn) have also been reported. Some patients experience paralytic ileus. Other autonomic features include absence of sweating and erectile dysfunction.

The presence of persistent significant orthostatism, which is neurogenic in origin, is one of the hallmarks of the disease. The neurogenic orthostatic hypotension (NOH) is due to a failure of reflexive sympathetically mediated cardiovascular responses, sympathetic neurocirculatory failure [7]. Such failure produces characteristic abnormalities of beat-to-beat blood pressure associated with the Valsalva maneuver. In patients with NOH, systolic blood pressure decreases progressively during the maneuver. After release of the maneuver, systolic pressure increases slowly toward the baseline value, and there is no pressure overshoot. A neurochemical index to detect NOH is the plasma norepinephrine response to orthostasis. Normally, plasma norepinephrine levels approximately double within 5 minutes of standing. In NOH, plasma norepinephrine usually increases by at least 60%. Patients with NOH typically also have cardiovascular baroreflex failure, which explains why heart rate responses to the Valsalva maneuver or deep breathing usually are subnormal in NOH. These responses are mediated mainly by the parasympathetic nervous system.

Patients with chronic AAG have been described by Klein and colleagues [8]. For these patients, the age at disease onset is older than the patients with acute or sub-acute progression.

The main differential diagnosis for patients with a chronic course of AAG is pure autonomic failure (PAF), a degenerative disease with slowly progressive autonomic dysfunctions and with only symptomatic treatment available [9]. It is important to make the distinction, since the correct diagnosis provides the opportunity to administer the proper treatment. This distinction can be difficult to make since autoantibodies directed against the ganglionic nicotinic receptors are found in only 50% of patients with the typical features of AAG [4]. In PAF, there is marked sympathetic denervation that can be seen by neuroimaging [10], which indicates post-ganglionic noradrenergic denervation. In both PAF and AAG the plasma norepinephrine

level is low, but the plasma DHPG/norepinephrine ratio is high in AAG and low in PAF.

Paraneoplastic autonomic neuropathy must be considered. The tumors most commonly associated with paraneoplastic autonomic disorders include small-cell lung carcinoma (SCLC), ovarian carcinoma, breast carcinoma, lymphoma, and thymoma. Paraneoplastic autonomic neuropathy typically presents as a sub-acute panautonomic neuropathy, indistinguishable from AAG. Limited presentations may also occur, most notably severe gastrointestinal dysmotility without other autonomic features (paraneoplastic enteric neuropathy). As with other paraneoplastic disorders, the symptoms usually precede the diagnosis of cancer [11]. The autoantibody most commonly associated with paraneoplastic autonomic neuropathy is anti-Hu, also known as antineuronal nuclear antibody type 1 (ANNA-1) [12]. It is indicated to exclude neoplastic disease in every suspected case of AAG.

Other differential diagnoses include neurological diseases (multiple system atrophy and Lambert-Eaton syndrome) and systemic diseases (amyloidosis, diabetes mellitus, and Sjögren's syndrome).

Multiple system atrophy (MSA) is a neurological degenerative disease characterized by parkinsonism, cerebellar ataxia, and autonomic failure. Erectile failure in men, neurogenic orthostatism, and rapid eye movement (REM) sleep behavior disorder can precede motor symptoms by years. MSA and AAG have some similar sympathetic abnormalities and normal MIBG scans, thus at least in the first stages it may be difficult to differentiate if the specific antibodies for AAG are negative. The pathophysiology of these diseases is very different. In MSA the autonomic disturbances are due to degeneration of neurons in the central nervous system (CNS). In MSA, the postganglionic sympathetic neurons are intact but are not modulated appropriately by the CNS. In AAG the postganglionic sympathetic neurons are also intact but they are blocked by antibodies. DaTSCAN, a functional imaging of the dopamine transporter (123 I-FP-CIT) in the brain, defines integrity of the striatal dopaminergic system and may provide a marker for presynaptic neuronal degeneration. DaT scanning is abnormal even in the earliest clinical presentation of parkinsonism associated with nigrostriatal degeneration as in MSA [13] and could be used for helping differentiate MSA from sero-negative AAG.

Lambert-Eaton myasthenic syndrome (LEMS) is an acquired antibody mediated disorder of neuromuscular junction transmission. Approximately 50 to 60% of adult LEMS patients have a malignancy, most commonly SCLC. Weakness and fatigue are the usual presenting complaints, but autonomic symptoms are present in about 75% of patients. The autonomic symptoms are mild, and particularly postural hypotension is less common than cholinergic autonomic symptoms. Examination shows symmetrical proximal weakness. The diag-

nosis is based on the presence of antibodies against P/Q-type voltage-gated calcium channels [14].

Mixed sensory and motor peripheral neuropathy and/or autonomic neuropathy may occur and are prominent features in some of the heritable amyloidosis (called familial amyloidotic polyneuropathy) and in amyloid light-chain amyloidosis. The characteristic combination of small-fiber neuropathy with autonomic involvement and cardiac disease should always raise the suspicion of hereditary amyloid neuropathy, especially if there is a family history. Peripheral neuropathy and severe autonomic symptoms (severe neurogenic orthostatism and urinary and fecal incontinence) can be seen for months before the presentation of other systemic symptoms in AL amyloidosis. The presenting symptoms depend on the distribution of nerves affected [15]. The diagnosis of amyloidosis can be confirmed only by tissue biopsy.

