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RESEARCH ARTICLE

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Excretion and clearance of Sabin-like type 3 poliovirus in a child diagnosed with severe combined immunodeficiency

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ABSTRACT

Children with primary immunodeficiency disorder (PID) are at higher risk of developing vaccine-associated paralytic poliomyelitis (VAPP) or vaccine-derived polioviruses (VDPV) infection when inadvertently expose to poliovirus vaccine, oral (OPV). A pilot study was initiated to describe the epidemiology of immunodeficiency-associated VDPV (iVDPV) and to estimate the risk of iVDPV shedding among individuals with PID. Children under 18 years of age newly diagnosed with PID were recruited for investigation and tested for poliovirus excretion. Children with poliovirus-positive stool samples had regular follow-up testing for poliovirus excretion and determination of clinical prognosis. A patient with severe combined immunodeficiency (SCID) with compound heterozygous mutations in the *RAG1* gene was found to be excreting Sabin-like type 3 (SL3) poliovirus. Excretion stopped six weeks after hematopoietic stem-cell transplantation (HSCT). Graft versus host disease (GVHD) and poor graft function (PGF) occurred after HSCT, resulting in failure of hematopoiesis and immune system reconstitution. Given deficient innate and adaptive immunity, immune-mediated destruction of gastrointestinal (GI) tract caused by GVHD and inflammatory diarrheal illness of the girl may have contributed to her clearance of SL3 poliovirus. Intermittent surveillance of immune system parameters for iVDPV excreters receiving HSCT should be included in the PID surveillance program for further understanding poliovirus clearance mechanisms.

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Introduction

The Global Polio Eradication Initiative (GPEI) that was launched in 1988 has resulted in a more than 99.9% decline in wild poliovirus (WPV) cases, largely through global use of poliovirus vaccine, oral (OPV). WPV serotypes 2 and 3 were declared eradicated in 2015 and 2019, respectively.[1] Despite the significant impact of OPV administration on global elimination of WPV, the live attenuated Sabin-strain OPV virus can mutate during prolonged circulation in low-immunity populations and through prolonged replication in persons with primary immunodeficiency. Mutations in the OPV can lead to the emergence of genetically divergent, neurovirulent vaccine-derived polioviruses (VDPVs).[2] In rare cases, this can result in vaccine-associated paralytic poliomyelitis (VAPP).[3]

Children paralyzed by WPVs or VDPVs can be detected by China's sensitive nationwide acute flaccid paralysis (AFP) surveillance system – the mainstay of poliovirus surveillance in China and globally. AFP surveillance is active surveillance that identifies WPVs and VDPVs by investigating, reporting, and testing for presence of poliovirus in all children <15 years of age presenting to the health care system with acute flaccid paralysis. Environmental surveillance (ES) supplements AFP surveillance by sampling and testing wastewater for poliovirus excreted from infected individuals.

Children with primary immunodeficiency disorder (PID) are at higher risk than otherwise healthy children of developing VAPP or generating a VDPV when inadvertently exposed to OPV. Prolonged intestinal replication and mutation of the vaccine virus in PID patients can result in immunodeficiency-associated VDPVs (iVDPVs). To complement AFP and ES poliovirus surveillance, the Chinese Center for Disease Control and Prevention (China CDC) launched a pilot iVDPV surveillance program in 2021. In 2022, this program detected a type 3 iVDPV (iVDPV3) in stool specimens from a nonparalyzed infant with SCID.[4] Here, we present another child diagnosed with SCID in 2023 who was excreting Sabin-like type 3 (SL3) polioviruses. We describe the clinical course of the child, compare her course with other reports of iVDPV infections in PID patients, and discuss possible mechanisms of poliovirus clearance.

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Methods

Study type

This is a cross-sectional study. As polio is nearing eradication, a less appreciated threat to eradication is gaining in prominence: emergence of iVDPVs. Following World Health Organization (WHO) recommendations to extend poliovirus surveillance to individuals with PIDs, in 2021, China CDC launched a pilot iVDPV surveillance program in four children's hospitals located in four large cities (Shenzhen, Shanghai, Zhengzhou, and Chongqing). Children newly diagnosed with PID are enrolled for investigation and poliovirus testing.

