Overview of neuralgic amyotrophy associated with COVID-19 vaccines

Introduction
Due to the Covid-19 pandemic and its big impact on society various vaccines have been authorized and used for immunization against Covid-19 in The Netherlands: the mRNA vaccines Comirnaty® (Pfizer/BioNTech) [1] and Spikevax® (Moderna) [2], the adenovirus vector vaccines Vaxzevria® (Oxford/AstraZeneca) [3] and Jcovden® (Janssen) [4], and the protein based vaccine Nuvaxovid® (Novavax) [5]. These vaccines have been used in the vaccination campaign in different populations and in different numbers.

Neuralgic amyotrophy
Neuralgic amyotrophy (NA), also known as Parsonage Turner syndrome or brachial neuritis/plexopathy, is a disorder of the peripheral nervous system which is typically characterised by a sudden-onset pain in the shoulder or upper arm followed by patchy paresis, atrophy and sensory symptoms, mostly involving the long thoracic, suprascapular, and anterior interosseous nerves [6-8]. In the majority of patients, the right shoulder is affected, and in two-thirds of the patient the conspicuous winging of the shoulder blade can be observed [6]. Recovery can take months to years, with a large subset of patients at risk for developing long term complaints [7].

Not only the shoulder can be affected
In some of the patients, NA can also manifest with involvement of other peripheral nerves, solely or in varying combinations, such as the median nerve (resembling anterior interosseous nerve syndrome) and radial nerve (resembling posterior interosseous nerve syndrome), or the lower brachial plexus with sympathetic nervous system involvement (resembling complex regional pain syndrome), lumbosacral involvement (resembling radiculopathy), and phrenic nerve involvement (often manifesting as “unexplained dyspnoea”) [8-11].

Idiopathic and hereditary
NA includes both an idiopathic (INA) and hereditary form (HNA). The latter form is genetically heterogeneous, but in 55% of affected families, neuralgic amyotrophy is associated with a point mutation or duplication in the SEPT9 gene on chromosome 17q25 [8]. The disease has a complex and incompletely understood pathophysiology, in which immunologically triggered attacks are thought to affect mechanically vulnerable peripheral nervous system structures in genetically predisposed individuals [8]. There are several triggering factors reported for NA, such as viral and bacterial infections, trauma, rheumatic disorders, strenuous exercise, pregnancy, radiation therapy and vaccinations [12].

Incidence and patient characteristics
NA has an estimated incidence of 1 per 1,000 individuals [13]. The disease is more common in men than in women (ratio 2 to 1) and individuals of any age can be affected, with a median onset age of around 40 years for the idiopathic form and around 25 years for the hereditary form [7]. In the idiopathic form, patients usually suffer only one attack in their life, but up to 25% may go on to suffer a recurrence. In the hereditary form, attacks recur more frequently, in almost 75% of the patients [6-7].

NA is difficult to diagnose
Although most patients with NA develop the “classic” symptoms, NA can also manifest with less typical symptoms, such as involvement of other peripheral nerves [12], or without pain [7]. In practice, the disorder is quite often not recognized which leads to a delay in the mean time to diagnosis of several months [7].

This signal provides an overview of all reports of neuralgic amyotrophy (NA) following COVID-19 vaccinations reported to the Netherlands Pharmacovigilance Centre Lareb, up to July 4th.
Reports
In the period from January 6th, 2021 until July 4th, 2022 the Netherlands Pharmacovigilance Centre Lareb received 84 spontaneous reports of NA associated with administration of COVID-19 vaccines (see table 1). The most reports were related to the Pfizer/BioNTech vaccine (Comirnaty®) and the Moderna vaccine (SpikeVax®). However, these two vaccines were administered twice as often than the other vaccines (see table 2).

Sex
According to the literature, NA is more common in men than in women (ratio 2 to 1) [7]. The data below does not match this distribution. The percentage of male patients is between 14 and 47. No explanation was found for this difference.

Age
The median onset age for NA is around 40 years for the idiopathic form and around 25 years for the hereditary form [7]. Our data shows a higher median onset age, namely 50 to 57 years. Figure 1 shows the age differentiation of reported NA following COVID-19 vaccines.

To find a possible explanation for the difference, the vaccination coverage was included in the analysis (see table 3). There is indeed a higher vaccination coverage in people aged 50 and older, but the difference in vaccination coverage between the age groups is not large enough to fully explain the higher median onset age.

