Intracranial Aneurysm and Hemorrhagic Stroke in Glucocorticoid-remediable Aldosteronism

W. Reid Litchfield, Bruce F. Anderson, Rueudger J. Weiss, Richard P. Lifton, Robert G. Dluhy

Abstract—There are anecdotal reports of early cerebrovascular complications occurring in patients with glucocorticoid-remediable aldosteronism (GRA). The issue has never been systematically evaluated. In this study, we retrospectively reviewed the International Registry for GRA to see if there was an association between cerebrovascular complications and GRA. We searched the records of 376 patients from 27 genetically proven GRA pedigrees for premature death or cerebrovascular complications. Each case was subsequently verified through the referring physician, or autopsy reports. The number of complications occurring in patients with proven GRA were compared to GRA negative subjects from the same pedigrees. There were 18 cerebrovascular events in 15 patients with proven GRA (n = 167) and none in the GRA negative group (n = 194, P < 0.001). There were an additional 15 events in 15 subjects that were suspected of having GRA based on clinical history. Seventy percent of events were hemorrhagic strokes, the overall case fatality rate was 61%. The mean (± SD) age at the time of the initial event was 31 ± 11.3 years. In total, 48% of all GRA pedigrees and 18% of all GRA patients had cerebrovascular complications, which is similar to the frequency of aneurysm in adult polycystic kidney disease. GRA is associated with high morbidity and mortality from early onset of hemorrhagic stroke and ruptured intracranial aneurysms. Screening for intracranial aneurysm with magnetic resonance angiography is advised for patients with genetically proven GRA. (Hypertension. 1998;31[part 2]:445-450.)

Key Words: glucocorticoid-remediable aldosteronism • hyperaldosteronism • cerebrovascular disease • intracranial aneurysm • hemorrhagic stroke

Glucocorticoid-remediable aldosteronism (GRA) is a rare form of primary aldosteronism that results from a characteristic gene duplication. In this syndrome, which has an autosomal dominant inheritance pattern, aldosterone is produced and secreted under the sole control of adrenocorticotropic hormone (ACTH). Clinically, GRA is characterized by moderate to severe hypertension with onset very early in life. Plasma renin activity is generally suppressed. Our evaluation of several GRA pedigrees diagnosed at our center, also revealed a prominent history of hemorrhagic stroke at an early age. In order to investigate a possible relationship between GRA and cerebrovascular complications, we evaluated 27 GRA pedigrees from the International Registry for GRA for a history of cerebrovascular disease or premature death.

Methods

Subject Classification

The International Registry for GRA was used to search for a history of sudden or premature death and cerebrovascular death. Because many of the events were documented in deceased individuals, not every patient was available for testing to confirm the diagnosis of GRA. Subjects were therefore classified as having proven GRA if they tested positive for GRA through genetic screening, had characteristic dexamethasone-suppression testing, or were known to be obligate carriers of the GRA gene. Subjects were classified as suspected GRA if they had a clinical history consistent with GRA (such as early onset of hypertension) and were a member of a known GRA pedigree.

Vascular Event Documentation

Written consent for the release of medical records and/or death certificate was obtained from the subject or, if deceased, from the next-of-kin. Documentation of the type of event was obtained through verification of the event by the attending physician or by reviewing of medical records, death certificate, autopsy report, or radiographic report (magnetic resonance imaging [MRI], CT scanning, arteriography). If none of the above were possible, witnesses and/or surviving family members were interviewed to establish the nature of the event. In these cases, the family’s recollection of the medical cause of death (as explained to them by the physician) was compared to the clinical history (sudden headache, loss of consciousness, neurological symptoms, etc). Events that could not be corroborated by these criteria were excluded from the study.

