

COVID-19 infections and vaccination in patients with hereditary hemorrhagic telangiectasia – a cohort study*

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Abstract

Background: Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant orphan disease, leading to malformations of blood vessels. Regarding the pandemic, both, the course of COVID-19 infection and the response to the vaccination and its possible side effects, such as increased bleeding episodes, are still poorly investigated.

Methodology: Retrospective single-center cohort study at the Department of Otolaryngology / Head & neck Surgery (University Hospital of Zurich, Switzerland) between February 14th and March 21th 2022. Among the 32 eligible adult patients with HHT, we collected patient- and disease-specific characteristics. The course of a COVID-19 infection including severity of the disease and symptoms were noted. We assessed changes in the Hereditary Hemorrhagic Telangiectasia Epistaxis Severity Score (HHT-ESS) before and after vaccination.

Results: Out of the 32 patients, 5 patients suffered a COVID-19 infection, thereby mainly experiencing loss of taste and smell and cough. No significant change of the HHT-ESS before and after vaccination was observed. The median HHT-ESS before and after the vaccination was 4.06.

Conclusions: There was no significant change in bleeding severity (HHT-ESS) before and after COVID-19 vaccination. Based on these findings, the vaccination for HHT patients does not seem to worsen the further course of the disease. The overall symptoms, risks and complications after Sars-CoV-2 vaccination and infection seem to be comparable to the general population.

Key words: Hereditary hemorrhagic telangiectasis (HHT), COVID-19, Sars-CoV-2, vaccination, infection, Osler

Introduction

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant genetic disease, causing the formation of abnormal blood vessels ⁽¹⁾. The pathologic angiogenesis leads to vascular malformations, including telangiectasias ^(1,2). From a clinical point of view, the most common symptom of HHT patients is recurrent epistaxis ⁽³⁾. With an estimated prevalence of approximately 1:5000, HHT qualifies as an orphan disease ⁽⁴⁾. Thus, the data regarding the course of COVID-19 infections and treatment recommendations in HHT patients is limited ⁽⁵⁾.

During the COVID-19 pandemic, caused by Sars-CoV-2, an

RNA-virus of the group of the Coronaviruses, HHT patients were confronted with particular difficulties. Their bleeding episodes may have required medical intervention or even hospitalization. However, due to closure of outpatient clinics and diminished health care resources, HHT patients had to make an additional effort to receive state-of-the-art treatment, potentially resulting in an increased risk of COVID-19 infection ⁽⁵⁻⁷⁾. Furthermore, HHT patients have a known risk of bleeding and clotting events, mainly due to vulnerable vascular malformations, which cause difficulties in primary hemostasis ⁽⁸⁾. In particular, alterations in the regulation of the endothelial surface and significant higher levels of Von Willebrand Factor and Factor VIII lead to higher

risk of clotting⁽⁸⁻¹⁰⁾. Analogically, a COVID-19 infection, which mainly presents as a respiratory disease, may exhibit hypercoagulability^(7, 11, 12). This common pathophysiological aspect raises the questions, whether HHT patients harbor an increased risk of complications, when infected with COVID-19. Additionally, the role of protective measures for these patients, such as the COVID-19 vaccinations, should be assessed. As for the vaccines Moderna (Sars-CoV-2-Spike-Glycoprotein, mRNA-1273) and Pfizer-BioNTech (Tozinameranum) have been shown highly protective against serious complications and deaths associated with COVID-19⁽¹³⁻¹⁵⁾. By the time of this study, these two vaccines were the only ones available in Switzerland.

The primary aim of this study on HHT patients was 1) to investigate a potentially increased risk of COVID-19 vaccination, especially intensifying of the bleeding episodes and 2), to assess the course of COVID-19 infection in HHT patients.