Lareb Intensive Monitoring Study
In addition to the spontaneous monitoring system, Lareb also follows a cohort of vaccinated persons through an Intensive Monitoring Study (LIM). In this cohort, there were no persons reporting NA following COVID-19 vaccination. A possible reason could be that the vaccinated persons had not yet been diagnosed with NA before the end of the study, because of the difficulty to diagnose NA in the early stage. Symptoms that may indicate NA have been reported several times.

Table 1. Overview of reported cases of NA in the Netherlands for COVID-19 vaccines (spontaneous reports)

<table>
<thead>
<tr>
<th>Brand</th>
<th>Comirnaty®</th>
<th>SpikeVax®</th>
<th>Jcovden®</th>
<th>Vazzevria®</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Total</td>
<td>45</td>
<td>23</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N Men</td>
<td>21 (47%)</td>
<td>4 (17%)</td>
<td>4 (44%)</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>N Women</td>
<td>24 (53%)</td>
<td>19 (83%)</td>
<td>5 (56%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age (range)</td>
<td>50 years (23 – 80)</td>
<td>55 years (21 – 88)</td>
<td>52 years (22 – 62)</td>
<td>57 years (33 – 64)</td>
</tr>
<tr>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After Dose 1</td>
<td>19 (42%)</td>
<td>7 (30%)</td>
<td>9 (100%)</td>
<td>6 (86%)</td>
</tr>
<tr>
<td>After Dose 2</td>
<td>20 (44%)</td>
<td>9 (39%)</td>
<td>-</td>
<td>1 (14%)</td>
</tr>
<tr>
<td>After Dose 3</td>
<td>2 (4%)</td>
<td>5 (22%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>After Dose 4</td>
<td>-</td>
<td>2 (9%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>After multiple doses*</td>
<td>4 (9%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Latency time</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean TTO1 (range)</td>
<td>17 days (0 – 196)</td>
<td>8 days (0 – 67)</td>
<td>46 days (2 – 160)</td>
<td>25 days (1 – 66)</td>
</tr>
<tr>
<td>Median TTO2 (IQR)</td>
<td>7 days (3 – 18)</td>
<td>3 days (1 – 9)</td>
<td>14 days (11 – 35)</td>
<td>15 days (9 – 39)</td>
</tr>
<tr>
<td>(Partially) recovered at time of reporting</td>
<td>19 (42%)</td>
<td>14 (61%)</td>
<td>2 (22%)</td>
<td>3 (43%)</td>
</tr>
</tbody>
</table>

** Four patients developed NA following the first and second vaccination

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1 TTO = Time to onset
2 IQR = Inter Quartile Range
Table 2. Most recent overview of number of doses administered per vaccine in the Netherlands [15]

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>Startdate vaccination</th>
<th>Number of vaccinations up to May 15th, 2022</th>
<th>Number of reported NA cases up to July 4th, 2022</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comirnaty®</td>
<td>January 6th, 2021</td>
<td>24,612,595</td>
<td>45</td>
</tr>
<tr>
<td>SpikeVax®</td>
<td>February 12th, 2021</td>
<td>7,986,592</td>
<td>23</td>
</tr>
<tr>
<td>Vaxzevria®</td>
<td>January 25th, 2021</td>
<td>2,780,129</td>
<td>7</td>
</tr>
<tr>
<td>Jcovden®</td>
<td>April 21st, 2021</td>
<td>869,040</td>
<td>9</td>
</tr>
</tbody>
</table>

Figure 1. Age differentiation of reported NA following COVID-19 vaccines

Table 3. Vaccination coverage per age group in the Netherlands for COVID-19 vaccines (up to September 4th, 2022) [15]

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Completed primary series</th>
<th>Booster vaccination</th>
</tr>
</thead>
<tbody>
<tr>
<td>80+</td>
<td>92%</td>
<td>87%</td>
</tr>
<tr>
<td>70 – 79</td>
<td>93%</td>
<td>88%</td>
</tr>
<tr>
<td>60 – 69</td>
<td>89%</td>
<td>81%</td>
</tr>
<tr>
<td>50 – 59</td>
<td>86%</td>
<td>70%</td>
</tr>
<tr>
<td>40 – 49</td>
<td>80%</td>
<td>57%</td>
</tr>
<tr>
<td>30 – 39</td>
<td>71%</td>
<td>45%</td>
</tr>
<tr>
<td>18 – 29</td>
<td>70%</td>
<td>39%</td>
</tr>
</tbody>
</table>
Detailed description of 10 well-documented reports

Lareb received 84 reports of NA associated with administration of COVID-19 vaccines. Circa 20% of the reports of net onset NA were well documented thanks to the attached results of neurological examinations and/or the diagnosis of a neurologist. In another 20% of the reports a recurrent episode of NA was reported. A selection of these reports is shown below.