Ethical considerations

This program was reviewed and approved by the Institutional Review Board of China CDC on December 4, 2020.

Diagnosis

According to the updated classification of inborn errors of immunity (IEI) compiled by the International Union of Immunological Societies (IUIS) Expert Committee in 2019 and 2022, PIDs are divided into ten categories[5,6]: 1) combined immunodeficiencies; 2) combined immunodeficiencies with syndromic features; 3) predominantly antibody deficiencies; 4) diseases of immune dysregulation; 5) congenital defects of phagocytes; 6) defects in intrinsic and innate immunity; 7) autoinflammatory diseases; 8) complement deficiencies; 9) bone marrow failure; and 10) phenocopies of inborn errors of immunity. When PID is suspected, immune deficiency genetic defects and dysregulation can be identified through whole exome sequencing (WES). WES and evaluation of immunological and clinical phenotypes are valuable tools for molecular diagnosis of patients.

Procedures for data collection

Children under 18 years of age newly diagnosed with a PID and hospitalized in Children's Hospital of Chongqing Medical University (CHCMU) were recruited for investigation. The exclusion criteria is acquired immunodeficiency syndrome (AIDS). Written, informed consent was obtained from participants or legal guardians as appropriate. Trained staff used a standardized questionnaire to obtain data on demographic characteristics, vaccination status, and PID diagnosis. Detailed poliovirus vaccination histories were obtained on participants from the Chongqing Immunization Planning Information Management System or from official vaccination records kept by the parents. Two adequate stool samples, collected at least 24 hours apart, were sent to the Chongqing sub-national Polio Reference Laboratory for virus isolation. Stool samples were processed and cultured in L20B cells (a transgenic mouse cell line expressing poliovirus receptors) and RD cells (rhabdomyosarcoma cells) according to the WHO polio laboratory manual.[7] Isolated polioviruses were transported to the National Polio Reference Laboratory of China CDC, Beijing, for genomic sequencing using the Sanger method. If poliovirus was detected, monthly follow-up visits were conducted to complete additional questionnaires and obtain stool specimens until the stool specimens were negative for poliovirus for two consecutive months.

Results

Case description

The child was a 1-year-old girl born on May 2, 2022 in a village of Qianjiang district, located in the south-east of Chongqing. She was the second child of a family with a healthy 4-year-old brother and both parents. She had received the routinely recommended Bacille Calmette-Guérin vaccine (BCG) on the first day of life. She had received two doses of IPV at 4 and 7 months of age (September 19 and December 12, 2022) and received one dose of bOPV at 10 months of age (March 5, 2023). She had recurrent low leukocyte counts detected through several routine blood tests that were described as low absolute lymphocyte counts (ALC) and absolute neutrophil counts (ANC) by local hospitals. The lowest leukocyte count was 2.8×10^9/L and the range was $2.8–4.46\times10^9$/L. Platelet counts were low in June 2022 with a count of 19×10^9/L. She was admitted to the immunology division of CHCMU at 12 months of age, presenting with persistent diarrhea, fevers, and diffuse small hemorrhagic spots, leading to consideration of a PID. Molecular studies identified a pair of compound heterozygous mutations in the *RAG1* gene(c.339-352del and c.3074dup), which disrupt *T*- and B-lymphocyte receptor formation.[8] Her diagnosis was SCID; complete blood counts at the time of diagnosis when she was 13 months are shown in Table 1.

Poliovirus isolation and characterization

The child was enrolled in the iVDPV surveillance program during her initial hospitalization at CHCMU after PID was diagnosed. Stool specimens were obtained on May 29 and 30, 2023 and sent to the Chongqing sub-national Polio Reference Laboratory for testing. Characterization by the laboratory identified an enterovirus in the stool samples to be an SL3 poliovirus. Poliovirus was isolated in L20B cell

Table 1. Complete blood counts at PID diagnosis, before HSCT* of the patient in study of PID surveillance.

