Reflex Sympathetic Dystrophy Diagnosis

Number: 0147

Policy

*Please see amendment for Pennsylvania Medicaid at the end of this CPB.

Aetna considers the following tests experimental and investigational for the diagnosis of reflex sympathetic dystrophy (RSD), also known as complex regional pain syndrome (CRPS), because there is insufficient scientific evidence to support the effectiveness of these approaches.

- Antioxidant profile (e.g., enzymatic activities consisting of serum glutathion peroxidase (GPX), glutathione S-transferase (GST), and superoxide dismutase (SOD))
- Computed tomography
- Determination of highly unsaturated fatty acids and trans fatty acid status
- Intravenous phentolamine (Regitine)
- Laser Doppler flowmetry
- Magnetic resonance imaging
- Measurement of serum anti-neuronal antibodies/autoantibodies
- Musculoskeletal ultrasonography
- Plain film radiography

Policy History

Last Review 01/26/2017
Effective: 04/10/1997
Next Review: 01/25/2018

Review History

Definitions

Additional Information

Clinical Policy Bulletin Notes
Thermography

For autonomic testing for reflex sympathetic dystrophy (e.g., quantitative sudomotor axon reflex test (QSART), resting sweat output (RSO), and resting skin temperature (RST)), see CPB 0485 - Autonomic Testing/Sudomotor Tests (../400_499/0485.html).

See also CPB 0447 - Complex Regional Pain Syndrome (CRPS) / Reflex Sympathetic Dystrophy (RSD) (../400_499/0447.html).

Background

Reflex sympathetic dystrophy (RSD), one of the major causes of disability, is a general descriptive term for a set of symptoms and signs without any implication of pathophysiology or etiology. It is characterized by diffused burning pain, allodynia (pain on light touch), and autonomic dysfunction with sweating, temperature change, and redness or cyanotic mottling. Reflex sympathetic dystrophy occurs in adults and children, and usually develops in a limb after a relatively minor injury. It can be temporary, permanent, episodic, or migratory, and may occur in one area or more. In an attempt to clarify the subject, the International Association for the Study of Pain listed 4 diagnostic criteria for RSD. All 4 of the following criteria must be met for the diagnosis of RSD to be established: (i) the presence of an initiating noxious event, or a cause of immobilization; (ii) continuing pain, allodynia, or hyperalgesia with which the pain is disproportionate to the initiating event; (iii) confirmation at some time of edema, changes in blood flow, or abnormal sudomotor activity in the area of the pain such as changes in skin temperature, skin color, or sweating; and (iv) the absence of other conditions that would account for the pain and dysfunction.

Despite intensive clinical investigations in the past 5 decades, the diagnostic and therapeutic approaches for RSD remain controversial. In this regard, some researchers have advocated the use of systemic sympathetic blockade with phentolamine as a diagnostic test for this condition. Phentolamine mesylate
(Regitine) is a short-acting alpha-adrenergic blocking agent that acts at both alpha-1 and alpha-2 adrenergic receptor sites. As a test to diagnose RSD, patients are usually given an intravenous infusion of 25 to 75 mg phentolamine for 20 mins. Pain relief following phentolamine administration is then taken as a confirmation of RSD. However, the value of the phentolamine test in diagnosing RSD has been challenged by many investigators.

In a recent review on complex regional pain syndrome (CRPS) (Wasner et al, 2003), the phentolamine test is not listed as a diagnostic test for this syndrome. Furthermore, Atkins (2003) stated that CRPS is a clinical diagnosis and there is no single diagnostic test.

Laser Doppler flowmetry has been used evaluate blood flow in patients with CRPS because it has been suggested that CRPS may be associated with vascular disturbances (e.g., a loss of cutaneous sympathetic vasoconstrictor activity). Vital capillaroscopy is a technique using Doppler flowmetry to gauge anatomical vascular mapping and capillary blood flow in the affected extremity.