The event was labeled as a vascular dissection or vascular aneurysm only if it was documented by radiographic imaging, autopsy/death certificate, physician verification or if the event required surgical intervention. Cerebral or subarachnoid hemorrhage was used to describe events only if there was a proven intraparenchymal or subarachnoid hemorrhage without evidence of aneurysm. Early stroke described cerebrovascular events that were not hemorrhagic in nature that occurred prior to age 55. Sudden death was used to describe events in which there was no obvious cause of death.
Events in GRA negative subjects from known GRA pedigrees were used as a comparison group for patients with proven GRA (suspected GRA patients were not included in this analysis to minimize ascertainment bias) GRA patients that suffered complications were also compared to GRA patients without history of complications. The number of events per patient year in GRA patients were also compared to the incidence rates of these events in the Framingham study. Data are presented as mean ± standard deviation (SD) unless otherwise noted. Statistical analysis was performed using the Student’s t test and χ2 test, with an alpha value of 0.05.

### Results

Sufficient historical information was available in 376 members of 27 GRA pedigrees. In total, 151 individuals were positive for the gene duplication that causes GRA on genetic testing. In addition, 2 subjects had a positive dexamethasone suppression test, and 14 subjects were obligate carriers of the GRA gene. Another 15 individuals, all of whom were at risk of inheriting the GRA gene, were suspected of being GRA positive on the basis of their clinical history. These subjects were compared to 194 individuals from GRA pedigrees that underwent genetic screening and were negative for the GRA gene (Table 1). Patients were similar with respect to age, body mass index, gender, systolic blood pressure and plasma aldosterone. There were more subjects with a history of hypertension in the GRA positive group than the GRA negative group (72.7% versus 26.1%, P < 0.001) and significant differences with respect to age (34.1 ± 18.8 versus 44.9 ± 21.9 years, P < 0.001), diastolic blood pressure (85.6 ± 17.6 versus 77.8 ± 12.5 mm Hg, P < 0.001), plasma renin activity (0.21 ± 0.33 versus 0.76 ± 0.50 ng/L, P < 0.001), serum potassium (4.06 ± 0.54 versus 4.32 ± 0.45 mmol/L, P < 0.001), and age at which hypertension was documented (17.8 ± 10.4 versus 39.4 ± 14.2 years, P < 0.0001) in GRA positive and negative subjects, respectively. In total, vascular and cerebrovascular events were identified in 13 GRA pedigrees (48%).

### Proven Cases of GRA

We found a total of 18 events in 15 proven GRA patients from 7 GRA pedigrees. The diagnosis of GRA was confirmed through genetic testing in 9 individuals and through administration of a dexamethasone suppression test in 2 individuals. The remaining 4 patients were obligate carriers based on the genotype of other family members that underwent genetic testing.

Events (Table 2) consisted of early stroke (n = 3), ruptured vascular aneurysm (n = 6), intracranial aneurysms that required surgical clipping (n = 2), cerebral hemorrhage without evidence of aneurysm (n = 2), sudden death (n = 1), vascular dissection (n = 1), and subarachnoid hemorrhage without evidence of aneurysm (n = 3). Three patients had two separate events consisting of recurrent early stroke, recurrent intracranial aneurysm after prior aneurysmal rupture, and vascular dissection of the carotid associated with an asymptomatic intracranial aneurysm that required neurosurgical clipping. One additional patient, who died of a ruptured middle cerebral artery aneurysm, was also found to have a second unruptured basilar artery aneurysm at autopsy.

The events were documented by autopsy (n = 3), death certificates (n = 2), radiographic imaging (n = 11), and physician verification (n = 2). Gender distribution was similar (9 male and 6 female), and the mean age of the patient at the time of their initial event was 50.5 ± 11.0 years. The case fatality rate was 39% (7 fatalities in 18 events).

