Autonomic Neuroscience: Basic and Clinical 220 (2019) 102559

Contents lists available at ScienceDirect

Autonomic Neuroscience: Basic and Clinical

journal homepage: www.elsevier.com/locate/autneu

Pure autonomic failure presenting as Harlequin syndrome

James D. Triplett, Eduardo E. Benarroch, Jeremy K. Cutsforth-Gregory*

Department of Neurology, Mayo Clinic, Rochester, MN, United States of America

ARTICLE INFO

Keywords:
Autonomic
Peripheral neuropathology
Pure autonomic failure
Harlequin syndrome

ABSTRACT

Pure autonomic failure (PAF) is a progressive syndrome of neurogenic orthostatic hypotension, widespread anhidrosis, urinary retention, and constipation without other neurologic manifestations. It is generally considered a peripheral ganglionic synucleinopathy. Natural history studies have described risk factors for the conversion of PAF to Parkinson's disease, multiple system atrophy, or dementia with Lewy bodies, yet the early stages of PAF are not well characterized. We present a patient with unilateral anhidrosis, contralateral facial flushing and hyperhidrosis consistent with Harlequin syndrome that, over 6 years, progressed to PAF, suggesting that PAF may present with focal autonomic impairment prior to generalized autonomic failure.

1. Introduction

The presentation of impaired facial sweating secondary to ipsilateral sympathetic dysfunction is uncommon, with patients often complaining of the compensatory hyperhidrosis rather than the primary anhidrosis. A variety of eponymous syndromes – including Harlequin, Horner, Ross, and Raeder paratrigeminal syndrome – present with such asymmetrical sweat responses.

Harlequin syndrome, initially described by Lance et al. (1988) is characterized by unilateral facial flushing and sweating with contralateral anhidrosis. It is caused by hemifacial cutaneous sympathetic denervation and dysfunction of sympathetic vasodilatory and sudomotor fibers from the stellate or superior cervical ganglion (Drummond, 1994; Drummond and Finch, 1989). The majority of cases are idiopathic, though congenital and post-traumatic presentations have been reported (Tascilar et al., 2007; Vidal Esteban et al., 2016).

Horner syndrome – homolateral ptosis, miosis, and anhidrosis – may accompany Harlequin syndrome, particularly when caused by trauma or other disruption of the sympathetic chain. Raeder paratrigeminal syndrome, characterized by Horner syndrome plus trigeminal neuropathy, results from disruption of the autonomic fibers traveling with the internal carotid artery in the paratrigeminal area of the middle cranial fossa (Nagal et al., 2010). Ross syndrome is a rare condition of unknown etiology with classical findings of segmental anhidrosis, areflexia, and tonic pupils (Mishra et al., 2017). These impairments of focal and segmental sudomotor dysfunction represent mild sympathetic dysfunction and are in contrast to the widespread autonomic abnormalities of pure autonomic failure (PAF).

PAF is defined as a syndrome of neurogenic orthostatic hypotension with evidence of more widespread autonomic failure including anhidrosis, urinary retention, and constipation and is usually considered a peripheral synucleinopathy (The Consensus Committee of the American Autonomic society and the American Academy of Neurology, 1996). PAF is generally progressive and may evolve to Parkinson disease (PD), multiple system atrophy (MSA), or dementia with Lewy bodies (DLB). Recent natural history studies have described risk factors for the conversion of PAF to a central synucleinopathy, yet the literature is sparse regarding the early stages of the disease (The Consensus Committee of the American Autonomic society and the American Academy of Neurology, 1996; Kaufmann et al., 2017; Singer et al., 2017).

Here we present the clinical course of a patient who initially presented with Harlequin syndrome but over 6 years developed severe PAF.

At age 55, a woman began to notice left facial flushing and sweating after playing tennis, whilst the right side remained pale and dry. By the time of initial evaluation at our institution at age 57, she had also experienced 1 year of mild postural lightheadedness. Neurologic examination was normal, but thermoregulatory sweat test (TST) showed anhidrosis affecting 20% of anterior body surface area, predominantly the right head, neck, and upper limb. Autonomic reflex screen (ARS) revealed asymptomatic orthostatic hypotension with preserved cardiac responses to deep breathing and Valsalva maneuver (Fig. 1A). Serum norepinephrine was normal at 119 pg/mL in the supine position (normal range 70–750 pg/mL) and rose adequately upon standing to 454 pg/mL (normal standing value is 2–3 times the supine level). The distribution of anhidrosis was consistent with impairment or disruption of the upper sympathetic outflow at the T1-T2 level. CT of the chest did not show Pancoast tumor or other abnormalities. The patient was