Materials and methods

Study design

This single-center retrospective cohort study included adult HHT patients treated at the clinic of Otorhinolaryngology / Head and Neck surgery at the University Hospital of Zurich, Switzerland. The study was approved by the ethics committee of the canton of Zurich, Switzerland (2021-02099). The patients were identified with the internal clinical information system (KISIM) key word search (search terms were: HHT, hereditary hemorrhagic telangiectasia, Osler and variations/German translations of these terms). Eligibility criteria included the definitive diagnosis of hereditary hemorrhagic telangiectasia according to the Curaçao criteria and the minimum age of 18 years. Before study inclusion, verbal informed consent was obtained by each patient. All patients were asked to answer the same interview protocol, consisting of different questions: 1) if they have received a COVID-19 vaccination, 2) the number and type of vaccination, 3) potential symptoms they experienced after vaccination, 4) the need for blood transfusions after vaccination, 5) current hemoglobin (HB) levels (last measurement) and 6) the HHT-EES before and after COVID-19 vaccination. This score is commonly used to determine the severity of the epistaxis episodes and evaluate the effectiveness of interventions⁽⁶⁾. The patients were contacted once by phone by the first author and answered questions regarding the two time points between January of 2020 until March 2022 (before and after vaccination) retrospectively. Furthermore, the interview included a question, whether the patients had suffered an infection with COVID-19, proven by a positive PCR test. In case of a positive answer, the course of the infection, accompanying symptoms and complications (such as thrombotic events) were noted.

In addition to this protocol, we used the SF-12 (short form 12, last four weeks) to evaluate the general physical and mental

health situation of the included HHT patients during the pandemic. The SF-12 is the short version of the SF-36 (short form 36) and contains different categories including questions about physical, mental and overall well-being in daily life. The SF-12 is comparable to the SF-36 and there is evidence for large similarities of the SF-36 between European countries^(16, 17).

Non-response bias was reduced by directly contacting the patients by telephone and sampling bias was avoided by contacting the entire HHT cohort in Zurich. Recall bias remains the main obstacle.

Statistical analysis

For the descriptive comparison the collected data of the HHT patients were analyzed and described by percentages, medians, interquartile ranges, and means with standard deviation. The HHT-EES before and after vaccination was compared by using R version 4.1.3 (tidyverse, readxl, ggpubr, MetBrewer) for statistical analyses (two-tailed paired t-test). Furthermore, a pearson correlation test in R was used to investigate correlation between age and change in HHT-EES before and after vaccination.

For the comparison of the infection rates of our cohort and the general population a binomial test was used.

Analysis of the results of the SF-12 is composed of the physical component summary (PCS) and the mental component summary (MCS) in comparison to a reference population⁽¹⁷⁾. This score was not used for any comparisons but was chosen to evaluate general quality of life in this specific cohort.

To compare the SF-12 results of our cohort with a normative population, a t-test was performed. As a reference sum scales of a German norm sample from 1994, stratified by gender and age, served as the norm population.

Post hoc power analysis for the paired t-test of ESS-HHT score before and after vaccination revealed that 29 patients would be required to identify a 0.5 point mean difference in score with a power of 95%.

Results

Patients' characteristics

From the 79 patients that were identified, 57 were eligible. Twenty-two were not eligible, because they either did not have a definitive diagnosis of HHT, were not patients of the clinic of otorhinolaryngology and head and neck surgery of the University hospital of Zurich or were under the age of 18 years at the time of the study. Among the 57 patients, 1 patient had already died at the beginning of the study, 15 could not be contacted and 9 did refuse to participate. The deceased patient had a severe neurosurgical disorder and died without an apparent COVID infection. Finally, the study cohort consisted of 32 HHT patients (18 women, 14 men). The average age was 53 years with a standard deviation of 15.17, with an average disease duration of 17.5 years (Figure 1). Recent hemoglobin levels could be col-

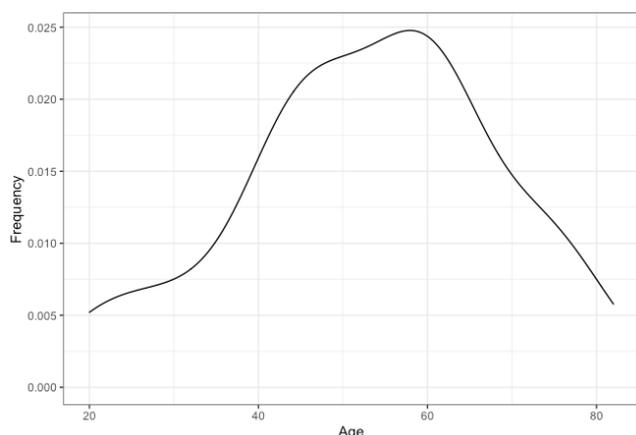


Figure 1. Age distribution of HHT patients.

lected in 17/32 patients, with a mean of 11.5 g/dl.

