NOSOLOGICAL ENTITIES?

Ramsay Hunt syndrome

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Abstract

The strict definition of the Ramsay Hunt syndrome is peripheral facial nerve palsy accompanied by an erythematous vesicular rash on the ear (zoster oticus) or in the mouth. J Ramsay Hunt, who described various clinical presentations of facial paralysis and rash, also recognised other frequent symptoms and signs such as tinnitus, hearing loss, nausea, vomiting, vertigo, and nystagmus. He explained these eighth nerve features by the close proximity of the geniculate ganglion to the vestibulocochlear nerve within the bony facial canal. Hunt's analysis of clinical variations of the syndrome now bearing his name led to his recognition of the general somatic sensory function of the facial nerve and his defining of the geniculate zone of the ear. It is now known that varicella zoster virus (VZV) causes Ramsay Hunt syndrome.

Compared with Bell's palsy (facial paralysis without rash), patients with Ramsay Hunt syndrome often have more severe paralysis at onset and are less likely to recover completely. Studies suggest that treatment with prednisone and acyclovir may improve outcome, although a prospective randomised treatment trial remains to be undertaken. In the only prospective study of patients with Ramsay Hunt syndrome, 14% developed vesicles after the onset of facial weakness. Thus, Ramsay Hunt syndrome may initially be indistinguishable from Bell's palsy. Further, Bell's palsy is significantly associated with herpes simplex virus (HSV) infection. In the light of the known safety and effectiveness of antiviral drugs against VZV or HSV, consideration should be given to early treatment of all patients with Ramsay Hunt syndrome or Bell's palsy with a 7–10 day course of famciclovir (500 mg, three times daily) or acyclovir (800 mg, five times daily), as well as oral prednisone (60 mg daily for 3–5 days).

Finally, some patients develop peripheral facial paralysis without ear or mouth rash, associated with either a fourfold rise in antibody to VZV or the presence of VZV DNA in auricular skin, blood mononuclear cells, middle ear fluid, or saliva. This indicates that a proportion of patients

with "Bell's palsy" have Ramsay Hunt syndrome zoster sine herpette. Treatment of these patients with acyclovir and prednisone within 7 days of onset has been shown to improve the outcome of recovery from facial palsy.

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James Ramsay Hunt (1872–1937) received his MD from the University of Pennsylvania School of Medicine in 1893. His first academic appointment was Instructor at Cornell University School of Medicine. In 1924, he became a full professor at Columbia University School of Medicine.¹ Hunt described three discrete syndromes, the best known of which is zoster oticus with peripheral facial palsy (fig 1). The second Ramsay Hunt syndrome encompasses the clinical features produced by carotid artery occlusion.² A third Ramsay Hunt syndrome is dyssynergia cerebellaris progressiva,³ but a lack of pathological material has not allowed its adequate classification among the degenerative spinocerebellar disorders. The wide scope of Hunt's works included the first full description of deep palmar neuropathy attributed to median nerve compression between the abductor and short flexor muscles of the hypothenar eminence.⁴ Hunt's collated records from 15 patients with sciatica also described thickened oedematous nerves, including one of his own, in which a firm translucent substance of gelatinous consistency was deposited in the epineurium.⁵ His research on Parkinson's disease helped to reveal the structure and function of the basal ganglia, about which little was previously known. Indeed, Hunt has been described as "Olympian"⁶ for his contributions to our understanding of the nervous system.

By the early 1900s, it was well accepted that infection of ganglia and skin by a herpes virus produced the characteristic dermatomal distribution of pain and vesicular rash. The crucial study that provided this knowledge was detailed in a 270 page treatise that correlated dermatomal distribution of zoster with pathological changes in ganglia.⁷ Although the analysis of structure usually precedes that of function, these pioneering studies exemplify how clinical neurology helped to define the

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Figure 1 Clinical features of Ramsay Hunt syndrome. Note peripheral facial weakness characterised by a widened palpebral fissure and decreased forehead wrinkling and smile on the right, often associated with vesicles in the ipsilateral ear, on the hard palate, or on the anterior two thirds of the tongue.

dermatomal anatomy of the peripheral nervous system.