* Corresponding author at: Department of Neurology, Mayo Clinic, 200 1st St SW, Rochester, MN, 55905, United States of America.
E-mail address: cutsforthgregory.jeremy@mayo.edu (J.K. Cutsforth-Gregory).

https://doi.org/10.1016/j.autneu.2019.102559
Received 26 March 2019; Received in revised form 16 May 2019; Accepted 13 June 2019

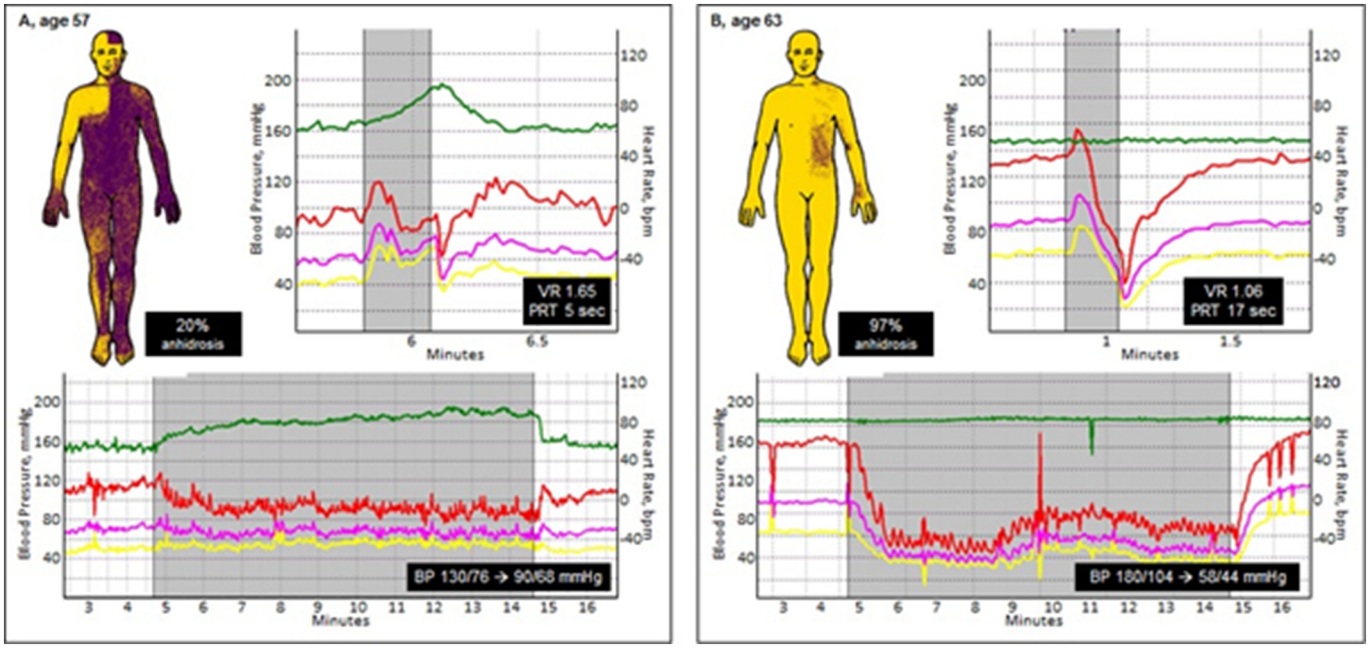

Fig. 1. (A) Investigations at presentation revealing approximately 20% anhidrosis by thermoregulatory sweat test (TST) primarily affecting right upper limb, face, and torso, though mild abnormality also present in right foot. Normal response to Valsalva and tilt table response revealing prolonged orthostatic hypotension with tilt and compensatory tachycardia. (B) Investigations 6 years following presentation revealing near total body anhidrosis on TST, abnormal response to Valsalva with phase 2 drop of > 40 mmHg and absent phase 4 response and tilt table revealing profound and persistent orthostatic hypotension without compensatory tachycardia.

diagnosed with Harlequin syndrome.