COVID-19 Infections

Five patients (15.6 %) suffered a PCR-test proven COVID-19 infection during the study period. The infection rate in our cohort differs significantly from the infection rate of 40.6% in the general population in Switzerland during the same period ($p < 0.05$).

The most frequent symptoms named by the patients were: loss of taste and smell (3/5 patients, 60%) and cough (4/5 patients, 80%). As shown in Figure 2a, less frequently reported symptoms were fever, chills, and headache. In addition to our questionnaire, four of the patients specifically reported either the consistent wearing of masks (2/32, 6.3%) or the restriction of social contacts (2/32, 6.3%). None of the COVID-19 positive HHT patients reported a serious course of disease with need for hospitalization.

Side effects and HHT-ESS before and after vaccination

Twenty-eight of the 32 patients were fully vaccinated (87.5%), 1 patient received only one vaccination (3.1 %) and 22 also received a second booster (68.8%).

In the distribution of the vaccines, 19 of the fully vaccinated patients received the Moderna (67.9%) and 9 BioNTech Pfizer (32.2%) product.

The reactions and symptoms after vaccination are shown in Figure 2b. Two patients reported an intensifying of the bleeding after vaccination and one of the patients received a blood transfusion three weeks after the first vaccination.

Comparing HHT-ESS before and after vaccination, no significant changes emerged ($p=0.62$) (Figure 3a). The median in both groups was an HHT-ESS score of 4.06 (Q1 2.93, Q3 5.76).

We could observe a trend of a positive correlation between increasing age and change in HHT-ESS before and after vaccination, representing an increase in the score in older patients.

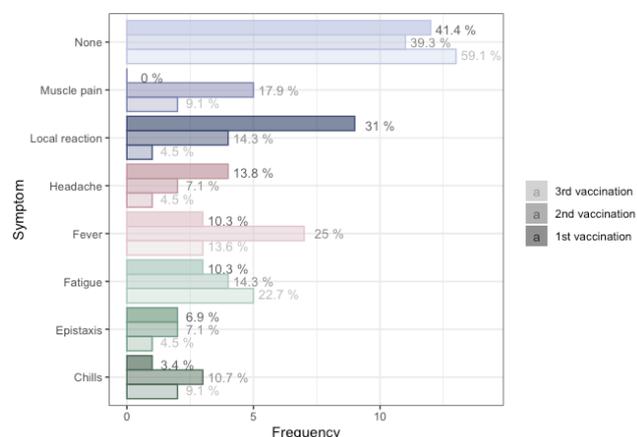
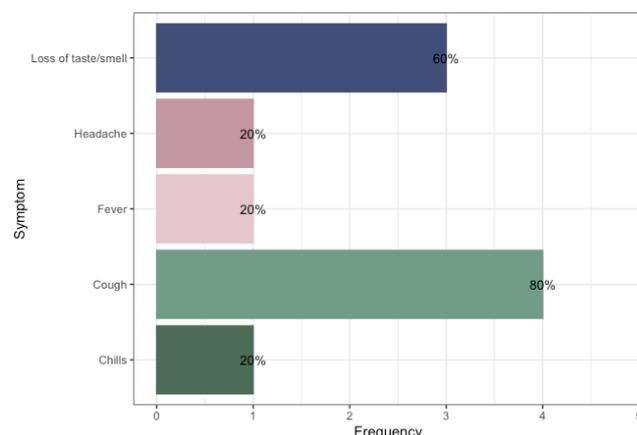


Figure 2. (a) COVID-19 Symptoms in HHT patients shown in frequency of named symptom ($n=5$). (b) Symptoms after COVID-19 vaccinations. Percentages of symptom occurrence after respective vaccination: 1st vaccination ($n=29$), 2nd vaccination ($n=28$) and 3rd vaccination ($n=22$) are shown.

(Figure 3b) Nevertheless this was not statistically significant ($p=0.06$).

Impact of HHT on quality of life

The mean score of the HHT patients in the physical component summary of the SF-12 was 45.02 with a standard deviation of 10.30 and in the mental component summary 47.25 with a standard deviation of 10.71. In comparison to a normative population (German standard sample) the HHT patients showed significantly lower SF-12 means in both the physical ($p < 0.05$) and the mental component summary ($p < 0.05$) (independent t-test) (17).