Test	Patient's result	Reference range [25]
WBC* count	3.92 X 10^9/L	5.5–13.6 X 10^9/L
Platelet count	310 X 10^9/L	191–516 X 10^9/L
RBC* count	3.89 X 10^{12}/L	4.1–5.5 X 10^{12}/L
Hemoglobin	88 g/L	104–143 g/L
ALC*	2.46 X 10^9/L	2.7–9.1 X 10^9/L
ANC*	1.05 X 10^9/L	0.9–5.5 X 10^9/L
Lymphocyte percentage	62.8%	35–76%
Neutrophil percentage	26.8%	13–54%
CRP*	43.2 mg/L	<8 mg/L

*HSCT, hematopoietic stem-cell transplantation; WBC, white blood cell; RBC, red blood cell; ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CRP, C-reaction protein. The reference range for WBC count, Platelet count, Hemoglobin, ALC, ANC, Lymphocyte percentage, and Neutrophil percentage are for children within 1–2 years old; Reference range for RBC count is for children within 6 months to 6 years old.

culture and confirmed positive for type 3 poliovirus by intertypic differentiation (ITD) real time polymerase chain reaction (RT-PCR). Sanger sequencing of the isolate by the National Polio Reference Laboratory of China CDC found 5–6 nucleotide changes from type 3 Sabin strain in the VP1 region (<1.0% divergence). Sabin-like polioviruses have limited divergence (<1% divergent for PV1 and PV3, or <0.6% divergent for PV2) in the VP1 nucleotide sequences from the original OPV strain.[9] Subsequent follow-up visits with stool sample collection were conducted monthly. Samples collected on June 28 and 29, 2023 showed 5–6 nucleotide changes in the nucleotide sequence of the VP1 region; isolates obtained on August 3 and 4, 2023, had 7 nucleotide changes. Mutations showed reversion at nucleotide site U2493C in VP1 of Sabin 3 poliovirus and were observed in all isolates; all 8 strains had mutations at nucleotide position 2636 of Sabin 3 poliovirus. Subsequent monthly stool samples (September 7 and 8, October 20 and 24) were negative for both poliovirus and non-polio enterovirus (NPEV).

Clinical course and hematopoietic stem-cell transplantation

On initial admission, the child was 87 cm tall and weighed 8.0 Kg. During hospitalization, she experienced recurrent pneumonia, gastrointestinal (GI) infections, and skin lesion; she was started on antibiotics and received intravenous immunoglobulin (IVIG) replacement therapy (10 g and 5 g, twice a month). At 14 months of age, July 2023, she underwent allogeneic HSCT from an HLA 9/10 related donor (her father). The MNC (mononuclear cell) and CD34+ counts in the graft were 9.72×10^8/kg and 6.04×10^6/kg, respectively. Short tandem repeats (STR) profile monitoring showed 100% after HSCT on August 7 and 20, September 23, and October 26, 2023.

Hematopoiesis was not completely reconstituted after transfusion and blood component transfusion was initiated due to granulocytopenia. Evans syndrome was suspected because she had progressively diminishing hemoglobin levels, reduced platelet counts and presence of haptoglobin. Bone marrow aspiration on August 25 showed inactive red lineage hyperplasia and reduced megakaryocytes, which deteriorated to myelosuppression with rarely existing megakaryocytes in bone marrow smears on October 7, 2023. Graft versus host disease (GVHD) II° occurred following HSCT has caused immune-mediated destruction of the skin, liver, and GI tract. Cyclosporine, methylprednisolone, methotrexate and CD25 monoclonal antibody were administered to minimize GVHD. The rash has subsided and intestinal GVHD has improved after two times administration of combined therapy. Additional post-HSCT complications included pulmonary fungal infections, septicemia, and severe pneumonia. Cefepime, meropenem, and cefoperazone were sequentially administered for treatment of infections. PCR testing of phlegm and blood suggested cytomegalovirus (CMV) infection. Phlegm culture was positive for *Stenotrophomonas maltophilia*. She died at home on December 15, 2023 after parent-requested discharge from the hospital on December 13, 2023 (Figure 1).