Most of the reports were medium documented. In contrast, there were also reports that contained few details, such as a missing diagnosis from the neurologist. In addition, not all patients report severe pain, which is one of the core symptoms. In these reports, causality between NA and vaccination is harder to prove.

NL-LRB-00715426 (reported by patient: new onset NA)
A 50-60-years-old female developed pain and muscle weakness in her arm and shoulder 2 days following vaccination with the Janssen COVID-19 vaccine (2nd dose). An EMG at the neurology department revealed neuralgic amyotrophy. The patient had not recovered at the time of reporting. The patient had no infection, overload of shoulder, trauma or surgery prior to vaccination.

Treatment: physiotherapy and ibuprofen
Concomitant medication: celecoxib, fluticasone nasal drops and levocetirizine
Medical history: nasal polyps and arthrosis (neck and lower back)

NL-LRB-00703821 (reported by patient: new onset NA)
A 30-40-years-old male developed nerve pain and loss of function in his right arm 2.5 weeks following vaccination with the Pfizer COVID-19 vaccine (2nd dose). An EMG was performed by a specialist and NA was diagnosed. The patient has not recovered at the time of reporting. The patient had no infection, overload of shoulder or trauma prior to vaccination.

Treatment: physiotherapy
Concomitant medication: not reported
Medical history: not reported

NL-LRB-00720308 (reported by patient: new onset NA)
A 60-70-years-old female developed nerve pain in her vaccinated arm following vaccination with the Pfizer COVID-19 vaccine (1st dose). The patient was hospitalized because a transient ischemic attack was suspected. Diagnostics (MRI, CT, EMG, angiography) showed no abnormalities. A few months later, the patient went to the another hospital for a second opinion. The diagnosis of neuralgic amyotrophy was made. The patient had not recovered from neuralgic amyotrophy at the time of reporting. The patient had no infection, overload of shoulder, trauma or surgery prior to vaccination.

Treatment: pregabalin, oxycodone and physiotherapy
Concomitant medication: codeine and paracetamol
Medical history: lower back pain due to hernia surgery (21 years ago)

NL-LRB-00566740 (reported by consumer: new onset NA)
A 60-70-years-old female developed loss of strength and muscle stiffness in her left arm 7 days following vaccination with the Pfizer COVID-19 vaccine (2nd dose). The neurologist diagnosed NA based on the EMG. The patient had not recovered at the time of reporting.

Treatment: not reported
Concomitant medication: amlodipine
Medical history: not reported

NL-LRB-00697914 (reported by physician: new onset NA)
A 60-70-years-old male developed muscle weakness in his left shoulder 7 days following vaccination with the AstraZeneca COVID-19 vaccine (1st dose). The diagnosis NA was confirmed by EMG. The patient was recovering at the time of reporting.

Treatment: analgesia and physiotherapy
Concomitant medication: none
Medical history: none
A 50-60-years-old male developed a winged scapula and severe pain, weakness and paresis in his arms, shoulders and neck following vaccination with the Pfizer COVID-19 vaccine (3rd dose). The patient visited 3 different GP's and a neurologist. The clinical symptoms showed bilateral NA of the shoulders. The patient was recovering from NA 1 month after onset. The patient had no infection prior to vaccination.

Treatment: paracetamol, oxycodone, diclofenac, tramadol and physiotherapy
Concomitant medication: none
Medical history: varicose veins, calcaneus fracture, smoker

A 50-60-years-old male developed NA 18 days after vaccination with the Moderna COVID-19 vaccine (2nd dose). An ECG and MRI were performed and the diagnosis NA was confirmed by a neurologist. After 6 weeks, the patient had less pain, but still suffered from severe loss of function of his shoulder. The patient had no infection or illness prior to vaccination.

Treatment: not reported
Concomitant medication: none
Medical history: none

A 50-60-years-old female, known with NA, experienced a recurrent episode of NA 2 days following vaccination with the Pfizer COVID-19 vaccine (1st dose). The patient was treated with prednisone and the pain was under control, but after the 2nd COVID-19 vaccination the neuritis flared up again within 2 days.

Treatment: prednisone
Concomitant medication: omeprazole, multivitamins
Medical history: arthrosis, plasminogen activator inhibitor type 1 deficiency, Bechterew disease, alopecia areata and NA

A 50-60-years-old female, known with NA, developed a recurrent episode of NA following vaccination with the Moderna COVID-19 vaccine (1st dose) and Pfizer COVID-19 vaccine (2nd dose). Due to the symptoms, the patient was partially incapacitated for work at the time of reporting.