Ramsay Hunt syndrome

Hunt's research on herpetic inflammation of the geniculate ganglion⁸ described, for the first time, the relation between the geniculate ganglion and somatic sensory function in the ear. His discovery of the general sensory function of the facial nerve led to the recognition that functions of the seventh cranial nerve are mixed and include brachial and visceral motor as well as special and general sensory components (fig 2). Before Hunt's eloquent description of the facial nerve sensory system, ear rash and pain had been attributed to inflammation of the gasserian ganglion or to neuritis of the auriculotemporal branch of the trigeminal nerve. However, after reviewing the results of ablative surgery for trigeminal neuralgia and occipitocervical neuralgia performed by Krause, Cushing, Frazier, and Spiller, Hunt deduced that somatic sensation from portions of the ear was not received by afferent fibres of the second or third dorsal root ganglion or the gasserian ganglion.⁴ In his review of 60 cases of zoster oticus, Hunt realised that the distribution of vesicular eruptions matched the areas of sensation spared by surgery. He concluded that sensation on the ear was derived either from the geniculate ganglion of the facial nerve, from the petrous ganglion and its accessory ganglion (Ehrenritter) of the glossopharyngeal nerve, or from the jugular ganglion and plexiform ganglion of the vagus nerve.⁹ Combining his clinical knowledge with anatomy, Hunt surmised that the geniculate zone included the

concha, antihelix, fossa of the antihelix, antitragus, incisura intertragica, and a portion of the lobule.¹⁰

Hunt had also long noted variability of the affected portion of the ear. He knew that the glossopharyngeal, vagal, and facial nerves derive from the same brachial arch, and that the auricular branch of the vagus and of the glossopharyngeal nerve travel together.¹¹ Thus, despite the anatomical variability of the auricular sensory representation by these three cranial nerves, Hunt concluded that they cooperatively detect somatic sensation from the posterior portion of the tympanum, auditory canal, posteromesial surface of the auricle, and adjacent mastoid.

Although Ramsay Hunt syndrome is traditionally defined as zoster oticus and lower motor neuron facial palsy, Hunt noted other regular symptoms and signs such as tinnitus, hearing loss, nausea, vomiting, vertigo, and nystagmus. He explained these eighth nerve features by the close proximity of the geniculate ganglion to the vestibulocochlear nerve within the bony facial canal. Based on clinical presentations that indicated involvement of more than one ganglion, Hunt surmised that the gasserian, geniculate, petrous, accessory, jugular, plexiform, and second and third cervical dorsal root ganglia comprised a chain in which inflammation of a single ganglion could extend to nearby ganglia. This hypothesis explained cases of unilateral facial palsy accompanied by contiguous cranial neuropathies associated with vesicles in the mouth—usually on the tongue or hard palate—or ear.⁹ Although this hypothesis remains valid, contiguous cranial neuropathies can also be explained based on the selective vulnerability of blood vessels to varicella zoster virus (VZV) and the blood supply from small branches of the carotid artery, middle meningeal, and ascending pharyngeal system to cranial nerves. For example, the ascending pharyngeal artery supplies the glossopharyngeal, vagal, accessory, and hypoglossal nerves, and a branch of the middle meningeal artery supplies the facial nerve as well as the maxillary and mandibular branches of the trigeminal nerve.¹² Transaxonal spread of VZV from one or more cranial nerve ganglionic afferent fibres to the vasa vasorum of cranial nerves could produce infarction with resultant zoster polyneuritis cranialis.

Hunt also noted that some cases of herpetic pharyngitis and laryngitis occurred together with glossopharyngeal or vagal neuropathy. Recognising that the seventh, ninth, and tenth cranial nerves derive from the same brachial arch, he speculated that all three nerves were represented in the mouth and ear. He postulated that the glossopharyngeal somatic sensory nerve supplied the posterolateral surface of the tongue, the pillars of the fauces, the tonsil, and the adjacent pharynx, and that the vagal somatic sensory nerve supplied the root of the tongue, the structures at the entrance to the larynx, and the adjacent pharyngeal region. Although there is no somatic sensory facial branch to the oropharynx or tongue, Hunt hypothesised correctly that a herpesvirus could

spread from either a seventh cranial nerve ves-tigial remnant to the oropharynx or from special sensory fibres to the anterior two thirds of the tongue.⁹