Proven GRA positive patients with and without events were compared to GRA negative subjects (Table 3). All patients with proven GRA that had a cerebrovascular event had a history of hypertension. Blood pressure measurements were available for 8/15 of these patients. The mean systolic and diastolic blood pressures were, respectively, 147.8 ± 15.4 and 100.8 ± 13.6 mm Hg. This was higher than either systolic or diastolic blood pressure in GRA negative (respectively, 133.3 ± 16.0 and 80.5 ± 10.5 mm Hg, P < 0.01) or GRA positive without events (respectively, 134.4 ± 22.5 and 84.4 ± 17.2 mm Hg, P < 0.05). Hypertension was diagnosed at 12.3 ± 6.4 years in GRA patients with events, which was significantly younger than both GRA negative patients (40.2 ± 15.2 years, P < 0.0001) and GRA positive patients without events (18.4 ± 10.3 years, P < 0.01). Similarly, GRA patients with events differed from both GRA negative and GRA positive patients without events with respect to plasma renin activity, and from GRA-negative patients with respect to plasma aldosterone and serum potassium (Table 3).

A comparison of the number of vascular complications and sudden deaths that occurred in subjects proven to have GRA was compared to 136 members of the same pedigrees that tested negative for the GRA gene. There were no events in the
TABLE 2. Cerebrovascular Events in Proven GRA Patients

<table>
<thead>
<tr>
<th>Event</th>
<th>Pedigree</th>
<th>DX of GRA</th>
<th>Sex</th>
<th>BP (mm Hg)</th>
<th>Age at Diagnosis of HTN (yr)</th>
<th>Age at Event (yr)</th>
<th>Description of Event</th>
<th>Event</th>
<th>Documentation</th>
<th>Location of Lesion</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>GS</td>
<td>F</td>
<td>NA</td>
<td>8</td>
<td>28</td>
<td>SAH</td>
<td>SAH</td>
<td>Angiogram</td>
<td>NA</td>
<td>Survived</td>
</tr>
<tr>
<td>2</td>
<td>155</td>
<td>GS</td>
<td>M</td>
<td>NA</td>
<td>21</td>
<td>41</td>
<td>SAH</td>
<td>ES</td>
<td>MD verification</td>
<td>NA</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>2061</td>
<td>Obligate</td>
<td>M</td>
<td>174/108</td>
<td>5</td>
<td>13</td>
<td>Ruptured aneurysm</td>
<td>Autopsy</td>
<td>Throat aorta</td>
<td>Thoracic aorta</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>2064</td>
<td>DST</td>
<td>M</td>
<td>166/110</td>
<td>5</td>
<td>35</td>
<td>SAH</td>
<td>SD</td>
<td>Autopsy</td>
<td>NA</td>
<td>Died</td>
</tr>
<tr>
<td>5</td>
<td>2064</td>
<td>GS</td>
<td>M</td>
<td>160/110</td>
<td>5</td>
<td>35</td>
<td>SAH</td>
<td>ES</td>
<td>CT Scan</td>
<td>Right temporal</td>
<td>Survived</td>
</tr>
<tr>
<td>6</td>
<td>2064</td>
<td>GS</td>
<td>F</td>
<td>160/120</td>
<td>14</td>
<td>47</td>
<td>Ruptured aneurysm</td>
<td>ES</td>
<td>CT Scan</td>
<td>Left temporal</td>
<td>Survived</td>
</tr>
<tr>
<td>7</td>
<td>2139</td>
<td>Obligate</td>
<td>F</td>
<td>NA</td>
<td>54</td>
<td>54</td>
<td>Ruptured aneurysm</td>
<td>ES</td>
<td>NA</td>
<td>NA</td>
<td>Died</td>
</tr>
<tr>
<td>8</td>
<td>2139</td>
<td>Obligate</td>
<td>F</td>
<td>140/110</td>
<td>21</td>
<td>21</td>
<td>Ruptured aneurysm</td>
<td>Angiogram</td>
<td>Right internal</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2139</td>
<td>GS</td>
<td>F</td>
<td>128/80</td>
<td>50</td>
<td>50</td>
<td>Clipped aneurysm</td>
<td>CT Scan</td>
<td>Unruptured aneurysm</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>11</td>
<td>GS</td>
<td>F</td>
<td>136/100</td>
<td>11</td>
<td>27</td>
<td>Clipped aneurysm</td>
<td>MRI</td>
<td>Unruptured right middle cerebral</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>2139</td>
<td>GS</td>
<td>F</td>
<td>NA</td>
<td>36</td>
<td>36</td>
<td>Ruptured aneurysm</td>
<td>Autopsy</td>
<td>Right middle cerebral</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>2815</td>
<td>GS</td>
<td>M</td>
<td>144/88</td>
<td>4</td>
<td>18</td>
<td>CH</td>
<td>Angiogram</td>
<td>NAF</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>2815</td>
<td>DST</td>
<td>M</td>
<td>140/90</td>
<td>7</td>
<td>28</td>
<td>Ruptured aneurysm</td>
<td>CT Scan</td>
<td>Anterior communicating</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>2815</td>
<td>GS</td>
<td>M</td>
<td>23</td>
<td>48</td>
<td>48</td>
<td>CH</td>
<td>MD verification</td>
<td>NA</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>2822</td>
<td>Obligate</td>
<td>M</td>
<td>14</td>
<td>30</td>
<td>30</td>
<td>Ruptured aneurysm</td>
<td>CT Scan</td>
<td>Right middle cerebral</td>
<td>Survived</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>2867</td>
<td>GS</td>
<td>M</td>
<td>12</td>
<td>13</td>
<td>13</td>
<td>SAH</td>
<td>MRI</td>
<td>NAF</td>
<td>Survived</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: F, female; M, male; GS, genetic screening; DST, dexamethasone suppression test; obligate, obligate carrier of GRA; SAH, subarachnoid hemorrhage; ES, early stroke; SD, sudden death; CH, cerebral hemorrhage; DC, death certificate; HTN, hypertension; BP, blood pressure levels on therapy prior to event; NA, not available; NAF, no aneurysm found.