Treatment: physical rehabilitation
Concomitant medication: candesartan, cholecalciferol and paracetamol
Medical history: suspected COVID-19 (1 year before vaccination), allergies (grass and NSAIDs), hypertension, rheumatic fever, pneumonia and NA

A 40-50-years-old female, known with NA, developed a recurrent episode of NA 2 weeks following vaccination with the Pfizer COVID-19 vaccine (2nd dose). The diagnosis NA was confirmed by EMG. The patient had not recovered at the time of reporting. The patient does not expect a full recovery.

Treatment: pregabalin and morphine
Concomitant medication: not reported
Medical history: suspected COVID-19 (1 year before vaccination) and NA
Other sources of information

SmPC
Neuralgic amyotrophy is not listed in the SmPC of the Covid-19 vaccines [1-5].

Other databases
In VigiBase, the WHO global database of individual case safety reports (ICSRs), 1,085 reports with PT neuralgic amyotrophy were found (version date dataset: 20-07-2022). This number includes the reports from the Netherlands. Circa two-third of the reports were related to the Pfizer/BioNTech vaccine (Comirnaty®) [14].

Literature
Several case reports described neuralgic amyotrophy as possible adverse event of COVID-19 vaccination [16-28]. Table 3 provides an overview of the case reports.

Table 3. Overview of the case reports found on PubMed

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Patient details</th>
<th>Vaccine details</th>
<th>Latency</th>
<th>Treatment details</th>
<th>Recovery</th>
<th>Medical history details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amjad et al. (2022)</td>
<td>Male, 78 years</td>
<td>BNT162b2 mRNA vaccine (2nd dose)</td>
<td>3 days</td>
<td>Prednisone and occupational therapy</td>
<td>Partial recovery</td>
<td>Coronary artery disease</td>
</tr>
<tr>
<td>Bernheimer &amp; Gasbarro (2022)</td>
<td>Female, 42 years</td>
<td>mRNA-1273 vaccine (2nd dose)</td>
<td>3 weeks</td>
<td>Prednisone, gabapentin and physical therapy</td>
<td>Partial recovery</td>
<td>Unknown</td>
</tr>
<tr>
<td>Burillo et al. (2021)</td>
<td>Male, 38 years</td>
<td>ChAdOx1-S recombinant vaccine (unknown dose)</td>
<td>4 days</td>
<td>Methy/prednisolone and prednisone</td>
<td>Full recovery</td>
<td>Coeliac disease</td>
</tr>
<tr>
<td>Civardi et al. (2022)</td>
<td>Female, 50 years</td>
<td>BNT162b2 mRNA vaccine (1st dose)</td>
<td>2 days</td>
<td>Prednisone, pregabalin and occupational therapy</td>
<td>Partial recovery</td>
<td>No recent infection</td>
</tr>
<tr>
<td>Coffman et al. (2021)</td>
<td>Female, 66 year</td>
<td>BNT162b2 mRNA vaccine (2nd dose)</td>
<td>Unknown days</td>
<td>Physical therapy</td>
<td>Partial recovery</td>
<td>Unknown</td>
</tr>
<tr>
<td>Diaz-Segarra et al. (2021)</td>
<td>Female, 35 years</td>
<td>BNT162b2 mRNA vaccine (1st dose)</td>
<td>9 days</td>
<td>Prednisone</td>
<td>Partial recovery</td>
<td>No history of neurologic diseases or allergies and no recent trauma or infection</td>
</tr>
<tr>
<td>Flikkema &amp; Brossy (2021)</td>
<td>Male, 43 years</td>
<td>BNT162b2 mRNA vaccine (1st dose)</td>
<td>2 days</td>
<td>Analgesia and IV steroids</td>
<td>Unknown</td>
<td>No pertinent medical or family history and no recent fevers, chills or trauma</td>
</tr>
<tr>
<td>Kim et al. (2021)</td>
<td>Female, 45 years</td>
<td>ChAdOx1-S recombinant vaccine (unknown dose)</td>
<td>2 days</td>
<td>Prednisolone</td>
<td>Partial recovery</td>
<td>No history of recent illness or trauma</td>
</tr>
<tr>
<td>Koh et al. (2021)</td>
<td>Male, 50 years</td>
<td>BNT162b2 mRNA vaccine (1st dose)</td>
<td>25 days</td>
<td>Corticosteroids</td>
<td>Partial recovery</td>
<td>No recent infection or other triggers of NA or family history suggestive of hereditary NA</td>
</tr>
<tr>
<td>Koh et al. (2021)</td>
<td>Male, 44 years</td>
<td>BNT162b2 mRNA vaccine (2nd dose)</td>
<td>4 days</td>
<td>None</td>
<td>Partial recovery</td>
<td>No recent infection or other triggers of NA or family history suggestive of hereditary NA</td>
</tr>
<tr>
<td>Mahajan et al. (2021)</td>
<td>Male, 50 years</td>
<td>BNT162b2 mRNA vaccine (1st and 2nd dose)</td>
<td>7 days</td>
<td>Methylprednisolone, betamethasone injection, phenylbutazone and prednisolone</td>
<td>Partial recovery</td>
<td>Unknown</td>
</tr>
<tr>
<td>Author</td>
<td>Patient</td>
<td>Vaccine</td>
<td>Latency</td>
<td>Treatment</td>
<td>Recovery</td>
<td>Medical history</td>
</tr>
<tr>
<td>-----------------</td>
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<td>---------</td>
<td>----------------------------------------------------------</td>
</tr>
<tr>
<td>Queler et al.</td>
<td>Male, 49</td>
<td>BNT162b2 mRNA vaccine (1st dose)</td>
<td>13 hours</td>
<td>NSAIDs and prednisone</td>
<td>Partial</td>
<td>Lyme disease (2 months prior and treated with doxycycline)</td>
</tr>
<tr>
<td>(2022)</td>
<td>years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male, 44</td>
<td>mRNA-1273 vaccine (2nd dose)</td>
<td>18 days</td>
<td>Gabapentin and physical therapy</td>
<td>Partial</td>
<td>Healthy</td>
</tr>
<tr>
<td>Vitturi et al.</td>
<td>Male, 51</td>
<td>ChAdOx1-S recombinant vaccine</td>
<td>4 days</td>
<td>Paracetamol, NSAID, pregabalin and physical therapy</td>
<td>Partial</td>
<td>No comorbidities and no recent trauma or infectious disease</td>
</tr>
<tr>
<td>(2021)</td>
<td>years</td>
<td>(1st dose)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Mechanism**

