Investigating COVID-19 burden in people with neurofibromatosis type 1

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Highlights

- COVID-19 can have significant consequences for people with some pre-existing conditions; it is not clear whether COVID-19 has similar consequences for people with neurofibromatosis (NF)
- We explored electronic healthcare record (EHR) data to learn more about COVID-19 in people with neurofibromatosis type 1 (we did not have enough data to systematically study NF2 or schwannomatosis)
- Our findings suggest that the proportion of COVID-19 positivity or severe outcomes in people with NF1 is not greater than the general age-matched population as documented in the National COVID Collaborative Cohort

Introduction

- People with pre-existing conditions like diabetes, respiratory disease, or cardiovascular disease appear to be more susceptible to severe or fatal COVID-19 when infected by coronavirus SARSCoV-2 [1,2].
- It is not known if being diagnosed with Neurofibromatosis (NF, a family of diseases including neurofibromatosis 1, neurofibromatosis 2, and schwannomatosis) affects the risk of being susceptible to infections or adverse effects of COVID-19.
- In this study, we explored the occurrence of COVID-19 and associated complications in people with neurofibromatosis in the National COVID Collaborative Cohort (N3C) patient population.
- We investigated (1) the proportion of COVID-19 positivity in people with NF1 and (2) the occurrence of severe outcomes for people with NF and COVID-19.
- There were too few patients with NF2 or schwannomatosis for inclusion, thus our analysis is limited to NF1.

National COVID Collaborative Cohort (v3.2)

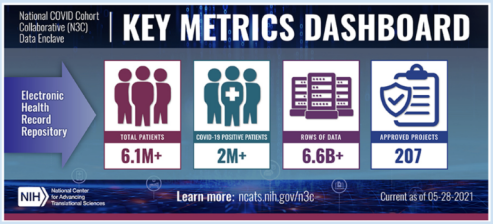

Figure adapted from: https://ncats.nih.gov/n3c/about/data-overview

- The N3C enclave has harmonized EHR data from 55 different contributing centers all around US [3]
- COVID positive and negative patients are included in the enclave in 1:2 ratio matched by demographics [4]
- This community resource is actively under development with new patients being added everyday
- The analyses in this presentation uses data last updated on June 6, 2021

Data Acknowledgement and References

- The analyses described in this presentation were conducted with data or tools accessed through the NCATS N3C Data Enclave (https://covid.cd2h.org) and N3C Attribution & Publication Policy v 1.2-2020-08-25b supported by NCATS U24 TR002306 and the Neurofibromatosis Therapeutic Acceleration Program.
- This research was possible because of the patients whose information is included within the data and the organizations (https://ncats.nih.gov/n3c/resources/data-contribution/data-transfer-agreement-signatories) and scientists who have contributed to the on-going development of this community resource [https://doi.org/10.1093/jamia/ocaa196]
- Refs: [1] Roth GA, JAMA, 2021, [2]Pratichizzo F, Diab Metab, 2021, [3] Haendel M, JAMIA 2021, [4] N3C Phenotype acquisition github [5]https://www.cdc.gov/cancer/uscs/technical_notes/stat_methods/rates.htm, [6] Bennett T, MedRxiv preprint, 2021

NTAP

CHILDREN'S TUMOR FOUNDATION ENDING NF THROUGH RESEARCH

Size and demographics of selected patient cohorts

A

Condition	Total cohort size	Is rare disease
Neurofibromatosis	2357	true
Tuberous sclerosis	807	true
Acute myeloid leukemia	9,637	true
Fragile X syndrome	91	true
General population without NF	5.4M	false
Diabetes mellitus Type 1	63,697	false
Controlled hypertension	1.6M	false

B

Figure 1. Cohort demographics. (A) The N3C population was stratified into various disease types to form comparison cohorts using definitions or "concept sets" that include ICD9/10 and SNOMED codes for each disease type. The cohort size for each disease is noted in (A). **(B)** The top and bottom plots show race and gender information for the NF1 cohort respectively.