Discussion

Main findings

In this single-center retrospective cohort study we investigated the courses of both, COVID-19 infections and vaccinations in HHT patients at a tertiary referral center in Switzerland. During

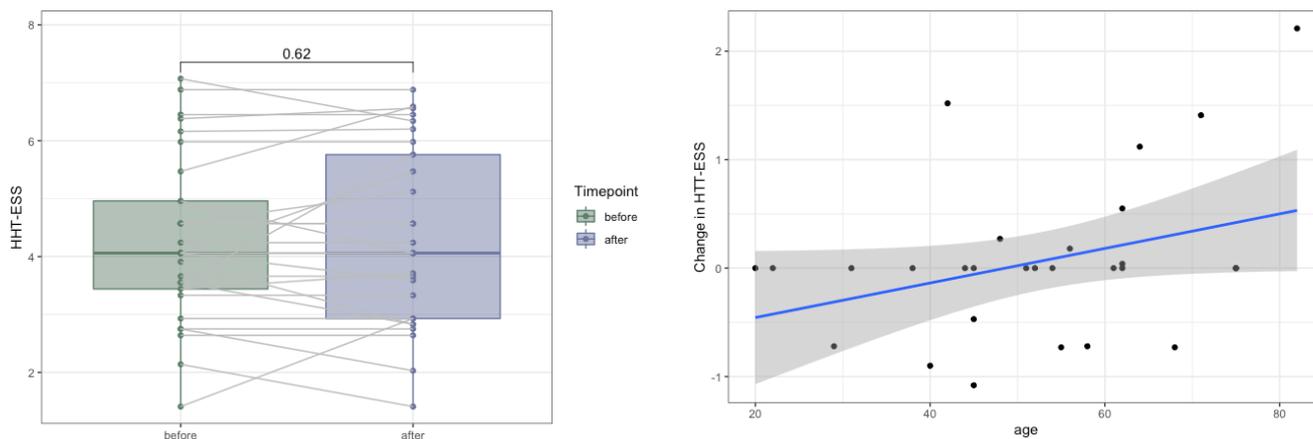


Figure 3. (a) Comparison of mean HHT-ESS before and after vaccination (paired t-test, n=29). (b) Trendwise correlation between age of HHT patients and change in HHT-ESS before and after vaccination (r=0.35, p=0.06).

the study period, 5/32 patients (15.6%) were diagnosed with COVID-19. Overall, loss of taste and smell and cough were the most frequent reported symptoms. No COVID-19 positive HHT patient reported a serious course of disease with need for hospitalization. Regarding the HHT-ESS and when comparing before vs. after vaccination, no significant change in the score was observed. Although a weak positive trend in the change of the HHT-ESS and increasing age could be observed, there was no significant correlation.

Results in the context of preexisting literature

A) COVID-19 infection

There were no hospitalizations or severe complications due to COVID-19 in our HHT cohort. A rather mild presentation of the COVID-19 infection in most of the HHT patients was also observed in the cohort of Suppressa et al. In contrast to their study, we did not only focus on the first wave, but also included data throughout the pandemic until March 2022 (5).

The COVID-19 infection rate of 15.6 % in our cohort was significantly lower than the infection rate of 40.6 % in the total population of Switzerland during the same period (5, 18). However, in contrast to this hypothesis, Marcos et al. found higher infection rates in HHT patients, when compared to the general population. The authors claimed that this might be explained by an increased awareness and consecutively increased testing rates of HHT patients. The fact that the course of disease was usually mild in their HHT cohort, underlines this hypothesis (19).

The observation that the COVID-19 infection displays a rather mild course of disease could be confirmed in our study. The most common symptoms were loss of taste and smell and cough, whereas no hospitalizations or complications were observed. This is in line with the results of Marcos et al. Others reported fever to be the most common symptom (5). The majority of the patients included by the study of Suppressa et al.

also had a benign clinical course, two of their patients suffered a more severe form of COVID-19 and there were no fatal outcomes recorded. The study therefore concluded that there was a comparable infection risk of the HHT patients and the general population (5).