Discussion

Trivalent OPV (tOPV), that contained Sabin strain types 1, 2 and 3 was introduced nationwide in China in 1965. In 1978, tOPV was included in China's free, Expanded Program on Immunization (EPI) in a 4-dose schedule, with doses administered at 2, 3, and 4 months and 4 years of age. In April 2016, China changed the routine polio vaccination schedule to 1 dose of injectable inactivated polio vaccine (IPV), which contains all three serotypes, followed by 3 doses of bivalent OPV

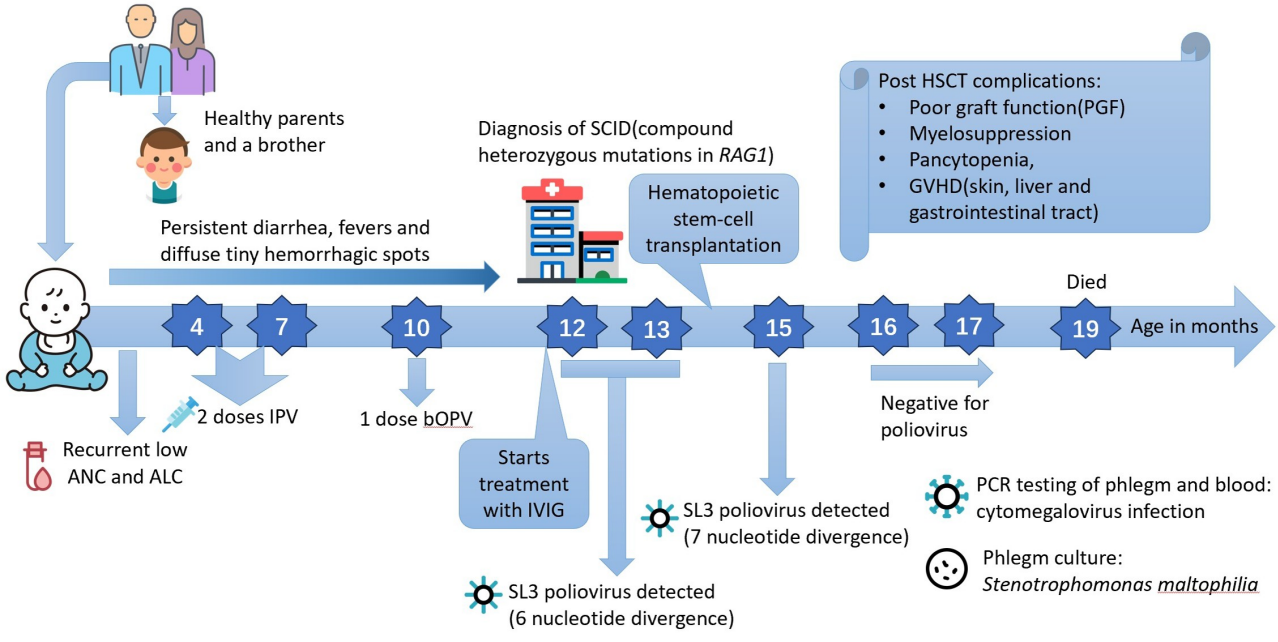

Figure 1. Schematic timeline of key events including poliovirus detections from birth to the post-HSCT period of the patient in study of PID surveillance. ANC, absolute neutrophil count; ALC, absolute lymphocyte count; IPV, inactivated poliovirus vaccine; bOPV, bivalent oral poliovirus vaccine; IVIG, intravenous immunoglobulin; SL3 poliovirus, Sabin-like type 3 poliovirus; HSCT, hematopoietic stem-cell transplantation; GVHD, graft versus host disease; PCR, polymerase chain reaction.

(bOPV), containing Sabin-strain poliovirus types 1 and 3. In January 2020, the schedule was further modified to 2 doses of IPV followed by 2 doses of bOPV to increase protection against type 2 poliovirus. Administration ages continue to be 2,3, and 4 months and 4 years of age.