GRA negative group which represents a highly significant difference ($\chi^2=13.6, P<.001$)

Suspected Cases of GRA

There were 15 events in 15 individuals suspected to have GRA from a total of 9 GRA pedigrees. None of the suspected GRA positive patients had genetically proven GRA, nor had they undergone dexamethasone suppression testing. However, all subjects were members of a genetically proven GRA pedigree.

The events observed in suspected GRA patients included early stroke (n=6), cerebral hemorrhage (n=6), ruptured vascular aneurysm (n=2), and sudden death (n=1). These events were documented by physician verification (n=1), clinical history (n=9), death certificate (n=4), and autopsy (n=1). Suspected cases had a mean age of onset of 32.7±11.6, and 12 of the 15 events occurred in males. The case fatality rate was 87%. Blood pressure measurements were not available in any of the suspected cases. However, 10 individuals were reported to be hypertensive, and none of the remaining subjects were reported to have normal blood pressures. When all of the events were considered together (proven plus suspected GRA patients), 70% of complications involved hemorrhagic stroke, and 91% of cases were of the cerebrovasculature (Fig 1). With one exception, all aneurysms were cerebrovascular in nature. The exception was the case of a 13-year-old boy with GRA proven through dexamethasone suppression testing that died of a ruptured thoracic aortic aneurysm. No cases of premature coronary artery disease were definitively documented. An autopsy was performed on 1 of 2 cases of sudden death, a 39-year-old male with genetically proven GRA. Evaluation of the coronary arteries in this subject revealed nonsignificant coronary occlusion that was not felt to be the cause of death. There was only one patient with vascular dissection.