Wasner et al (1999) examined cutaneous sympathetic vasoconstrictor innervation by laser Doppler flowmetry in 2 patients with CRPS and 1 normal control subject. This study was designed to investigate the pathophysiology of CRPS. However, the study did not demonstrate how well laser Doppler flowmetry would perform in establishing or excluding the diagnosis of CRPS. Nor did this study show how management is influenced and clinical outcomes are improved in patients with symptoms of CRPS. Baron and Maier (1996) assessed the role of the sympathetic nervous system in patients with RSD of the hand using laser Doppler flowmetry. Cutaneous blood flow, skin resistance and skin temperature were measured at the affected and contralateral hands. These investigators found that (i) side differences in skin temperature and blood flow are no static descriptors in RSD. They are dynamic values depending critically on environmental temperature. Thus, they
have to be interpreted with care when defining reliable
diagnostic criteria, (ii) vascular disturbances in RSD are not due
to constant over-activity of sympathetic vasoconstrictor
neurons. Changes in vascular sensitivity to cold temperature
and circulating catecholamines may be responsible for vascular
abnormalities. Alternatively, RSD may be associated with an
abnormal (side different) reflex pattern of sympathetic
vasoconstrictor neurons due to thermoregulatory and
emotional stimuli generated in the central nervous system.

function in patients with CRPS compared with healthy controls,
as measured by iontophoresis of vasoactive chemicals and laser
Doppler imaging. These researchers found that CRPS was not
associated with impairment of microvascular endothelial
function.

Laser Doppler flowmetry has been used as a research tool in
quantifying blood perfusion in persons with microvascular
disease due to diabetes and other vascular conditions.
However, there is insufficient evidence of the clinical value of
this study in improving the management of patients with
diabetes such that clinical outcomes are improved.

Thermography involves the use of an infrared thermometer to
measure several symmetrical points on the affected and
contralateral extremity, making comparisons between the 2
extremities. In general, a difference of 0.5 degrees C is
considered mildly asymmetrical, and a difference of 1.0 degrees
C is considered significant. Although asymmetries in
temperature have been found in persons with CRPS, it has been
reported that a lack of asymmetry does not exclude the
diagnosis (Rho et al, 2002).

Niehof et al (2007) found that, although observer assessment
of thermographic images may distinguish between CRPS1
patients and healthy controls, the reliability and repeatability of
this assessment was "rather low." This study aimed at
evaluating the sensitivity, specificity, reliability and repeatability
of observer assessment of thermographic images taken from CRPS 1. A computer program was developed to let observers rate the difference between randomly presented thermographic images of pairs of hands of individuals. The investigators reported that the sensitivity was 71 % and the specificity 85 %. The repeatability was 0.5267 and the reliability was 0.4967.

Gradl and colleagues (2003) reported that thermography had poor sensitivity and specificity for CRPS1. The investigators studied the value of clinical evaluation, radiography and thermography in the early diagnosis of traumatic CRPS1. A total of 158 patients with distal radial fractures were followed-up for 16 weeks after trauma. Apart from a detailed clinical examination 8 and 16 weeks after trauma, thermography and bilateral radiographs of both hands were carried out. At the end of the observation period 18 patients (11 %) were clinically identified as CRPS1. Sixteen weeks after trauma easy differentiation between normal fracture patients and CRPS1 patients was possible. The investigators reported that, 8 weeks after distal radial fracture, clinical evaluation showed a sensitivity of 78 % and a specificity of 94 %. On the other hand, thermography (58 %) and bilateral radiography (33 %) revealed poor sensitivities. The specificity was high for radiography (91 %) and again poor for thermography (66 %).

Schürmann et al (2007) compared several imaging studies in diagnosing post-traumatic CRPS. A total of 158 consecutive patients with distal radial fracture were followed-up for 16 weeks after trauma. A detailed clinical examination was carried out 2, 8, and 16 weeks after trauma in conjunction with bilateral thermography, plain radiographs of the hand skeleton, 3-phase bone scans (TPBSs), and contrast-enhanced magnetic resonance imaging (MRI). All imaging procedures were assessed blinded. At the end of the observation period 18 patients (11 %) were clinically identified as having CRPS I and 13 patients (8 %) revealed an incomplete clinical picture which were defined as CRPS borderline cases. The sensitivity of all diagnostic procedures used was poor and decreased between
the 1st and the last examinations (thermography: 45 % to 29 %; TPBS: 19 % to 14 %; MRI: 43 % to 13 %; bilateral radiographs: 36 %). In contrast a high specificity was observed in the TPBS and MRI at the 8th and 16th-week examinations (TPBS: 96 %, 100 %; MRI: 78 %, 98 %) and for bilateral radiographs 8 weeks after trauma (94 %). Thermography presented a fair specificity that improved from the 2nd to the 16th week (50 % to 89 %). The authors concluded that the poor sensitivity of all tested procedures combined with a reasonable specificity produced a low positive predictive value (17 % to 60 %) and a moderate negative predictive value (79 % to 86 %). These results suggested that those procedures can not be used as screening tests. Imaging methods are not able to reliably differentiate between normal post-traumatic changes and changes due to CRPS I. Clinical findings remain the gold standard for the diagnosis of CRPS I and the procedures described above may serve as additional tools to establish the diagnosis in doubtful cases.