The etiology and pathophysiology of NA is unclear, but has probably genetic, environmental, and immune-mediated components [7-8]. Possible immune-mediated mechanisms include molecular mimicry and bystander activation, both of which may ensue following either infection or vaccination [27]. The mRNA vaccines elicit potent type I interferon responses, which induce inflammation and may be associated with increased risk of autoimmune reactions [7, 27, 29].

NA after vaccination was first reported by Rigal et al. in 1956 [30]. Over time, several case reports followed that established a relationship with, among others, the DTP vaccine (diphtheria, tetanus and polio), the tetanus vaccine, the hepatitis B vaccine, the typhoid vaccine, the influenza vaccine, the human papilloma virus vaccine and the shingles vaccine. [31-40]. In addition, several case reports have appeared on neuralgic amyotrophy following COVID-19 vaccination [16-28]. NA is also associated with COVID-19 disease as was described by Ismail et al. in their review [41].

**Discussion and conclusion**

From January 6th, 2021, until July 4th, 2022, the Netherlands Pharmacovigilance Centre Lareb received 84 reports of NA associated with administration of COVID-19 vaccines. Of these, 20 (24%) reported a recurrent episode in patients familiar with NA. Three quarters of the reports were reported by consumers.

Most patients (76%) in the Lareb reports were between 40 and 70 years old with a median age of 52 years. They developed NA between 0 and 196 days with a median time of onset of 7 days. Most patients were female (64%). The data of the reports received by Lareb has been compared with the data from the case reports in the literature. In the literature, 16 patients with NA following COVID-vaccination were described. The median age of these patients was 47 years. They developed the symptoms between 0 and 30 days with a median time of onset of 4 days. 10 out of 16 patients (63%) were male.

Neuralgic amyotrophy is considered a rare peripheral nervous system disorder, but in practice seems grossly under recognized. This is also the reason why we did not use observed-over-expected ratios in this analysis; the ratios simply don't match the right amount of patients with NA.

A possible mechanism for vaccine-induced NA has not yet been found. The mechanism probably contains genetic, environmental, and immune-mediated components. NA is also described following COVID-19 infection.

The most reports to Lareb and to the WHO global database were related to the Pfizer/BioNTech vaccine (Comirnaty®). However, this vaccine has been given to most people by far. The number of reports per vaccine is reasonable in proportion to the number of vaccines given. Most case reports in the literature were also associated with the Pfizer/BioNTech vaccine.

Based on the reports of NA and the lack of other potential causes, a causal relationship for NA and COVID-19 vaccination should be further investigated.
References


This signal has been raised on October 27, 2022. It is possible that in the meantime other information became available. For the latest information, including the official SmPC’s, please refer to website of the MEB www.cbg-meb.nl