Another significant contribution was Hunt's description of a painful neuralgia that occurred with facial paralysis and zoster oticus. Pain was deep in the face, often radiating to the ear, and sometimes associated with lacrimation, nasal congestion, and salivation. Relief was obtained by section of the nervus intermedius.¹³ The implication that this neuralgia was a vascular headache variant led to studies that established a relation between cranial neuropathies, headache pain, and the sympathetic nervous system. For example, Sluder described sphenopalatine neuralgia characterised by pain deep in the nose, orbit, upper jaw and teeth, thought to represent involvement of the sphenopalatine ganglion and perivascular plexus of the internal maxillary artery.¹⁴ That study was followed by the description of "lower half headache": pain in the nose, cheeks, lips, tongue and jaw

relieved by stripping the external carotid artery of nerve fibres. At the same time, Gardner *et al*¹⁵ described petrosal neuralgia, another disorder of facial nerve function in which paroxysms of facial pain were associated with lacrimation and nasal congestion; relief was obtained in 75% of patients by section of the greater superficial petrosal nerve.

Epidemiology

Ramsay Hunt syndrome is the second most common cause of atraumatic peripheral facial paralysis. Before 1986, the frequency of zoster in patients with peripheral facial paralysis was estimated to be 4.5%-8.9%.¹⁶ However, a retrospective review of 1507 consecutive Kaiser insured patients presenting with unilateral facial palsy identified Ramsay Hunt syndrome in 185 (12% patients) based on the triad of facial paralysis, ear pain, and herpetic eruptions in any cranial dermatome.¹⁷ Viral aetiology was confirmed in 46 patients by a fourfold rise in antibody to VZV. There were

Figure 2 Functional anatomy of the facial nerve. Proximally, the four cranial nerve nuclei involved in facial nerve functions are shown at the pontomedullary junction: the motor nucleus of VII, the nucleus of the solitary tract, the superior salivatory nucleus, and the spinal nucleus of V. Special visceral efferent motor fibres from the motor nucleus of VII (solid red line) exit the brain stem and travel through the internal acoustic meatus to enter the bony facial canal and exit through the stylomastoid foramen to supply facial muscles. In Ramsay Hunt syndrome, these fibres are affected as they pass through the geniculate ganglion, disrupting motor functions of the seventh cranial nerve. The solitary tract receives special visceral afferent taste fibres (solid blue line) emanating from the anterior two thirds of the tongue. These fibres travel with the chorda tympani through the petrotympanic fissure (not shown). The cell bodies of these special visceral afferent fibres are in the geniculate ganglion which is the site of VZV reactivation when vesicles erupt on the tongue. The fibres reach the brain stem via the nervus intermedius and can be affected by local inflammation as they pass the geniculate ganglion. Special visceral efferent parasympathetic fibres (thin dotted red line) to the lacrimal and salivary glands emanate from the superior salivatory nucleus, travel in the nervus intermedius, and branch at the geniculate ganglion into the greater petrosal and chorda tympani nerves. Decreased lacrimation may result from involvement of these fibres as they branch at the level of the geniculate ganglion. Special visceral efferent sympathetic fibres (thick dotted red line) emanate from the carotid plexus on the internal carotid artery and join the greater petrosal nerve as these structures pass through the foramen lacerum (not shown). The sympathetic fibres parallel the parasympathetic fibres as they supply the same areas. The spinal nucleus of V receives general somatic afferent fibres from the geniculate zone of the ear via the chorda tympani. Cell bodies of these neurons are located in the geniculate ganglia and are the site of VZV reactivation in classic Ramsay Hunt syndrome causing vesicular eruptions in geniculate zones.

20% more women (101) with Ramsay Hunt syndrome than men (84), and 56 (30%) were younger than 24 years, indicating a sampling bias due to the younger age of the patients. In another study of 152 patients with Ramsay Hunt syndrome, 19% had an abnormal audiogram, but no correlation between severity of facial weakness and hearing loss was found.¹⁸