Niehof et al (2008) evaluated the validity of skin surface temperature recordings, based on various calculation methods applied to the thermographic data, to diagnose acute CRPS1 fracture patients. Thermographic recordings of the palmar/plantar side and dorsal side of both hands or feet were made on CRPS1 patients and in control fracture patients with/without and without complaints similar to CRPS1 (total in the 3 subgroups = 120) just after removal of plaster. Various calculation methods applied to the thermographic data were compared using receiver operating characteristics analysis to obtain indicators of diagnostic value. There were no significant differences in demographic data and characteristics among the 3 subgroups. The most pronounced differences among the subgroups were vasomotor signs in the CRPS1 patients. The involved side in CRPS1 patients was often warmer compared with the non-involved extremity. The difference in temperature between the involved site and the non-involved extremity in CRPS1 patients significantly differed from the difference in temperature between the contralateral extremities of the 2 control groups. The largest temperature difference between
extremities was found in CRPS1 patients. The difference in temperature recordings comparing the palmar/plantar and dorsal recording was not significant in any group. The sensitivity and specificity varied considerably between the various calculation methods used to calculate temperature difference between extremities. The highest level of sensitivity was 71 % and the highest specificity was 64 %; the highest positive predictive value reached a value of 35 % and the highest negative predictive 84 %, with a moderate 0.60 greater than or equal to area under the curve less than or equal to 1.65. The authors concluded that the validity of skin surface temperature recordings under resting conditions to discriminate between acute CRPS1 fracture patients and control fracture patients with/without complaints is limited. Furthermore, in a review on CRPS, Albazaz and colleagues (2008) stated that no specific diagnostic test is available. Thus, diagnosis is based mainly on history, clinical examination, and supportive laboratory findings.

Krumova et al (2008) evaluated long-term skin temperature changes under everyday circumstances in 22 patients with CRPS, 18 patients with limb pain of other origin and 23 healthy controls. The asymmetries in skin temperature and oscillation number (Q Oscill), the percentage of assessed time with a-synchron temperature changes on both body sides and the determination coefficient of the individual regression (r2 id) were compared between the groups. Patients with CRPS differed significantly from healthy controls in nearly all parameters. Minor differences between both patient groups were found regarding the percentage of assessed time with side difference greater than 2 degrees C (DeltaT2). However, both patient groups differed significantly in parameters characterizing the skin temperature dynamics. A sum score (2 *Q Oscill +r2 id +DeltaT2) allowed diagnosing CRPS with a specificity of 67 % versus patients with other painful diseases and 79 % versus healthy controls (sensitivity: 73 %, and 94 %, respectively) and reflected the severity of the dysfunction in CRPS better than the mean skin temperature side differences alone.
Cohen and Raja (2009) stated that measurement of skin temperature dynamics differentiated between CRPS and arm pain secondary to other etiologies with a sensitivity of 73% and a specificity of 67%. Although the technique Krumova and colleagues (2008) used is more practical than those previously described, it is still too onerous for patients and physicians to routinely employ. These researchers anticipate that improved identification of pain mechanisms will translate into better treatment outcomes, but this hypothesis remains to be tested.

In a pilot study, Ramsden and colleagues (2010) compared the omega-6 (n-6) and omega-3 (n-3) highly unsaturated fatty acids (HUFA), and trans fatty acid (trans FA) status of CRPS patients to pain-free controls. A total of 20 patients that met the Budapest research diagnostic criteria for CRPS and 15 pain-free control subjects were included in this study. Fasting plasma fatty acids were collected from all participants. In CRPS patients, pain was assessed using the McGill Pain Questionnaire-Short Form. In addition, results from the perceived disability (Pain Disability Index), pain-related anxiety (Pain Anxiety Symptom Scale Short Form), depression (Center for Epidemiologic Studies Depression Scale Short Form), and quality of life (Short Form-36 [SF-36]) were evaluated. Compared with controls, CRPS patients reported elevated concentrations of n-6 HUFA and trans FA. No differences in n-3 HUFA concentrations were observed. Plasma concentrations of the n-6 HUFA docosatetraenoic acid were inversely correlated with the "vitality" section of the SF-36. Trans FA concentrations positively correlated with pain-related disability and anxiety. The authors concluded that these preliminary data suggest that elevated n-6 HUFA and trans FA may play a role in CRPS pathogenesis. They stated that these findings should be replicated, and more research is needed to explore the clinical significance of low n-6 and trans FA diets with or without concurrent n-3 HUFA supplementation, for the management of CRPS.