The risk to global polio eradication posed by WPV1 endemic countries and ongoing use of OPV can be seen in the transmission of WPV1 and VDPVs in under-vaccinated communities.[1] VDPVs can even cause outbreaks in places where vaccine coverage is low. WPV1 transmission remains endemic in Afghanistan and Pakistan and an importation into Malawi and Mozambique resulted in an outbreak of nine WPV1 cases genetically linked to Pakistan during 2021–2022; and 37 outbreaks of circulating VDPVs (cVDPVs) were detected during 2022–2023 in 28 priority countries, including 7 cVDPV1 and 30 cVDPV2 emergence groups.[10] Although China was declared free of all WPV transmission in 2000, it continues to face the threat of importation of WPV and also the emergence of circulating VDPVs. AFP surveillance successfully discovered a 21-case import-related WPV outbreak in Xinjiang in 2011,[11] and 24 VDPV-infected cases have been detected by AFP surveillance throughout China during 2000–2022.[12,13] These detections were essential for maintaining polio-free status. A sensitive AFP surveillance system can detect iVDPV cases in children with paralysis who subsequently are diagnosed with PID. Because the entry point for AFP surveillance is paralysis, iVDPV excretion in children with PID but without paralysis can only be identified through active poliovirus surveillance in children diagnosed with PID.

There were only 149 iVDPV cases identified and reported from 1961 to 2020 globally.[14] In China, 11 paralyzed iVDPV cases were detected by AFP surveillance through 2021. Among these, four died and seven stopped excreting polioviruses. Studies have shown that approximately 30% of patients who excrete iVDPVs never become paralyzed,[15] and therefore, a substantial number of iVDPV cases cannot be detected through AFP surveillance. The prevalence of asymptomatic and prolonged iVDPV infection worldwide remains undetermined, as only a few countries have implemented poliovirus surveillance in PID patients. ES can identify iVDPV circulation, but ES is geographically limited, not universally used, and does not identify individual iVDPV cases. Because of the rarity of iVDPV cases, there is limited scientific literature on the burden and management of asymptomatic iVDPVs during their clinical course with poliovirus excretion.[2,16]

Children with PID form a heterogeneous group, with a variety of inherited disorders resulting from developmental defects or dysfunction of immune system components.[17] These patients are prone to prolonged (6 months to 5 years) or chronic (more than 5 years) excretion of VDPVs because of impaired systemic or mucosal immunity. Early diagnosis of PIDs allows infants to proceed to definitive therapy such as stem cell transplantation or gene therapy prior to facing potentially fatal infections. With advances in medicine and improved supportive care of PID patients, some individuals with PID can live a long time and excrete iVDPV for many years.[18,19] With improved survival, the inability to clear iVDPV infections in these children leads to prolonged or chronic polioviruses excretion in the community, threatening polio eradication efforts. The most recent follow-up reports of outcomes of 149 iVDPV cases worldwide are: alive and still excreting iVDPV (16,10.7%); alive and stopped excreting (52, 34.9%); died (65, 43.6%); and lost to follow up (16, 10.7%). Despite circulation of a cVDPV2 in the Philippines being associated with detection of an iVDPV2 infection in an immunodeficient individual, there is no scientific consensus of how or whether iVDPVs can contribute to cVDPV outbreaks.[14]

The ability to identify and prevent iVDPV circulation by clearing virus excretion is an important part of the polio eradication strategy. Options for clinical management of iVDPV excreters include administering IVIG, use of HSCT[2,16] where appropriate, or consideration of antiviral medication such as pocapavir. Complete clearance of poliovirus has been observed in some patients with these measures.[2,16,20] Regular IVIG administration is not effective at clearing infection in all patients. Different IVIG preparations, doses, and settings for immunoglobulin replacement therapy may contribute to variation in effectiveness of treatment. Infection clearance following HSCT may in part be attributable to the recovery of immune cells shortly after HSCT and immune system reconstitution.

Innate immunity involving lymphocytes and natural killer cells is crucial in the early response to viral infections. The adaptive immune response of secretion of neutralizing antibodies by B lymphocytes is thought to be efficient at iVDPV clearance.[2] Children with SCID have inherited immune system disorders characterized by disturbed or absent T and B cell functions. In general, children with SCID do not spontaneously clear poliovirus excretion. The child in our study had received one dose of bOPV at 10 months of age, which was before her SCID diagnosis was made. This single dose is considered the probable infective exposure. In the short period of only 3 months, the vaccine-strain polioviruses evolved into SL3 polioviruses with 5/6 nucleotide changes in the VP1 region. During the next two months, the virus acquired two additional nucleotide changes for a total of seven changes. The virus strain continued replicating and shedding in the immunodeficient individual.