A retrospective review of 2076 patients presenting with unilateral facial palsy, with or without vesicles, from 1976 to 1996 in Japan¹⁹ disclosed a similar incidence of Ramsay Hunt syndrome in adults and children over age 6 years. In that study, the syndrome was defined as unilateral facial palsy, herpetic vesicles on the ear or oral mucosa, and vestibulocochlear dysfunction. It was diagnosed in 16.7% of children and 18.1% of adults with facial palsy. The incidence was higher in children older than 6 (24.3%) than in children younger than 6 (10.5%). Compared with adults, the appearance of vesicles was delayed in children, with 50% of children younger than 16, and 31.9% of adults displaying vesicles after facial palsy. In children younger than 16 and in adults, associated symptoms included hearing loss (24.4% and 52.7%, respectively), tinnitus (11.1% and 24.7%, respectively), and vertigo (17.4% and 31.8%, respectively); 2.9% of adults also showed glossopharyngeal/vagal symptoms.

In a retrospective review of 4395 patients with peripheral facial paralysis,¹⁶ 147 (3.3%) ultimately were diagnosed with Ramsay Hunt syndrome, based on the presence of facial palsy and ipsilateral vesicles, erythema, and/or crusts. In the absence of vesicles, patients with facial paralysis were also diagnosed as having the syndrome if they showed a rising titre of VZV antibodies, a decrease in hearing threshold of at least 20 dB, or objective vestibular signs. No significant differences were found in sex or age of onset (mean 47 years old in men and 50 years old for women).

Natural history

A retrospective study of 102 untreated patients with Ramsay Hunt syndrome analyzed age, extent of paralysis, time, and location of rash.¹⁶ Using a subjective muscle strength scale and response to facial nerve stimulation, the investigators found that maximal loss of function was complete within 1 week. Complete paralysis was twice as frequent as incomplete paralysis, and occurred more often in patients older than 50. Lack of nerve excitability, complete paralysis, and age over 50 were statistically significant factors for poor prognosis. Of the patients with partial clinical or electrical function at onset, 66% recovered completely, whereas only 10% of patients who presented with complete loss of clinical and electrical function recovered completely, and all of them had residual synkinesis. Increasing clinical severity predicted the development of synkinesis. In patients with complete facial paralysis and a partial electrical response, oral synkinesis developed in 70% and eyelid synkinesis in 60%, whereas in patients with incomplete

paralysis both electrically and clinically, synkinesis of the mouth and eyelids occurred in 10% and 15%, respectively.

Facial strength was evaluated with the House-Brackmann grading system used by Hato *et al*¹⁹ in their retrospective review of Ramsay Hunt syndrome in children and adults. Complete recovery occurred in 85/173 (49%) adults, and in 33/42 (78%) patients younger than 16. Serial audiograms showed complete recovery in 66% of children with audiometry documented hearing loss compared with 37.7% of adults.

In the retrospective Kaiser series,¹⁷ 80% of patients presenting with ipsilateral facial palsy were treated orally with 60 mg prednisone daily for 6 days which was decreased by 10 mg daily for the next 5 days. If pain returned or paralysis progressed, or if there was evidence of further denervation, prednisone was increased to 60 mg daily for 5 to 7 more days. Use of the objective serial four points tests of nerve excitability to compare patients with Bell's palsy and patients with Ramsay Hunt syndrome in this study showed that patients with Ramsay Hunt syndrome were statistically more likely to have severe and complete denervation with persistent synkinesis; patients with Ramsay Hunt syndrome treated with prednisone were less likely to progress to complete facial paralysis than untreated patients.

Histopathology

Despite Hunt's eloquent clinical descriptions, he examined ganglia from only one patient after death and, unfortunately, the geniculate ganglion was not available. The first histopathological examinations of dorsal root ganglia affected by VZV involved 20 elderly and often premonitory patients with clinical zoster 3 to 500 days before death.⁷ Postmortem examination disclosed a temporally dependent range of pathological changes. Necrotic dorsal root ganglia with mononuclear cell infiltrates were seen in zoster occurring just before death. Zoster that occurred months to years before death was characterised by fibrotic ganglia. In stark contrast with the necrotic ganglionitis described by Head and Campbell,⁷ only mild inflammation has been seen in geniculate ganglia of patients with a history of Ramsay Hunt syndrome 4–36 weeks before death.^{20–21} Thus, the very existence of geniculate ganglionitis has been debated.