Ringer and colleagues (2012) stated that to date, no attempt has been made to investigate the agreement between
qualitative bone scintigraphy (BS) and the presence of CRPS 1 and the agreement between a negative BS in the absence of CRPS 1. These investigators summarized the existing evidence quantifying the concordance of qualitative BS in the presence or absence of clinical CRPS 1. They searched Medline, Embase, Dare and the Cochrane Library and screened bibliographies of all included studies; and selected diagnostic studies investigating the association between qualitative BS results and the clinical diagnosis of CRPS 1. The minimum requirement for inclusion was enough information to fill the 2-by-2 tables. A total of 12 studies met inclusion criteria and were included in the meta-analysis. The pooled mean sensitivity of twelve 2-by-2 tables was 0.87 (95% CI: 0.68 to 0.97) and specificity was 0.69 (95% CI: 0.47 to 0.85). The pooled mean sensitivity for the subgroup with clearly defined diagnostic criteria (seven 2-by-2 tables) was 0.80 (95% CI: 0.44 to 0.95) and specificity was 0.73 (95% CI: 0.40 to 0.91). The authors concluded that based on the findings of this study, clinicians must be advised that a positive BS is not necessarily concordant with presence or absence of CRPS 1. Moreover, they noted that given the moderate level of concordance between a positive BS in the absence of clinical CRPS 1, discordant results potentially impede the diagnosis of CRPS 1.

**Antioxidant Profile**

Baykal et al (2014) stated that the mechanism and pathogenesis of CRPS still remains unknown. Some findings indicating oxidative stress have been reported. These researchers examined the role of oxidative stress in patients with CRPS. A total of 20 patients (13 women and 7 men) with CRPS and 20 age- and sex-matched healthy controls were enrolled in this study. Complex regional pain syndrome was diagnosed according to the modified International Association for the Study of Pain (IASP) criteria. These investigators evaluated demographic, clinical and laboratory characteristics of the patients. Antioxidant enzymatic activities consisting of serum glutathion peroxidase (GPX), glutathione S-transferase (GST) and superoxide dismutase (SOD) activities were measured using
appropriate methods and compared with healthy controls. The mean age of the patients was 39.5 years and the mean duration of symptoms was 5.5 months. Complex regional pain syndrome developed after a traumatic event in 90% of patients. In 10% of patients there were no traumatic events; GPX, GST and SOD levels were significantly higher in patients with CRPS than healthy controls (p = 0.036, p = 0.016, and p = 0.012, respectively). The authors concluded that their findings suggested a possible role of oxidative stress in the pathogenesis of CRPS. The role of antioxidant profile in the diagnosis of CRPS has yet to be established.

**Musculoskeletal Ultrasonography**

Vas and Pai (2016) noted that musculoskeletal ultrasonography (MSK-US) can identify myofascial structural lesions. In a retrospective study, these investigators described the observational findings of US data of muscles from limbs affected with neuropathic pain in 7 patients and compared them with muscles affected with CRPS-1 in 7 patients. These researchers highlighted findings that distinguish between the 2 conditions. Musculoskeletal US of muscles in CRPS was characterized by a variable or/and global intramuscular structural disruption with loss of muscle bulk. Adjacent muscles coalesced with one another to present an uniform hyper-echogenic mass of tissue. Muscle edema was found in some patients. In comparison, MSK-US in muscles affected by neuropathic pain exhibited structural normalcy, but also showed considerable reduction in muscle bulk. The authors concluded that MSK-US showed promise as a diagnostic modality to distinguish between these 2 conditions that currently have only clinical diagnostic criteria to aid diagnosis.

**Other Experimental and Investigational Procedures**

An UpToDate review on “Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis” (Abdi, 2015) states that “Plain radiographs often demonstrate patchy osteoporosis but the sensitivity of this finding for CRPS is
very low .... Autonomic tests that have been used to evaluate patients with suspected CRPS include the resting sweat output (RSO), the resting skin temperature (RST), and the quantitative sudomotor axon reflex test (QSART). Some experts advocate serial measurement of skin temperatures, based upon evidence from one small study that a 2°C difference for the affected versus unaffected side was supportive of the diagnosis of CRPS. However, this method requires monitoring for five to eight hours with recording of skin temperature at one minute intervals using temperature sensors applied to the index fingers. Thus, it is not practical as a routine clinical test .... There is no clear role for MRI or CT scanning in the evaluation of suspected CRPS, nor is there any role for the response to sympatholysis to confirm the diagnosis of CRPS”.