Age adjusted proportion of COVID-19 positive patients in N3C seems to be lower in NF1 compared to other diseases

A

N3C	Neurofibromatosis	Tuberous sclerosis	Acute myeloid leukemia	Fragile X	Non- NF	Diabetes Mellitus Type 1	Controlled Hypertension
Age Adjusted proportion of COVID positive per 100,000 US std. population	13139	17120	15868	29230	26159	21212	21378
Approx proportion of COVID Positive	13.1	17.1	15.8	29.2	26.1	21.2	21.3

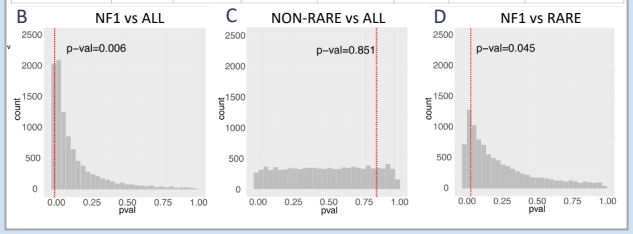

Figure 2. Comparison of age adjusted proportions of COVID positive people in NF1 and various cohorts of rare and non-rare diseases.[5]
(A) Table of proportion of COVID positivity in the various cohorts in N3C. The likelihood of observing these age adjusted proportions for different cohorts were then compared through 10,000 iterations of bootstrap analysis.
(B-D) The distribution of bootstrapped estimates (grey bars) of p-val for age adjusted proportion of COVID positive patients in NF1 vs all cohorts, non-rare disease vs all cohorts, NF1 vs rare disease cohorts. The red lines denote the actual p-value of the comparison of different cohorts.

Age adjusted severity among COVID-19 positive patients in NF1 is not significantly different than other disease cohorts

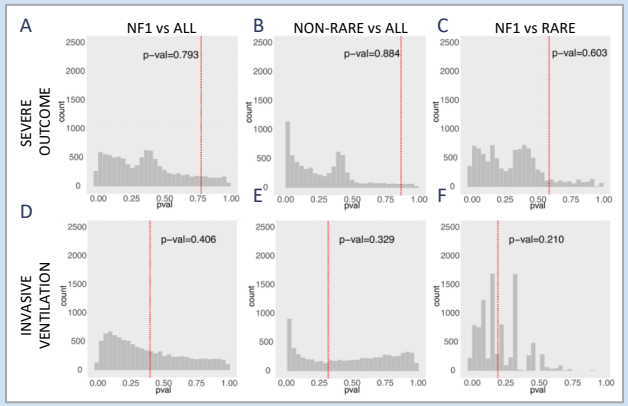

Figure 3. Comparison of age adjusted proportions of COVID related severe outcomes in NF and various cohorts of rare and non-rare diseases. Severity scores were based on criteria including AKI, ECMO, invasive ventilation, and COVID related death.[6]
(A-C) Bootstrapped estimates of p-values for severe outcomes in NF1 vs all cohorts, non-rare disease vs all cohorts, NF1 vs rare disease cohorts (iterations = 10,000).
(D-F) Bootstrapped estimates of p-values for documented invasive ventilation in NF1 vs all cohorts, non-rare disease vs all cohorts, NF1 vs rare disease cohorts (iterations = 10,000). **(A-F)** The red lines denote the actual p-value of the comparison of different cohorts.

Discussion & Future Directions

- Our preliminary analyses show that in N3C, the proportion of COVID positivity in people with NF was lower than other comparable diseases and the general population. The severity of the outcomes in people with NF1 who tested positive for COVID-19 did not seem to be higher compared to the general population or other diseases.
- Important caveats of the dataset include low representation of chronic diseases, low representation of rare diseases, and missed information.
- Further analyses with new incoming data to the N3C is still ongoing, and vigilance towards COVID-19 by applying common prevention measures is highly recommended for people with NF1.