In 1944, Denny-Brown *et al*²¹ described a 62 year old man who developed a vesicular, painful rash in the right occiput, neck, and external ear canal. Eleven days later, he developed right peripheral facial palsy, right tongue deviation, and decreased right C2–3 distribution pain and temperature sensation. Two CSF examinations showed a lymphocytic pleocytosis with a normal protein and glucose. Four weeks later, he died from a massive gastrointestinal haemorrhage. Pathological changes at postmortem examination showed a necrotic second cervical dorsal ganglion and increased microglial proliferation in the grey matter of the second and third cervical posterior and anterior horns. Mild lymphocytic infiltrates were seen in the

meninges and in patchy areas of the seventh cranial nerve. The geniculate ganglion was normal. The hypoglossal, trigeminal, and glossopharyngeal nerves were not examined. This single case illustrates the variable histopathological changes associated with herpes zoster.

Two case studies of pathological changes 6 and 9 weeks after the onset of Ramsay Hunt syndrome reported similar findings.^{22, 23} In both patients, perivascular lymphocytic inflammation, demyelination, and axonal loss along the seventh nerve, and mild lymphocytic infiltration of the geniculate ganglion were seen. One patient showed extensive haemorrhage in the auditory nerve at the internal auditory meatus with complete destruction of the apex of the organ of Corti. In both of these cases, most histopathological changes occurred outside the geniculate ganglion.

Aleksic *et al*²⁰ reported on a patient who died of a brain tumour 9 months after the onset of Ramsay Hunt syndrome. Serial lumbar punctures showed a fourfold rise in complement fixing antibody to VZV in CSF. There was moderate fibre loss in the proximal portion of the facial nerve. The distal seventh nerve terminated in a "traumatic" neuroma. Moderate depletion of neurons was seen in the ipsilateral geniculate ganglion with some of the remaining neurons showing chromatolysis and coarse vacuolation. Small collections of lymphocytes and macrophages were noted in the focally rarefied stroma of the geniculate ganglion.

Together, these four cases demonstrate the variability of histopathological changes in Ramsay Hunt syndrome. Many authors have suggested that the data do not confirm Hunt's original concept of geniculate ganglionitis but rather illustrate viral attack of the facial nerve itself. By contrast with VZV induced dorsal root ganglionitis, the temporal range of histopathological findings in Ramsay Hunt syndrome is unknown. The geniculate ganglia and the facial nerve are not commonly dissected at necropsy, and there are few reported cases. Thus the debate surrounding the existence of geniculate ganglionitis awaits further information.

Diagnosis and treatment

The history and neurological examination remain the bases for diagnosing Ramsay Hunt syndrome. Examination of CSF and gadolinium enhanced MRIs have had no diagnostic or prognostic value.²⁴ Polymerase chain reaction (PCR) to detect VZV in exudates from the geniculate zone of the ear is more sensitive than VZV PCR performed on tears or blood mononuclear cells.²⁵ In the same study, 5/7 (71%) patients were shown to be PCR positive in ear exudates before the development of vesicles. Although further research is needed, geniculate zone VZV PCR may help to distinguish between patients with Bell's palsy and patients with early Ramsay Hunt syndrome.

The largest retrospective Ramsay Hunt syndrome treatment study²⁶ showed a statistically significant improvement in patients treated with prednisone and acyclovir within 3 days of

onset. Eighty patients were separated into groups based on the time treatment was started—that is, less than 3 days, 3–7 days, and after 7 days. All patients were treated with oral prednisone (1 mg/kg/day for 5 days followed by a 10 day taper), as well as with intravenous acyclovir (250 mg three times daily), or oral acyclovir (800 mg five times daily). Patients were followed up for 6–12 months with repeated clinical examinations, nerve excitability testing, and audiograms in patients who complained of tinnitus or hearing loss. Complete recovery was seen in 21 (75%) patients treated within the first 3 days ($p < 0.05$), 14 (48%) patients treated at 4–7 days, and seven (30%) when treatment was not started until after 7 days. Further, 26 (50%) patients who were not treated in the first 3 days progressed to a complete loss of response to facial nerve stimulation. No statistically significant differences were noted among patients treated with intravenous or oral acyclovir. Of 12 patients with mild to moderate hearing loss who were followed up with serial audiograms, six recovered completely, three had partial recovery, and three remained stable. Audiological outcome did not differ significantly among the treatment groups.