Over the next 9 months, the patient suffered more troublesome orthostatism, particularly in the morning. She also complained of neck and shoulder ache upon standing (coat hanger pain of paraspinal muscle ischemia due to orthostatic hypotension). TST revealed progressive anhidrosis, now affecting the right abdomen, right hand, and distal left leg and foot. Cardiovagal impairment and the degree of orthostatic hypotension also worsened (Table 1). Paraneoplastic autoantibody testing, including ganglionic nicotinic acetylcholine receptor autoantibodies, was negative. Based on these findings, and the absence of other neurologic abnormalities, the patient was diagnosed with PAF.

Table 1
Thermoregulatory sweat test Composite Autonomic Severity Score over time.

Age	Sudomotor	Cardiovagal		Adrenergic		CASS-TST[f]
	TST %[a]	HR_{DB}[b]	VR[c]	PRT[d]	ΔSBP to tilt[e]	
57	20	12.6	1.65	5	40	2
58	21	9.9	1.58	12	64	4
59	33	11.0	1.33	16	58	7
60	50	2.9	1.39	16	58	9
63	97	2.4	1.06	17	122	10

Autonomic testing indices demonstrate progressive failure of sudomotor, cardiovagal, and adrenergic function in the 6 years following presentation.

[a] TST % = thermoregulatory sweat test (TST) quantifies anhidrosis as a percent of anterior body surface area.

[b] HR_{DB} = heart rate variation with deep breathing is the average difference between maximal and minimal heart rate during 5 consecutive breaths at 6/min. Normal values decrease with age, ≥ 9 beats/min (bpm) for women 50–59 years and ≥ 7 bpm for 60–69 years.

[c] VR = valsalva ratio is the ratio of maximal to minimal heart rate during the Valsalva maneuver. Normal values decrease with age, > 1.36 for women 50–59 years and > 1.29 for women 60–69 years.

[d] PRT = pressure recovery time is the duration from termination of the Valsalva maneuver to recovery of systolic blood pressure to pre-Valsalva baseline.

[e] ΔSBP to tilt = change in systolic blood pressure during 70° head-up tilt.

[f] CASS-TST = Composite Autonomic Severity Scale sums sudomotor, cardiovagal, and adrenergic dysfunction from 0 (normal) to 10 (severe). The CASS sudomotor domain can be derived from QSART or TST values, reported here as a function of TST percent anhidrosis.

In ensuing years, the patient developed right ptosis and miosis (Horner syndrome) and progressive heat intolerance and orthostatic hypotension requiring pyridostigmine, fludrocortisone, midodrine, and compression garments. The patient had no complaints of tremor, gait disturbance, anosmia, or REM sleep behavioral disorder (RBD). TST documented progressive sudomotor dysfunction culminating in 97% global anhidrosis by 6 years after initial presentation (Fig. 1B).

Postganglionic sudomotor (quantitative sudomotor axon reflex test, QSART) responses were initially normal at all sites, but lower limb responses later became reduced or absent. Cardiovagal responses were also initially normal and became impaired over time. At later evaluations she had hypertension when supine and after each dose of midodrine regardless of body position (Fig. 2). Repeat serum norepinephrine showed it to be low supine and standing (45 pg/mL supine, 66 pg/mL standing).

The progression from Harlequin syndrome to PAF observed in our patient provides valuable information about the natural history of these rare disorders. PAF is generally considered a synucleinopathy involving severe loss of sympathetic noradrenergic neurons, but cases of autoimmune autonomic ganglionopathy (AAG) with antibodies against the ganglionic nicotinic acetylcholine receptor and mimicking PAF have been described (Goldstein et al., 2017). The etiology of atraumatic Harlequin syndrome remains unknown, with para-infectious, post-infectious, and autoimmune processes affecting the stellate ganglion cells suggested.

Our case illustrates that PAF may begin segmentally, perhaps due to focal impairment of the preganglionic sympathetic neurons of the intermediolateral cell column of the spinal cord or of selected regions of the sympathetic chain. The gradual progression of symptoms in our patient, with worsening sudomotor, noradrenergic, and then cardiovagal failure, suggests a neurodegenerative process. The early postural lightheadedness in our patient may have been a clue to evolving PAF rather than isolated Harlequin syndrome, and yet autonomic

dysfunction beyond sudomotor abnormalities is described in nearly 50% of reports of Harlequin syndrome (Bremner and Smith, 2008; Galvez et al., 2008).