The child was treated with semimonthly administrations of IVIG; she stopped shedding poliovirus about 6 weeks after HSCT. Adequate immune system reconstitution is the most important determinant of survival after HSCT, and delayed immune reconstitution might have led to prolonged infections or relapse.[21] HSCT status is evaluated by chimerism analysis, which dynamically monitors the relative amount of living donor cells and residual recipient cells in peripheral blood or bone marrow samples through STR profiles. The child had achieved full donor chimerism, as her STR profiles were all >99% after HSCT, indicating a stable engraftment. However, poor graft function (PGF) after HSCT, characterized by pancytopenia, was observed in this girl, resulting in failure of hematopoiesis and immune system reconstitution. CMV infection can also inhibit hematopoiesis and decrease the expression of bone stroma secretion factors and may have led to PGF in this child.

In the literature, 5 of 6 combined immunodeficiency (CID) patients were observed to clear iVDPVs (maximum divergence, 1.0%–4.4%) infection in 4–7 weeks after HSCT, with survival.[2] Five of these six children were diagnosed with SCID; two had T-B-NK+ immunophenotype, and one had MHC class II

deficiency immunophenotyping CID. Two boys from the United Kingdom diagnosed with CID (X-linked CD40 ligand deficiency and MHC class II deficiency, respectively) were reported to have cleared iVDPVs (maximum divergences 1.6% and 3.4%, respectively) with increased IVIG doses for the first child, and following HSCT for the second child; both had healthy survivals. The child in our study received regular IVIG therapy but did not clear poliovirus. Her HSCT outcome was not stable compared with the above reported cases; her immune recovery was tapered and she could not mount adequate immunologic responses. The clearance of SL3 poliovirus in this girl might not be attributed to either innate or humoral immunity because she had low B cell counts as indicated by her granulocytopenia post-HSCT, resulting in PGF.

Because poliovirus replication is believed to occur in the subepithelial interstitium of the GI mucosa,[3] another proposed mechanism is that clearance may be facilitated by destruction of the GI epithelial lining and infected enterocytes. This could occur as a result of inflammatory diarrheal disease or cytotoxicity of engrafted lymphocytes. Natural iVDPV clearance without HSCT was observed in a 4-year-old boy after 2 years of excretion.[22] It is presumed that in the absence of B cells and sufficiently activated T/NK cells, macrophages could be activated to produce inflammatory cytokines to clear infection by damaging the GI epithelial lining or infected enterocytes. The child in our study had recurrent diarrhea before and after HSCT, likely due to the combination of SCID, infection, and GVHD. Acute GVHD may have caused immune-mediated tissue damage of the girl's target organs – especially skin, liver, and GI tract – by releasing proinflammatory cytokines from recipient tissues and activation of donor immune cells,[23,24] which we believe might be the main reason she cleared the SL3 polioviruses.

Limitations of our report include that we did not have detailed profiles of immune cell subsets and circulating cytokines on early immune reconstitution through periodic immunologic monitoring after HSCT. As we cannot explain the association of CMV infection and GI-GVHD with enterovirus clearing, further studies on immune reconstitution and virus–host interactions are needed to better understand the immune mechanisms of poliovirus clearance in PID patients.

This encouraging evaluation and our finding of two non-paralyzed type 3 iVDPV and SL3 polioviruses cases in the PID pilot project supports development of a long-term plan and guidance for iVDPV surveillance. Intermittent monitoring of immune parameters should be conducted for iVDPV excreters receiving HSCT to further understand the immune mechanisms contributing to poliovirus clearance.

Author contributions statement

Conceptualization: H.Y., N.W., ZD.Y., FZ.W., Q.W.; Resources: ZY.Z., M. T., JW.X., Q.W.; Investigations: M.T., N.Y., Y.L.; Laboratory analysis: WJ. X., H.Z.; Manuscript writing-original draft: N.Y., Y.L.; Manuscript writing-review and editing: LE.R., ZY.Z.

Data sharing statement

Deidentified participant data can be made available upon reasonable request.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethical approval

Obtained from the institutional review board of China CDC on December 4, 2020.

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