Despite the lack of randomised, controlled prospective treatment trials for Ramsay Hunt syndrome, data from the collective case reports and retrospective reviews suggest that both prednisone and acyclovir, if given early, improve the overall prognosis. Microvascular decompression and rhizotomy are therapeutic options but have usually been reserved for resistant neuralgic syndromes.²⁷

Virology

Primary VZV infection usually produces chickenpox after which the virus becomes latent in neurons of cranial nerve ganglia (including the geniculate ganglia) and dorsal root ganglia along the entire neuraxis. Latent VZV DNA is extrachromosomal (non-integrated), probably in a circular or concatameric (end to end) configuration. At least five VZV genes, corresponding to open reading frames 4, 21, 29, 62, and 63, are transcribed, and one VZV protein corresponding to gene 63 is expressed in latently infected ganglia. The abundance of latent VZV varies from 37 to slightly more than 3500 copies/100 ng ganglionic DNA.²⁸ Although virus cannot be cultured from ganglia, VZV has been detected in ganglia by Southern blot analysis, by PCR, and by in situ hybridisation with or without PCR (reviewed in Gilden *et al*²⁹).

In a landmark study that attempted to identify the cause of Bell's Palsy, Murakami *et al*³⁰ analyzed endoneurial fluid and posterior auricular muscle obtained from numerous patients with peripheral facial paralysis. Among them were nine patients with Ramsay Hunt syndrome studied 12 to 87 days after onset of facial palsy. Use of VZV gene 29 specific primers in PCR disclosed VZV DNA, but not HSV or Epstein-Barr virus DNA, in eight of the nine patients. Endoneurial fluid and muscle were positive in seven and six patients, respectively.

In a prospective study,²⁵ a bedside method for rapid identification of VZV reactivation was evaluated in 51 patients with unilateral facial palsy and 14 asymptomatic controls. Of the 51 symptomatic patients, 12 (24%) presented with vesicles in the ear and seven (14%) developed vesicles within 1 week. A search for VZV DNA in blood mononuclear cells, in tears, and in skin ear exudates obtained by scraping the geniculate zone of the ear with a needle and absorbed with a sterile Schirmer's strip was undertaken in the total 65 patients. Acute and convalescent serum VZV antibody were also determined in all 65 patients. Polymerase chain reaction detected VZV DNA from the ear scrapings in all 12 patients with Ramsay Hunt syndrome and in five (72%) of the seven patients with delayed vesicle formation. Polymerase chain reaction from ear skin was uniformly negative in 26 patients with Bell's palsy and in 14 controls. Not surprisingly, VZV PCR was more sensitive using ear material than with tears or blood mononuclear cells.

Ramsay Hunt syndrome zoster sine herpette

Zoster sine herpette is normally defined as localised radicular pain with virological evidence of VZV infection, a condition originally verified by the presence of VZV DNA in the CSF of two patients with chronic radicular pain in the absence of rash that responded clinically and virologically to acyclovir treatment.³¹ The counterpart among patients with Ramsay Hunt syndrome is characterised by peripheral facial paralysis without ear or mouth rash, and the presence of either a fourfold rise in antibody to VZV or the detection of VZV DNA in skin, blood mononuclear cells, or middle ear fluid. In the retrospective study by Hato *et al.*,¹⁹ of 1705 patients with ipsilateral facial palsy without vesicles, the data imply that 42 (2.4%) had zoster sine herpette. In a study of 32 patients with isolated peripheral facial palsy, Murakami *et al.*²⁵ identified zoster sine herpette in six (19%) of the patients based on a fourfold rise in serum antibody titre to VZV. Four of these six patients had a positive PCR for VZV when the geniculate zone skin scraping was tested. Further, Morgan *et al.*³² found that 9.3% of patients with Bell's palsy seroconverted to VZV, and Terada *et al.*³³ found that blood mononuclear cells from four of 17 patients with Bell's palsy were positive for VZV DNA by PCR. Thus, a small proportion of patients with "Bell's palsy" have zoster sine herpette. Finally, in a study to determine the effect of antiviral agents on recovery from facial palsy in patients with zoster sine herpette (confirmed by a positive PCR test on saliva), all 13 patients who received acyclovir-prednisone treatment within 7 days of onset recovered completely.³⁴

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