Various ocular abnormalities are described in Harlequin syndrome, including both sympathetic and parasympathetic dysfunction. When seen, these may suggest a more widespread underlying process. A review of 39 patients with Harlequin syndrome identified pupillary abnormalities in 64%, nearly always postganglionic in nature, with ipsilateral Horner syndrome most common (46%) (Bremner and Smith, 2008). Progressive disease with contralateral segmental hypohidrosis of limbs and body, seen in one-third of patients, or the development of Horner syndrome has occasionally been described as "atypical Harlequin syndrome," but these presentations may instead represent evolving PAF (Lance et al., 1988; Bremner and Smith, 2008; Galvez et al., 2008).

AAG is associated with impaired pupillary light reflexes and anhidrosis – focal, distal, regional, or global – and occasionally may be confused with Harlequin syndrome (Suarez et al., 1994). In AAG, sudomotor dysfunction is ganglionic/postganglionic, while in Harlequin syndrome it has been described as preganglionic (KIimpinski et al., 2012; Wasner et al., 2005). In PAF, postganglionic sudomotor testing may be normal or abnormal (Singer et al., 2017). In our patient, initial QSART (postganglionic) testing was normal even in areas anhidrotic on TST (which tests the entire sudomotor pathway), indicating preganglionic dysfunction. The subsequent development of reduced proximal leg and absent distal leg and foot QSART responses in our patient may suggest spread of the underlying pathology to postganglionic structures or be a secondary phenomenon of more severe, chronic impairment of the corresponding pre-ganglionic cell bodies and/or axons causing postganglionic axonal loss from reduced sympathetic innervation (KIimpinski et al., 2012). A similar process of early preganglionic and late postganglionic sudomotor dysfunction is seen in MSA (Coon et al., 2017).

Further evidence of postganglionic dysfunction (cardiovagal and adrenergic domains) in our patient is found in her response to midodrine, a peripheral α_1-receptor agonist. Hypertensive spikes after midodrine administration and postural tachycardia (Fig. 2 – Online supplement) result from cardiovascular denervation hypersensitivity. In the absence of normal basal norepinephrine release from postganglionic sympathetic neurons, α_1- receptors are up-regulated on the vascular smooth muscle fibers and exhibit exaggerated responses to even low-dose agonists. This finding localizes the pathophysiological injury to postganglionic structures.

We do not have tissue pathology from our patient, who remains alive and independently functional in daily life. In other reported cases of PAF, degeneration of peripheral autonomic neurons along with α-synuclein–positive, Lewy body–like inclusions in sympathetic ganglia and widespread α-synuclein deposits in autonomic neurons characterize the disorder as a restricted, non-motor synucleinopathy (Kaufmann et al., 2001). The occurrence of RBD and anosmia suggest α-synuclein deposition in central structures (Goldstein and Sewell, 2009; Goldstein et al., 2008), and the progression from a PAF phenotype to more widespread synucleinopathies including PD, MSA, and DLB is widely reported (Kaufmann et al., 2017; Singer et al., 2017; Goldstein and Sewell, 2009; Goldstein et al., 2008). Approximately 8% of patients with PAF will convert to MSA, and 26% will develop Lewy body diseases (Kaufmann et al., 2017; Singer et al., 2017). Risk factors for converting to MSA include RBD, stridor, young age at onset, severe bladder and bowel dysfunction, and preserved olfaction and cardiovagal function. In contrast, anosmia, RBD, longer duration of symptoms, and more severe cardiovagal impairment predict Lewy body diseases. PAF that remains as such is associated with lack of RBD, low serum norepinephrine, preserved olfaction, and slow resting heart rate, all of which were eventually seen in our patient.

Though progression of PAF to other diseases is now well established, the natural history of the early stages of this disease is poorly understood. This case highlights insidious progression from focal onset sudomotor dysfunction to severe generalized autonomic failure, suggesting that PAF may start focally and then spread, even as it remains in the peripheral autonomic structures. Alternatively, it could be a disorder of early dispersed pathology that only gradually causes neural dysfunction. Further long-term follow up of patients presenting with idiopathic segmental sudomotor dysfunction may yield further evidence of progression to PAF, and histopathological analysis of such cases may identify α-synuclein deposits to establish a common pathophysiological mechanism.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autneu.2019.102559.