Sjögren's syndrome is a chronic autoimmune inflammatory disorder characterized by diminished lacrimal and salivary gland function. The clinical manifestations include both exocrine gland involvement and extraglandular features. Mild autonomic dysfunction is common in Sjögren's syndrome; however, the involvement of different components of the autonomic nervous system has been debated. Clinically overt autonomic neuropathies are rare and manifested by severe orthostatic hypotension, hypohidrosis or anhidrosis, abdominal pain, constipation, diarrhea, and Adie's pupils [16].

The clinical course of AAG is typically monophasic, and patients often show spontaneous stabilization or recovery. The recovery is typically incomplete [6]. The mainstay of treatment is symptomatic management of autonomic failure, including blood pressure support, bowel management, and supplemental moisture for dry eyes and mouth. Orthostatism management includes supportive measures, such as elevation of the head of the bed at night, adequate fluid intake, small snack-like meals, compression socks or an abdominal binder, and salty food. The pharmacological measures are midodrine (an alpha-adrenoceptor agonist) and mineralocorticoids. Acetylcholinesterase inhibitors have been used to alleviate neurogenic orthostatic hypotension [17]. In our experience, we did not find benefit of these treatments for orthostatism but they can improve bowel functions.

Randomized trials are needed in order to inform therapy of AAG. Intravenous (IV) immunoglobulin (IVIg) or plasma exchanges have been reported to be effective in case reports [18,19]. There was also a case report of treatment by plasma exchanges and rituximab [20] with significant improvement, as in our experience.

One study shows that seronegative putative AAG patients respond to immunomodulatory therapy. This suggests the need to treat patients with an AAG phenotype even if seronegative for ganglionic AChR antibodies, as occurs in other autoimmune neurologic disorders such as myasthenia gravis [21].

Improvement in symptoms and deficits occurs with considerable heterogeneity. There is an immediate and drastic response to plasma exchange, but symptoms recur quickly as the antibodies build up again. There is a chronic need for long-lasting combined immunotherapy, including rituximab, plasmapheresis, and steroids.

We suggest that early diagnosis and treatment of AAG is important for a positive outcome.

CONCLUSIONS

In conclusion, AAG is an overlooked disease that can lead to severe complications. It is worthwhile to recognize this entity since good therapeutic options exist that can greatly improve quality of life.

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Capsule

Host factor drives the big bend

Bacteria have a highly adaptable DNA detecting and editing machine called CRISPR-Cas to ward off virus attack. The Cas1-Cas2 integrase, with the help of an accessory protein called integration host factor (IHF), captures foreign DNA motifs into bacterial CRISPR loci. These motifs then act as sensors of any further invaders. By analyzing the integrase complex structure, **Wright** and co-authors showed how Cas1-Cas2 recognizes the CRISPR array for site-specific integration. IHF sharply bends

DNA, which allows DNA to access two active sites within the integrase complex to ensure sequence specificity for the integration reaction. The features of the CRISPR integrase complex may explain the natural divergence of CRISPR arrays in bacteria and can be exploited for genome-tagging applications.

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Eitan Israeli

Capsule

Legitimizing a chemoattractant receptor

The orphan receptor GPR15 mediates the trafficking of lymphocytes to the colon and skin, and the recruitment of effector T cells to inflamed intestinal tissue. Using porcine colonic extracts, **Suply** and colleagues purified a ligand (GPR15L) that activated GPR15 but not other chemoattractant receptors. In mice, GPR15L recruited T cells to skin grafts,

and loss of the ligand was associated with decreased graft rejection. Because *GPR15L* mRNA is abundant in psoriatic lesions, these results suggest that the GPR15-GPR15L axis could be targeted to treat inflammatory skin conditions.

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Eitan Israeli

Capsule

Migration bound to neurotransmitter

Interneurons in the brain that use GABA (γ -aminobutyric acid) as a neurotransmitter are essential for functional circuits. During development, these interneurons migrate tangentially from their birthplace in embryonic ganglionic eminences to their functional homes in the neocortex. In mice lacking the distal-less homeobox genes (*Dlx1* and *-2*), this migration is disrupted. Studying mouse brain development, **Le** et al. showed

that *Dlx1* and *-2* regulate not only interneuron migration but also production of GABA. These genes bind to and regulate promoters of genes encoding glutamic acid decarboxylase (GAD), which converts the excitatory neurotransmitter glutamate into the inhibitory neurotransmitter GABA.

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Eitan Israeli

“Listen to the mustn’ts, child. Listen to the don’ts. Listen to the shouldn’ts, the impossibles, the won’ts. Listen to the never haves, then listen close to me... Anything can happen, child. Anything can be”

Shel Silverstein, (1930–1999), American poet, singer-songwriter, cartoonist, screenwriter, and author of children's books

“If you’re not failing every now and again, it’s a sign you’re not doing anything very innovative”

Heywood “Woody” Allen, (born 1931), American filmmaker, writer, actor, comedian, and musician whose career spans more than six decades