**Anti-Neuronal antibodies/Autoantibodies:**

Dirckx et al (2015) noted that autoimmunity has been suggested as one of the pathophysiologic mechanisms that may underlie CRPS. Screening for anti-nuclear antibodies (ANA) is one of the diagnostic tests, which is usually performed if a person is suspected to have a systemic autoimmune disease. Anti-neuronal antibodies are autoantibodies directed against antigens in the central and/or peripheral nervous system. These researchers compared the prevalence of these antibodies in CRPS patients with the normal values of those antibodies in the healthy population; 27 (33 %) of the 82 CRPS patients of whom serum was available showed a positive ANA test. This prevalence was significantly higher than in the general population; 6 patients (7.3 %) showed a positive result for typical anti-neuronal antibodies. This proportion, however, did not deviate from that in the general population. The authors concluded that these findings suggested that autoantibodies may be associated with the pathophysiology of CRPS, at least in a subset of patients. Moreover, they stated that further research is needed into defining this subset and into the role of autoantibodies in the pathogenesis of CRPS.

**Response to Systemic Chemical Sympatholysis:**
An UpToDate review on “Complex regional pain syndrome in adults: Pathogenesis, clinical manifestations, and diagnosis” (Abdi, 2016) states that “Other tests and interventions -- There is no clear role for MRI or CT scanning in the evaluation of suspected CRPS, nor is there any role for the response to sympatholysis to confirm the diagnosis of CRPS. MRI may be useful for excluding some conditions in the differential diagnosis; but is not useful for confirming the diagnosis of CRPS. Limited data suggest that CT scanning can show focal areas of osteoporosis in a Swiss cheese-like appearance. However, weighing the cost, radiation dose, and limited experience with use of CT scanning in evaluation of patients with CRPS, we suggest not using CT as a diagnostic test.

Historically, abrupt transient relief from pain and dysesthesia with a systemic chemical sympatholysis (i.e., intravenous regional anesthesia, also termed a Bier block, and/or a regional sympathetic nerve block such as stellate ganglion or lumbar sympathetic nerve blocks) was considered necessary to make the diagnosis of CRPS. However, as the role of the sympathetic nervous system in the pathogenesis of CRPS remains unclear and contradictory, it is now widely accepted that a positive response to sympathetic block is not diagnostic of CRPS. Rather, such a response is an important indicator of sympathetically maintained pain”.

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<th>CPT Codes / HCPCS Codes / ICD-10 Codes</th>
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<td>Information in the [brackets] below has been added for clarification purposes. Codes requiring a 7th character are represented by &quot;+&quot;:</td>
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<td>CPT codes not covered for indications listed in the CPB:</td>
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<tr>
<td>0249T - 0250T</td>
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<td>72170, 72190</td>
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Complete bilateral non-invasive physiologic studies of upper or lower extremity arteries, 3 or more levels (eg, for lower extremity: ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental blood pressure measurements with bidirectional Doppler waveform recording and analysis at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental volume plethysmography at 3 or more levels, or ankle/brachial indices at distal posterior tibial and anterior tibial/dorsalis pedis arteries plus segmental transcutaneous oxygen tension measurements at 3 or more level(s), or single level study with provocative functional maneuvers (eg, measurements with postural provocative tests or measurements with reactive hyperemial)

### HCPCS codes not covered for indications listed in the CPB:

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<td>J2760</td>
<td>Injection, phentolamine mesylate, [Regitine], up to 5 mg</td>
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### ICD-10 codes not covered for indications listed in the CPB (not all-inclusive):  

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<th>Code</th>
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<td>G90.50 - G90.9</td>
<td>Complex regional pain syndrome I (CRPS I)</td>
</tr>
</tbody>
</table>

The above policy is based on the following references:

1. Fine PG, Roberts WJ, Gillette RG, Child TR. Slowly developing placebo responses confound tests of intravenous phentolamine to determine mechanisms

2. Verdugo RJ, Ochoa JL. 'Sympathetically maintained pain.'


34. Dirckx M, Schreurs MW, de Mos M, et al. The prevalence
of autoantibodies in complex regional pain syndrome type I. Mediators Inflamm. 2015;2015:718201.

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Amendment to
Aetna Clinical Policy Bulletin Number: CPB 0147
Reflex Sympathetic Dystrophy Diagnosis

There are no amendments for Medicaid.