Author contributions

JT performed study design and conceptualization, data acquisition, data analysis and drafting of the manuscript. AB performed study design and conceptualization, data analysis and interpretation drafting of the manuscript. JCG performed study design and conceptualization, data acquisition, data analysis, data interpretation and drafting of the manuscript.

Declaration of Competing Interest

Nothing to report.

References

Bremner, F., Smith, S., 2008. Pupillographic findings in 39 consecutive cases of harlequin syndrome. J. Neuroophthalmol. 28, 171–177.

Coon, E.A., Fealey, R.D., Sletten, D.M., et al., 2017. Anhidrosis in multiple system atrophy involves pre- and postganglionic sudomotor dysfunction. Mov. Disord. 32 (3), 397–404.

Drummond, P.D., 1994. Sweating and vascular responses in the face: normal regulation and dysfunction in migraine, cluster headache and harlequin syndrome. Clin. Auton. Res. 4, 273–285.

Drummond, P.D., Finch, P.M., 1989. Reflex control of facial flushing during body heating in man. Brain. 112, 1351–1358.

Galvez, A., Ailouti, N., Toll, A., et al., 2008. Horner syndrome associated with ipsilateral facial and extremity anhidrosis. J. Neuroophthalmol. 28, 178–181.

Goldstein, D.S., Sewell, L., 2009. Olfactory dysfunction in pure autonomic failure: implications for the pathogenesis of Lewy body diseases. Parkinsonism Relat. Disord. 15, 516–520.

Goldstein, D.S., Holmes, C., Sato, T., et al., 2008. Central dopamine deficiency in pure autonomic failure. Clin. Auton. Res. 18, 58–65.

Goldstein, D.S., Holmes, C., Sullivan, P., et al., 2017. Autoimmunity-associated autonomic failure with sympathetic denervation. Clin. Auton. Res. 27 (1), 57–62.

Kaufmann, H., Hague, K., Perl, D., 2001. Accumulation of alpha-synuclein in autonomic nerves in pure autonomic failure. Neurology. 56, 980–981.

Kaufmann, H., Norcliffe-Kaufmann, L., Palma, J.A., et al., 2017. Natural history of pure autonomic failure: a United States prospective cohort. Ann. Neurol. 81, 287–297.

KIimpinski, K., Iodice, V., Sandroni, P., Fealey, R.D., Vernino, Low P.A., 2012. Sudomotor dysfunction in autoimmune autonomic ganglionopathy: a follow-up study. Clin. Auton. Res. 22 (3), 131–136.

Lance, J.W., Drummond, P.D., Gandevia, S.C., et al., 1988. Harlequin syndrome: the sudden onset of unilateral flushing and sweating. J. Neurol. Neurosurg. Psychiatry 51, 635–642.

Mishra, A.K., Kharkongor, M., Kuriako, C.K., et al., 2017. Is Ross syndrome an autoimmune entity? A case series of 11 patients. Can. J. Neurol. Sci. 44, 318–321.

Nagal, M.A., Bert, R.J., Gilden, D., 2010. Reader syndrome produced by extension of chronic inflammation to the internal carotid artery. Neurology. 79 (12), 1296–1297.

Singer, W., Berini, S.E., Sandroni, P., et al., 2017. Pure autonomic failure: predictors of conversion to clinical CNS involvement. Neurology 88, 1129–1136.

Suarez, G.A., Fealey, R.D., Camilleri, M., Low, P.A., 1994. Idiopathic autonomic neuropathy: clinical, neurophysiologic, and follow-up studies on 27 patients. Neurology. 44, 1675–1682.

Tascilar, N., Tekin, N.S., Erdem, Z., et al., 2007. Unnoticed dysautonomic syndrome of the face: harlequin syndrome. Auton. Neurosci. 137 (1–2), 1–9.

The Consensus Committee of the American Autonomic society and the American Academy of Neurology, 1996. Consensus statement of the definition of orthostatic hypotension, pure autonomic failure and multiple system atrophy. Neurology. 46 (5), 1470.

Vidal Esteban, A., Natera-de Benito, D., Martınez Sanchez, D., et al., 2016. Congenital Harlequin syndrome as an isolated phenomenon: a case report and review of the literature. Eur. J. Paediatr. Neurol. 20 (3), 426–430.

Wasner, G., Magg, R., Ludwig, J., et al., 2005. Harlequin syndrome – one face of many etiologies. Nat. Clin. Pract. Neurol. 1 (1), 54–59.