Data from the Framingham study were used to compare the incidence rate of ischemic and hemorrhagic stroke in GRA with normal individuals. Incidence rates for ischemic stroke were similar in the two groups, but the incidence of hemorrhagic stroke was dramatically higher in GRA patients compared to normals (Table 4).
TABLE 3. Comparison of Clinical Features in GRA Positive Patients With Events Versus GRA Positive Patients Without Events and With GRA Negative Subjects From Pedigrees With Known Cerebrovascular Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>GRA Positive Subjects with Events</th>
<th>GRA Positive Subjects without Events</th>
<th>GRA Negative Subjects from Pedigrees with Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>15</td>
<td>152</td>
<td>136</td>
</tr>
<tr>
<td>Events</td>
<td>18</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Female (%)</td>
<td>40</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>Hypertensive by history (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at diagnosis of HTN (yrs)</td>
<td>12.3±6.4 (13)</td>
<td>18.4±10.3 (66)</td>
<td>40.2±15.2 (19) *</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>147.8±15.4 (8)</td>
<td>134.4±22.5 (78)</td>
<td>133.3±16.0 (65) *</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>100.8±13.6 (8)</td>
<td>84.4±17.2 (78)</td>
<td>80.3±10.5 (65) *</td>
</tr>
<tr>
<td>Plasma aldosterone (pmol/L)</td>
<td>1220±750 (5)</td>
<td>770±1220 (25)</td>
<td>320±190 (20) **</td>
</tr>
<tr>
<td>Plasma renin activity (ng/L)</td>
<td>0.04±0.01 (4)</td>
<td>0.23±0.35 (28)</td>
<td>0.79±0.5 (19) **</td>
</tr>
<tr>
<td>Serum potassium (mmol/L)</td>
<td>3.7±0.7 (5)</td>
<td>4.1±0.55 (60)</td>
<td>4.3±0.43 (31) **</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.4±4.1 (6)</td>
<td>24.5±5.4 (60)</td>
<td>25.1±3.3 (54)</td>
</tr>
</tbody>
</table>

Data presented as mean±standard deviation (number of observations). Abbreviations: BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HTN, hypertension.

*P<.05, GRA positive with events vs. GRA positive without events.
†P<.01, GRA positive with events vs. GRA positive without events.
**P<.001, GRA positive with events vs. GRA positive without events.
††P<.001, GRA positive with events vs. GRA negative.
†††P<.01, GRA positive with events vs. GRA negative.

Discussion

These findings indicate that GRA is associated with early hemorrhagic stroke. Seventy percent of all documented events in GRA patients consisted of hemorrhagic stroke. Since the majority of subarachnoid and intracerebral hemmorhages result from ruptured intracranial aneurysms,6 we believe that much of the observed cerebrovascular morbidity and mortality seen in these patients (overall case fatality rate, 61%) relates to ruptured intracranial aneurysms. Similar associations have been reported with autosomal dominant polycystic kidney disease,7-11 and appropriate screening of these individuals has enabled detection and treatment of these aneurysms prior to rupture.

The above conclusion is supported by several observations. First, there were no events in 136 GRA negative individuals versus 18 events in 167 GRA positive individuals from the same pedigrees. This represents a highly significant increase in cerebrovascular complications (P<.001). The significance of this observation would be even greater if events in suspected GRA subjects were also included. However, in order to keep ascertainment bias to a minimum, only proven GRA patients were considered in this analysis.

Second, the documented cerebrovascular events are distributed over 13 different GRA pedigrees (48%) and not clustered in only a few families. This argues against a chance association between GRA and cerebrovascular complications. Third, the prevalence of cerebrovascular complications is high, occurring in approximately 11% of patients with proven GRA and 18% of proven and suspected GRA patients. In particular, the observed number of hemorrhagic strokes is 14-fold to 22-fold higher than that reported in normotensive individuals of similar age from the Framingham study (Table 4).

The young age of onset of these cerebrovascular complications (approximately 30 years of age) is dramatically lower than what is expected in sporadic stroke or stroke in hypertensives.12 It is lower than what has been reported with sporadic intracranial aneurysm (52.5±12.4 years)13 and similar to the mean age at time of aneurysm rupture in patients with adult polycystic kidney disease (39.8±11.5 years).14

What is the underlying pathophysiology of this increased incidence of cerebrovascular complications in GRA? A num-
number of possibilities exist. Tobian and colleagues have reported that correction of hypokalemia in the stroke prone hypertensive rat reduces their high rate of cerebral hemorrhage, even when blood pressure remains elevated. Hypokalemia-induced cerebral hemorrhage is an unlikely explanation for our observations because, on average, GRA patients have been shown to have normal potassium levels and normal potassium homeostasis.