As there was no intensifying of the bleeding episodes after infection according to the 5 affected patients in our study, we feel that the infection has little effects on HHT-related symptoms, despite investigating a small cohort. Nonetheless, Marcos et al. reported one case of increased bleeding after Sars-Cov-2 infection (19). No thrombotic events were noted in our patients. Special attention should be paid to thrombotic complications in COVID-19 patients with HHT, as colleagues reported a fatal Sars-Cov-2 infection in an HHT case. However, an obvious thromboembolism in their case was not described (20).

B) COVID-19 vaccination

All the vaccinated patients in the cohort received either Moderna or BioNTech Pfizer vaccine. In the general population, common side effects of these vaccines include local swelling, fever, muscle pain and fatigue. Overall, the most common reported adverse effect was pain at the injection site with 92 % (Moderna) and 84.1 % (Pfizer) (21). Similarly, these symptoms could also be observed in our cohort. Interestingly, two patients reported intensifying of the nose bleeding episodes shortly after the vaccinations. However, there was no significant change of the HHT-ESS, indicating, that the vaccination has no lasting impact on the bleeding episodes in HHT patients. Regarding the vaccination distribution on April 12th 2022, 70.11 % of the population of Switzerland received at least one dose of the vaccine, whereas 69.12 % were fully vaccinated and 42.78 % received a 2nd booster (18). In contrast, these rates were substantially higher in our HHT cohort, with 87.5%, who were fully vaccinated and 68.8%, who received a 2nd booster. This may be explained by

an increased awareness of HHT patients of being at risk and consecutively an increased likelihood to initiate protective measures. In line with this observation, Suppressa et al. reported that in their patient cohort the majority of the HHT patients was wearing masks and performing hand hygiene measures⁽⁵⁾. Four of the patients in our cohort, also spontaneously mentioned restriction of social contacts and the consistent wearing of masks in the interview, but this was not further addressed in this study. Nevertheless, this could have also played a role in the compliance to social distancing and lockdown, which might have led to a lower infection rate^(5, 18).

Compared to the German population sample, the HHT patients showed significantly lower SF-12 means in both, the physical ($p < 0.05$) and the mental component summary ($p < 0.05$), indicating the negative impact of HHT on patient's physical and mental health⁽¹⁷⁾. This only proves the impact on QoL, however no conclusions can be drawn concerning the impact of the pandemic.

As shown by Baysal et al., the quality of life in HHT patients is significantly altered by the intensity of the bleeding episodes and improved with a decreasing HHT-ESS⁽²²⁾. The median HHT-ESS in this study showed a value of 4.06, which suggests a mild to moderate disease burden of disease. The mean hemoglobin level of 11.5 indicated, that most of the HHT patients suffer from anemia, which also leads to a decreased QoL⁽²³⁾. The mentioned hemoglobin levels were collected once and should be regarded as a side finding of our study^(8, 24, 25).

Strengths and limitations

Potential limitations of the study are set by the recall bias in the interviews regarding information such as symptoms, which occurred in the context of infection or vaccination during the past two years. It is important to mention, that the patients were contacted once and were asked to answer the questions retrospectively. The low number of participants, which is due to the rarity of the disease, represents another limitation. However, post hoc sample size calculation to find a difference of 0.5 ESS-HHT points showed that our population would be sufficient. This limitation could be overcome by a future multicenter study, where more patients with HHT could be included. In addition, HHT patients might be less likely to get a COVID-19 nose swab test, as it could aggravate their bleeding episodes, which could explain the

lower infection rate in our study population⁽²⁶⁾.

This study provides a reference to place recommendations regarding vaccination in HHT patients and might help HHT patients dealing with insecurities, which come along with the pandemic.

Conclusions

In summary, there was no significant change of the HHT-EES score before and after vaccination. The overall side effects after COVID-19 vaccination in our cohort with HHT seem to be mild. Thus, there appear to be no serious objections to recommend the COVID-19 vaccination for this specific patient group as a protective measure. In addition, no increased risk of infection, complications or hospitalizations due to Sars-CoV-2 were observed.

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Authorship contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by EG and MS. The first draft of the letter was written by EG and all authors commented on previous versions. All authors read and approved the final version.

Ethics approval and consent to participate

The questionnaire and methodology for this study was approved by the Human Research Ethics committee of the canton of Zurich, Switzerland (2021-02099), 26th of November 2021.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Conflict of interest

The authors have no competing interests to declare that are relevant to the content of this article.

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