A second possibility may relate to hyperaldosteronism. An association between cerebrovascular disease and primary aldosteronism has been described. In GRA patients with events, aldosterone levels tended to be higher than those patients without events (Table 3). Like GRA, autosomal dominant polycystic kidney disease is characterized both by aneurysm formation and aldosterone excess. Hyperaldosteronism has also been shown to induce fibrosis of the rat heart and the systemic vasculature. It is possible that mineralocorticoid-induced fibrosis of the cerebral vasculature could predispose these vessels to subsequent rupture. Whether long-term hyperaldosteronism is a causal link to intracranial aneurysm in both disorders is unknown.

Our findings could also relate to long-standing hypertension since most of the complications occurred in hypertensive individuals. Many studies show an increased risk of aneurysmal subarachnoid hemorrhage in patients with hypertension, but other studies have found no such association.

A final potential mechanism is that hypertension and/or mineralocorticoid excess during the early stages of cerebrovascular development could predispose to aneurysms. In support of this hypothesis are reports of increased cerebrovascular events (primarily cerebral hemorrhages) in a number of other congenital syndromes, including polycystic kidney disease, Liddle’s syndrome, and congenital 11β-hydroxylase deficiency.

The report of 4 cases of cerebral hemorrhage or premature death in a large Liddle’s syndrome pedigree is particularly noteworthy. Like GRA subjects, Liddle’s syndrome patients have suppressed plasma renin activity and generally have severe hypertension from childhood. In contrast to GRA, Liddle’s syndrome patients have suppressed aldosterone levels but are volume expanded due to mutations in the epithelial sodium channel which constitutively activate sodium reabsorption.

Although the number of events in this report are small, the similarity of findings suggests that the congenital nature of these hypertension syndromes may predispose to aneurysm formation.

Although not universally accepted, screening for asymptomatic intracranial aneurysm in polycystic kidney disease is widespread, and the frequency of complications in polycystic kidney disease (10 to 15%) is similar to that seen in GRA. As a result, we recommend that all patients with genetically proven GRA should have MR angiography to screen for intracranial aneurysm. Since the vast majority of events occurred after puberty, it seems reasonable to begin screening at this time. Based on the current practice in patients with autosomal dominant polycystic kidney disease, screening should probably be repeated every 5 years.

In conclusion, our review of 27 pedigrees with genetically proven GRA has documented an increased prevalence of early cerebrovascular complications, primarily cerebral hemorrhage, which is associated with high mortality (61%). The underlying mechanism of these intracranial hemorrhages relates to intracranial aneurysm. Since cerebrovascular complications were present in 18% of all patients shown to have GRA, we feel that screening of asymptomatic GRA patients with MR angiography should be performed, beginning at puberty and every 5 years thereafter (as in polycystic kidney disease).

Acknowledgments
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**TABLE 4. Incidence Rates For Ischemic and Hemorrhagic Stroke in Normal Individuals From The Framingham Study (5) and From GRA Patients In The Current Series**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Framingham Data (age 30-59 yrs)</th>
<th>Proven GRA</th>
<th>Proven &amp; Suspected GRA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient years</td>
<td>N/A</td>
<td>4607</td>
<td>5097</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>0.067%</td>
<td>0.065% (3)</td>
<td>0.14% (7)</td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>0.020%</td>
<td>0.026% (13)</td>
<td>0.45% (23)</td>
</tr>
</tbody>
</table>

Hemorrhagic stroke includes cerebral hemorrhage, subarachnoid hemorrhage and rupture or surgical repair of intracranial aneurysms. Incidence rates are expressed as percent (number of events are shown in parentheses).

References
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